Fast and Chemoselective Addition of in Deep Eutectic Solvent Generated Highly Polarised Lithium Phosphides (LiPR2) to Aldehydes and Epoxides at Room Temperature and Under Air

Luciana Cicco,a Alba Fombona-Pascual,b,c Alba Sánchez-Condado,b Gabino A. Carriedo,b Filippo M. Perna,a Vito Capriati,*,a Alejandro Presa Soto,*,b and Joaquín García-Álvarez*,c

Dedication ((optional))

[a] Dr. L. Cicco, Prof. F. M. Perna, and Prof. V. Capriati.

Dipartimento di Farmacia-Scienze del Farmaco.

Università di Bari "Aldo Moro", Consorzio C.I.N.M.P.I.S.

Via E. Orabona, 4, I-70125 Bari, Italy.

E-mail: vito.capriati@uniba.it

[b] A. Fombona-Pascual, A. Sánchez-Condado, Prof. G. A. Carriedo, and Prof. A. Presa Soto

Departamento de Química Orgánica e Inorgánica, (IUQOEM) Facultad de Química

Universidad de Oviedo

Julián Clavería, 8, 33006, Oviedo, Spain.

E-mail: presaalejandro@uniovi.es

[c] A. Fombona-Pascual and Prof. J. García-Álvarez

Laboratorio de Compuestos Organometálicos y Catálisis (Unidad Asociada al CSIC). Departamento de Química Orgánica e Inorgánica, (IUQOEM), Centro de Innovación en Química Avanzada (ORFEO-CINQA), Facultad de Química

Julián Clavería, 8, 33006, Oviedo, Spain.

E-mail: garciajoaquin@uniovi.es

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Abstract: Highly polarised lithium phosphides (LiPR2) have been synthesized, for the first time, in Deep Eutectic Solvents as sustainable reaction media, at room temperature and in the absence of protecting atmosphere, through direct deprotonation of both aliphatic and aromatic secondary phosphines (HPR2) by n-BuLi. The subsequent addition of in-situ generated lithium phosphides (LiPR2) to aldehydes or epoxides proceeds fast and chemoselectively, thereby allowing the straightforward access to the corresponding α-hydroxy- or β-hydroxy-phosphine oxides, respectively, under air and at room temperature (bench conditions); which are traditionally textbook-prohibited conditions in the field of polar organometallic chemistry of the s-block elements.

Introduction

Polar organometallic chemistry, and in particular the chemistry of compounds of s-block elements (typically organolithium and organomagnesium reagents), constitutes one of the

most commonly used instruments within the synthetic organic chemist´s toolbox to forge new C-C bonds [1]. In this sense, it is estimated that 95% of drugs in the pharmaceutical industry are manufactured making use of organolithium reagents at least in one of the steps of their synthesis [2]. In order to minimise the undesired and frequently occurring decomposition of these highly reactive organometallic compounds, these commodity reagents are traditionally employed: i) under inert atmosphere; ii) using rigorously dry aprotic organic solvents; and iii) at low temperatures (up to -78 °C) [1]. However, recently reported synthetic advances in this field have revealed the possibility to promote organic transformations with these reagents using unconventional solvents (e.g., water or bio-based solvents) and bench reaction conditions (air atmosphere and room temperature) [3]. Building new bridges between Green Chemistry [4] and s-block organometallic chemistry, we have recently reported on the successful generation of C-C bonds through the direct nucleophilic addition of organolithium (RLi) or organomagnesium (RMgX) reagents to different unsaturated organic electrophiles (e.g., ketones [5], imines or nitriles [6], and alkenes [7]), at room temperature and in the absence of protecting atmosphere, using the so-called Deep Eutectic Solvents (DESs) as sustainable reaction media [8]. These eutectic mixtures can be easily obtained by mixing in a fixed molar ratio hydrogen bond acceptors (HBAs) [e.g., the non-toxic and biorenewable ammonium salt choline chloride (ChCl; 2-hydroxyethyl(trimethyl)ammonium chloride)] with different hydrogen bond donors (HBDs) [e.g., glycerol (Gly), water, urea] [9].

Although a wide variety of synthetic methods have been developed to create C-N [10], C-O [11] and C-S [12] bonds, the number of useful protocols available to create new C-P connections are much more limited. Since the pioneering work of Hirao et al. [13], transition-metal catalysed cross-coupling reactions [14] involving various phosphorous sources like dialkyl/diaryl phosphites, H-phosphonates, or secondary phosphine oxides, have been privileged over oxidative [15] or radical [16] protocols for the construction of C-P bonds. In this context, the metal catalysed addition of phosphorus-nucleophiles to unsaturated bonds emerged as a flourishing research area [17]. Very recently, Mulvey et al. have extended this field to main-group-mediated organic transformations by developing an efficient and smart methodology to create C-P bonds by metalation of HPPh2 with mixed-metal lithium aluminates followed by reaction with a variety of alkynes [18]. However, these synthetic methodologies: i) usually require a large excess of catalyst/oxidant, ligand, or a P-H source (low atom and step economies); ii) need to be conducted under strictly anhydrous conditions; iii) involve expensive metal catalysts; and iv) are limited by a poor functional group tolerance. These shortcomings (among which is also included the notorious strong coordination of the phosphorus moiety to the metal catalyst) have precluded the wide application of these synthetic methodologies. Therefore, the development of sustainable and effective transition-metal-free protocols for the selective formation of new C-P bonds is highly desirable especially because phosphorous-containing organic scaffolds are key players in medicine, biochemistry, material science, catalysis, and organic synthesis [19]. In this last regard, and among the variety of organophosphorus compounds, tertiary phosphine oxide moieties (-P(O)R2) have been recently focused of special attention. In addition to their high air and moisture stability in comparison to phosphines, their weak coordinating abilities to various metal centres have been extensively exploited on a wide variety of catalysed organic transformations [20]. Interestingly, the Lewis base character of the phosphorus oxide moiety derived from the highly polarised P=O bonds, assists on controlling various organocatalysed reactions [21]. For instance, (2-hydroxybenzyl)diphenylphosphine oxide (Figure 1) promotes nucleophilic substitution reactions of primary and secondary alcohol (Mitsunobu-type reactions) [22],

whereas chiral 2,2´-bis(diphenylphosphino oxide)-1,1´-binaphthyl (BINAPO. Figure 1) is widely used as efficient organocatalysts for asymmetric transformations [21]. On the other hand, phosphine oxide moiety have been recently used as a perspective functional group in medical chemistry [23]. Its incorporation into the structure of targeted drugs is proved to enhance their medical properties. For instance, the presence of phosphine oxide functional group in both Brigatinib (Figure 1), an active inhibitor of anaplastic lymphoma kinase (ALK) [24], and AP23464 (Figure 1), a potent adenosine 5´-triphosphate (ATP)–based inhibitor of Src and Abl kinases [25], decreased lipophilicity, increased aqueous solubility, reduced protein binding, and enhanced the metabolic stability.

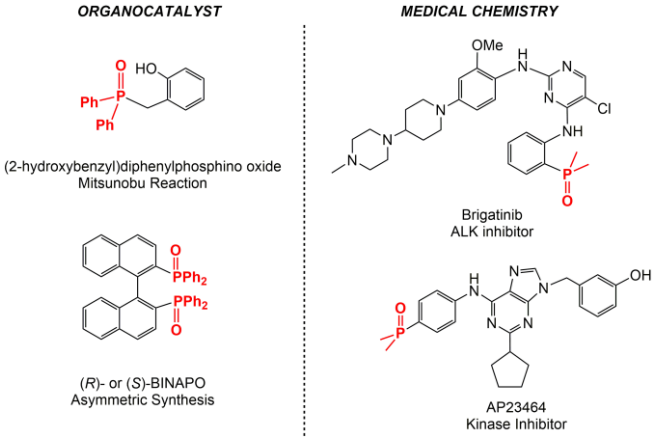
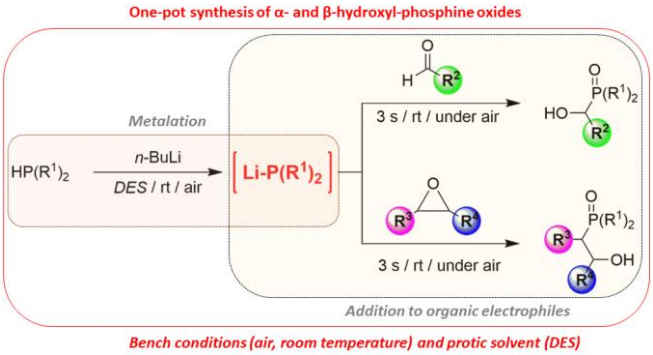


Figure 1. Representative examples of phosphine oxide containing molecules in synthetic and medicinal chemistry.

Bearing this idea in mind and trying to take the aforementioned aerobic organolithium-DESs partnership [5–8] into a new territory in synthetic organic chemistry, we decided to focus our attention on the organolithium-promoted formation of C-P bonds under greener and bench conditions (presence of air and at room temperature). Herein, we first describe the chemoselective and fast addition of in DES generated lithium phosphides (LiPR2) to either aldehydes or epoxides (see Scheme 1), under air and at room temperature (bench conditions), using DESs as environmentally responsible reaction media. Of note, this one-pot methodology: i) allows the straightforward utilisation of in-situ formed highly-reactive lithium phosphides, thus minimising both the required time and energy; ii) simplifies the practical aspects of the whole synthetic procedure (bench conditions); and, more importantly, iii) efficiently transfers the nucleophilicity from commercially available organolithium solutions to a variety of disubstituted phosphines (R2PH), finally leading to the incorporation of phosphine oxide functional group (R2P=O) into different organic electrophiles by selective C-P formation. The resulting α-hydroxy- and β-hydroxy-phosphine oxides (Scheme 1), in which the hydroxyl functional group is providing hydrophilicity to the molecule, are attractive candidates for designing phase-transfer catalysts [26]. α-hydroxy phosphine oxides are also precursors of phosphorylated vinyl ethers, interesting monomers to prepare phoshorus-containing polymers [27].

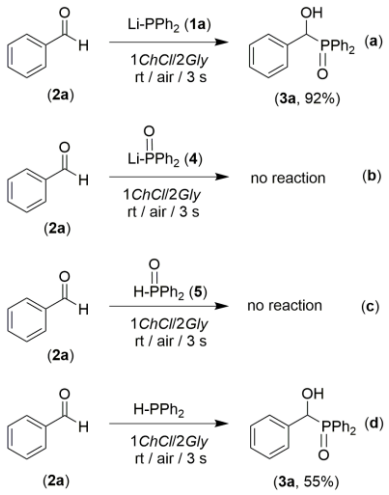


Scheme 1. In-situ generation of lithium phosphides and their one-pot chemoselective addition to aldehydes and epoxides, under air and at room temperature, in Deep Eutectic Solvents (DESs) as sustainable reaction media.

Results and Discussion

We firstly examined the operationally simple direct addition of an equimolecular amount of a preformed LiPPh2 (1a) to benzaldehyde (2a) at room temperature and in the presence of air (see Experimental Section) using the prototypical eutectic mixture 1ChCl/2Gly (Scheme 2a). The selective and high yield (92%) formation of the corresponding α-hydroxy-phosphine oxide 3a occurred after only 3 s reaction time as a result of the fast and selective addition of 1a to 2a followed by concomitant and spontaneous oxidation of the corresponding putative α-hydroxy-phosphine intermediate Ph2P-C(OH)Ph2. With regard to that, it has been reported that hydroxy phosphines are species “especially sensitive to air and moisture and must be handle with extreme care” [28]. Thus, it comes as no surprise that all the experimental efforts made to reduce its oxidation (i.e., use of both Schlenck-type techniques and rigorously deoxygenated eutectic solvents) were unsuccessful in our hands.

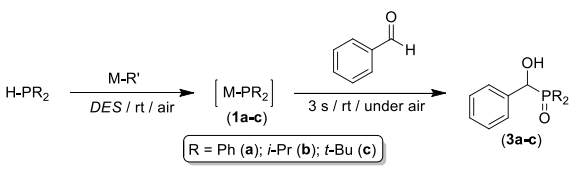
Trying to shed more light on this experimental observation, we decided to investigate whether the oxidized lithium phosphide LiP(=O)Ph2 (4) could also undergo addition to 2a to produce directly the expected phosphine oxide 3a (Scheme 2b). By employing the aforementioned reaction conditions, however, no addition took place, the reaction crude only containing the starting and unreacted 2a and the corresponding protonated phosphine oxide HP(=O)Ph2 (5), likely generated by a spontaneous acid/base reaction between 4 and the protic eutectic mixture 1ChCl/2Gly. In a subsequent experiment, we also ascertained that the addition of pure phosphine oxide 5 to 2a in the above eutectic mixture did not produce phosphine oxide 3a (Scheme 2c). All these experimental evidences point towards a fast and selective addition of the putative lithium phosphide 1a to 2a as the first step of the process, which is then followed by a spontaneous oxidation of the fleeting α-hydroxy-phosphine Ph2P-C(OH)Ph2. Finally, by reacting the secondary phosphine HPPh2 with 2a, adduct 3a could be isolated in a 55% yield only (Scheme 2d). 31P{1H} NMR analysis also disclosed the presence in the crude of a mixture of 3a (δP = 28 ppm) and 5 (δP = 22 ppm). Relative integration of both peaks revealed a 3a:5 proportion of 1:1.



Scheme 2. Addition of different organophosphorus reagents to benzaldehyde (2a), at room temperature and under air, in the eutectic mixture 1ChCl/2Gly as the solvent.

At this point, we explored the feasibility of developing a straightforward, one-pot protocol in which the lithium phosphide could be directly generated in-situ by deprotonating the secondary phosphine HPPh2 with n-BuLi in the eutectic mixture 1ChCl/2Gly (see Table 1). The direct addition of n-BuLi to a solution of the secondary phosphine in the 1ChCl/2Gly, under air and at room temperature, produced an instantaneous change of colour (from colourless to orange) in the reaction vessel, while the subsequent addition of 2a resulted in the instantaneous disappearance of the orange colour and the almost quantitative formation of 3a (95% yield, 1H-NMR analysis, see entry 1 of Table 1). These results are consistent with an in DES formation of the lithium phosphide 1a. A higher amount of the putative LiPPh2 was detrimental on both the yield of 3a (2 equiv: 72%; 3 equiv: 65%; entries 2-3, Table 1) and the overall chemoselectivity of the addition process as a variety of by-products also formed (31P{1H} NMR analysis). We then explored the effect of the s-block alkaline hydrides on the outcome of the reaction. By performing the deprotonation of HPPh2 with solid hydrides (e.g., NaH, KH) in the absence of any volatile organic compound (VOC) under strict stoichiometric conditions, immediately followed by the addition of 2a, adduct 3a formed in remarkably 85–91% yields (entries 4-5, Table 1). Although similar yields were attained compared to n-BuLi, we decided to employ the latter in the further optimisation of protocol design, essentially due to the easier handle of stock solutions of this commercially available reagent.

Table 1. Direct conversion of secondary phosphines (HPR2) into the corresponding anionic phosphides (M-PR2) through in-situ deprotonation with s-block reagents (M-R') and concomitant chemoselective and fast addition to benzaldehyde (2a) in different sustainable solvents.a



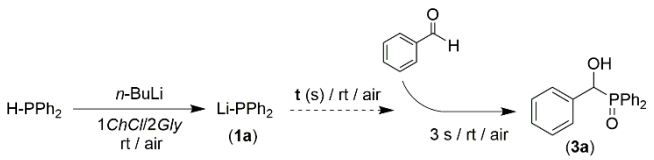
Entry	Solvent R	M-R'	M-PR2 (equiv.)	Yield (%)b
1	1ChCl/2Gly	Ph	n-BuLic Li-PPh2 (1)	3a: 95d
2	1ChCl/2Gly	Ph	n-BuLic Li-PPh2 (2)	3a: 72

3	1ChCl/2Gly	Ph	n-BuLi	c Li-PPh2 (3)	3a: 65
4	1ChCl/2Gly	Ph	NaH	Na-PPh2 (1)	3a: 91
5	1ChCl/2Gly	Ph	KH	K-PPh2 (1)	3a: 85
6	1ChCl/2Urea	Ph	n-BuLi	c Li-PPh2 (1)	3a: 90
7	1ChCl/2Frue	Ph	n-BuLi	c Li-PPh2 (1)	3a: 28
8	1ChCl/2Sorf	Ph	n-BuLi	c Li-PPh2 (1)	3a: 52
9	2Pro/5Glyg	Ph	n-BuLi	c Li-PPh2 (1)	3a: 26
10	H2O	Ph	n-BuLi	c Li-PPh2 (1)	3a: 65
11	Gly	Ph	n-BuLi	c Li-PPh2 (1)	3a: 93
12	1ChCl/2Gly	i-Pr	n-BuLi	c Li-P(i-Pr)2 (1)	3b: 72
13	1ChCl/2Gly	t-Bu	n-BuLi	c Li-P(t-Bu)2 (1)	3c: 76

a General conditions: reactions performed under air, at room temperature, using 1.62 mmol of H-PR2 and 1.62 mmol of the polar organometallic reagent M-R', in 1.6 mL of the desired solvent. b Yields determined by 1H NMR spectroscopy. c Commercial solution of n-BuLi (2.5 M in hexanes) was added at room temperature and under air. d Yield of 3a after isolation and purification: 90%. e Fru: D-fructose. f Sor: sorbitol. g Pro: L-proline.

The employment of 1ChCl/2Urea as the eutectic mixture provided 3a in 90% yield (entry 6, Table 1). On the other hand, by changing the HBD for sugar-based alcohols [e.g., D-fructose (Fru), sorbitol (Sor)] or the HBA for an amino acid like L-proline (Pro), the yield of 3a dropped down to 26–52%, the remaining being only starting material (entries 7-9, Table 1). No improvements in terms of yield were observed as well when using pure Gly or bulk water as the solvent (entries 10-11, Table 1). Pleasingly, not only aromatic (HPPh2) but also aliphatic secondary phosphines like HP(i-Pr)2 or HP(t-Bu)2 proved to be effective in promoting the addition of the corresponding phosphides to 2a as they furnished the desired α-hydroxy-phosphine oxides 3b,c in 72–76% yields (entries 12-13, Table 1).

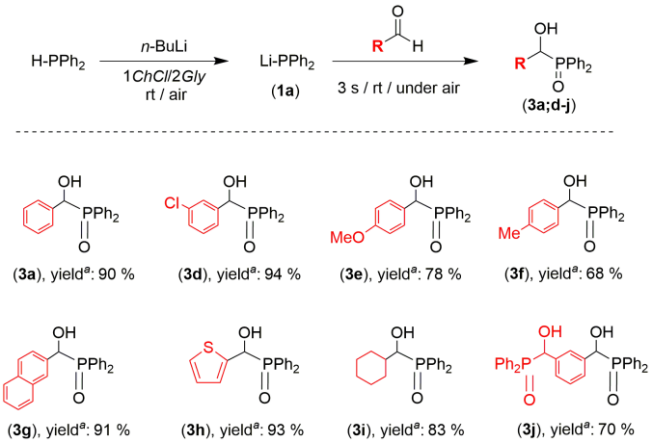
In order to support these results, we decided to study the lifetime of the LiPPh2 reagent in the protic eutectic mixture 1ChCl/2Gly. By stirring the in-situ generated LiPPh2 for 5 s before adding 2a, adduct 3a was still isolated in a remarkable yield (86%). Even after a half a minute interval, the yield of 3a was still good (77%). Conversely, the formation of 3a was almost totally supressed (<5% yield) after 1 min reaction time (Scheme 3).



t (s)	3a Yield (%)
3	95
5	86
30	77
60	2

Scheme 3. Lifetime of LiPPh2 in the protic eutectic mixture 1ChCl/2Gly.

With these optimised conditions in place (equimolecular amounts of LiPPh2 and aldehyde, ambient temperature, under air), we sought to capitalise on this process by exploring the scope of the reaction with a variety of aldehydes (Scheme 4). With regards to 1a, very good yields (64–94%) of the desired adducts (3d–f) were obtained after 3 s reaction time with aryl aldehydes bearing an alkyl substituent (Me, 3f), electron-donating (MeO, 3e) or electron-withdrawing (Cl, 3d) groups despite potential competitive side reactions like: i) a Li-Cl halogen-exchange reaction (3d); or ii) a deprotonation at the benzylic position (3f). Aldehydes decorated with a naphtyl or a heteroaromatic (thiophene) group as well as aliphatic aldehydes like cyclohexane carbaldehyde also participated smoothly in the nucleophilic addition triggered by 1a to afford α-hydroxy-substituted phosphine oxides 3g–i in 83–91% after 3 s reaction time (Scheme 4). In this context, it is worth mentioning that all the above adducts could be isolated by simply adding a brine aqueous solution to the eutectic mixture, which favored their precipitation, and thus their purification by filtration without the need of using organic and toxic VOCs. Even the addition of the solid aromatic dialdehyde isophthalaldehyde to a solution of 1a (2 equiv) in 1ChCl/2Gly straightforwardly furnished the bis(hydroxy-phosphine oxide) 3j in 70% yield (Scheme 4).

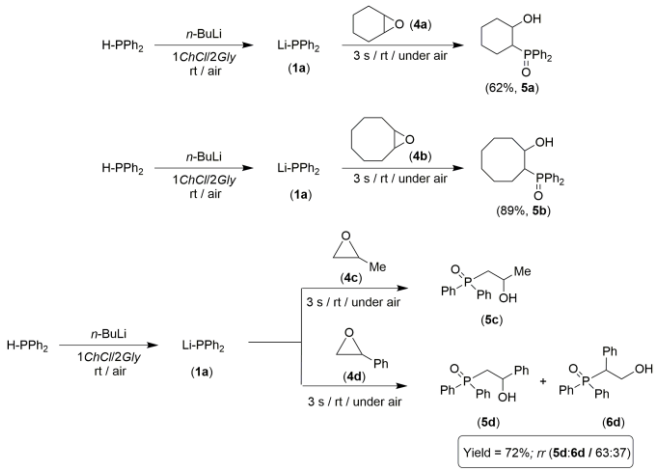


Scheme 4. Chemoselective and fast (3 s) addition of in DES prepared LiPPh2 to various aldehydes. General reaction conditions: 1.6 mL of DES per 1.62 mmol of HPR2, 1.62 mmol n-BuLi and 1.62 mmol of the desired aldehyde, under air and at room temperature. The yields reported are for isolated products.

To further explore the utility of this new protocol using eutectic mixtures, we investigated the nucleophilic addition of the in-situ generated LiPPh2 to epoxides, at room temperature and under air, for the preparation of β-hydroxy-phosphines as a result of the concomitant opening of the three-membered ring (Scheme 5). At this point, it is worth noting that such addition has always been reported to take place under strict Schlenk-type reaction conditions (that is, at low temperature, using anhydrous VOCs and inert atmospheres) [28]. In contrast, under the aforementioned reaction conditions, lithium phosphide 1a was found to add instantaneously to symmetric cyclohexene (4a) or cyclooctane (4b) epoxides to produce the corresponding cyclic β-hydroxyl phosphine oxides 5a-b in good (62%) to excellent (89%) yields and after only 3 s reaction time (Schemes 5a,b).

We then explored the regiochemistry of this ring-opening reaction in DES towards non-symmetric epoxides. The reaction of 1a with propylene oxide (4c) was found to proceed with complete regioselectivity, thus giving rise only to the adduct deriving by an exclusive attack at the less-substituted carbon atom, however, as an almost 1:1 mixture of the oxidized (5c) and

unoxidized (5c') form [5c (31P NMR at ca. 34 ppm) and 5c' (31P NMR at ca. -23 ppm)] with an 82% overall yield (Scheme 5c). These adducts could be separated and isolated by column chromatography on silica-gel (ESI). On the other hand, the addition of 1a to styrene oxide (4d), provided a regioisomeric mixtures of adducts 5d (31P NMR at 34.2 ppm) and 6d (31P NMR at 33.8 ppm) with a 72% overall yield, as the result of an attack at either the less- or the more-substituted carbon atom of 4d, respectively. 1H- and 31P NMR analysis of the reaction crude showed a regioisomeric ratio (rr) 5d:6d of 63:37 (Scheme 5d, ESI). Overall, the above described results mirror the outcome of ring-opening of mono-substituted epoxides with LiPPh2 already reported in the literature in hazardous VOCs and under inert atmospheres. Indeed, i) Pizzano et al. disclosed the regioselective formation of enantiopure 5c' by reaction of LiPPh2 with (R)- or (S)-propylene oxide in THF, at 0 °C, and under argon or nitrogen atmosphere [29], whereas ii) Müller et al. [28] and, more recently, Vidal-Ferrán et al. [30] reported that a 70:30 mixture of regioisomers formed by reacting 1a with 4d in THF at -30 °C.



Scheme 5. Addition of LiPPh2 to symmetric and non-symmetric epoxides at room temperature, under air and in 1ChCl/2Gly. Yields of 5a and 5b refer to isolated products. Yield of reaction of LiPPh2 (1a) with styrene oxide (4d) refers to the crude reaction mixture containing both regioisomers (5d and 6d). Regioisomeric ratio (rr) was calculated by 1H and 31P{1H} NMR analysis of the reaction crude.

Conclusion

In summary, this work demonstrate that the biorenewable eutectic mixture 1ChCl/2Gly can be used as an environmentally friendly reaction medium to promote a fast (within 3 s reaction time) and chemoselective addition of in-situ generated highly polarised lithium phosphides (LiPR2) to both aldehydes and epoxides, at room temperature and under air, thereby granting access to α-hydroxy- and β-hydroxy-phosphine oxides, respectively, in very good yields (68–94%). This new contribution reinforces the argument that it is possible to merge main-group polar organometallic chemistry with aerobic conditions and protic bio-based solvents, thus fulfilling several important Principles of Green Chemistry.

Experimental Section

All reagents were obtained from commercial suppliers and used without further purification with the exception of Deep Eutectic Solvents [choline chloride (ChCl)−glycerol (Gly) (1:2 mol/mol); ChCl−D-fructose (Fru) (1:2 mol/mol); ChCl−D-sorbitol (Sor) (1:1 mol/mol); ChCl−urea (1:2 mol/mol); ChCl−L-proline (Pro) (5:2 mol/mol)], which were prepared by heating under

stirring at 75 °C for 10–30 min the corresponding individual components until a clear solution was obtained. NMR spectra were obtained using a Bruker DPX-300 instrument at 300 MHz (1H), 121.5 MHz (31P), or 75.4 MHz (13C) with SiMe4 or 85% H3PO4 as standard. CDCl3, [D6]-DMSO or [D6]acetone were used as the deuterated solvents. Analytical thin layer chromatography (TLC) was carried out on precoated 0.25 mm thick plates of Kieselgel 60 F254; visualization was accomplished by UV light (254 nm).

Representative procedure for the synthesis of α-hydroxy-phosphine oxides 3a–j.

Synthesis of [hydroxy(phenyl)methyl]diphenylphosphine oxide (3a): A commercially available solution of n-BuLi (2.5 M in hexanes, 1.62 mmol) was added by rapidly spreading it out over a mixture of HPPh2 (1.62 mmol) in the eutectic mixture 1ChCl/2Gly, at room temperature, under air and with vigorous stirring, followed by the addition (after 3 s of reaction) of benzaldehyde (2a, 1.62 mmol). After additional 3 s, the reaction was quenched with brine, and this allowed the precipitation of a white solid from the aqueous mixture. The latter was filtered off by using a Buchner funnel and washed with brine, giving rise to an almost quantitative recovery of the corresponding α-hydroxy-phosphine oxide 3a in 90% yield.

Representative procedure for the synthesis of β-hydroxy-phosphine oxide 5a–d.

Synthesis of (2-hydroxycyclohexyl)diphenylphosphine oxide 5a: A commercially available solution of n-BuLi (2.5 M in hexanes, 1.62 mmol) was added by rapidly spreading it out over a mixture of HPPh2 (1.62 mmol) in the eutectic mixture 1ChCl/2Gly, at room temperature, under air and with vigorous stirring, followed by the addition (after 3 s of reaction) of cyclohexene oxide (4a, 1.62 mmol). After additional 3 s, the reaction was quenched with brine and the reaction mixture was extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over anhydrous Na2SO4, and then filtered off and evaporated under reduced pressure. The resultant crude was purified by silica gel column chromatography to afford the corresponding β-hydroxy-phosphine oxide 5a as a white solid in 62% yield.

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Keywords: Phosphine oxide • Organolithium • Deep Eutectic Solvent • organophosphorus • Sustainable Chemistry

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α-hydroxy- and β-hydroxy-phosphine oxides are successfully synthesized by a fast and chemoselective one-pot addition of the in-situ generated highly polarised lithium phosphides (LiPR2) to both aldehydes and epoxides using eutectic mixtures as biorenewable reaction

media. Despite the high air and moisture stability of organolithium reagents, the presented synthetic protocol allows to carry out the reaction at room temperature, using protic solvent, and under air atmosphere.

Institute and/or researcher Twitter usernames:

Prof. A. Presa Soto: @APresaSoto_Chem

Prof. V. Capriati: @Capriati_V

Prof. J. García-Álvarez: @JoaquinGA78