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

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Abstract: Highly polarized lithium phosphides (LiPR₂) have been synthesized, for the first time, in *Deep Eutectic Solvents* (DESS) 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 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 considered as textbook-prohibited conditions in the field of polar organometallic chemistry of 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 minimize 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 form new C–P connections is much more limited. Since the pioneering work of Hirao *et al.*,^[13] transition-metal catalyzed 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 catalyzed 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.^[18,19] 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.^[20]

Among the variety of organophosphorus compounds, particular attention has recently been paid to tertiary phosphine oxides ($P(=O)R_3$). 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 catalyzed organic transformations.^[21] Interestingly, the Lewis base character of the phosphorus oxide moiety, which is derived from the highly polarized P=O bond, assists on controlling various organocatalyzed reactions.^[22] For instance, chiral 2,2'-bis(diphenylphosphino oxide)-1,1'-binaphthyl (BINAPO, Figure 1) is widely used as efficient organocatalyst in asymmetric transformations,^[22] whereas (2-hydroxybenzyl)diphenylphosphine oxide (Figure 1) promotes nucleophilic substitution reactions of primary and secondary alcohols (Mitsunobu-type reactions).^[23] In addition, the phosphine oxide moiety has recently been employed as a perspective functional group in medicinal chemistry.^[24] Indeed, its incorporation into the scaffold of targeted drugs is known to enhance their medicinal properties. For instance, the presence of the phosphine oxide functional group in both Brigatinib (Figure 1), an active inhibitor of anaplastic lymphoma kinase (ALK),^[25] and AP23464 (Figure 1), a potent adenosine 5'-triphosphate (ATP)-based inhibitor of Src and Abl kinases,^[26] decreased lipophilicity, increased aqueous solubility, reduced protein binding, and enhanced the metabolic stability.

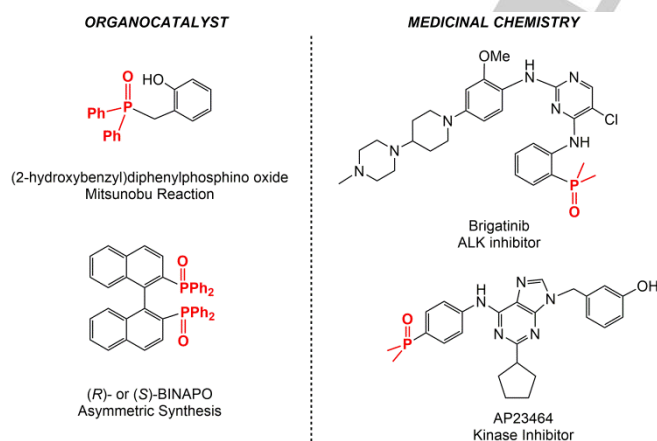
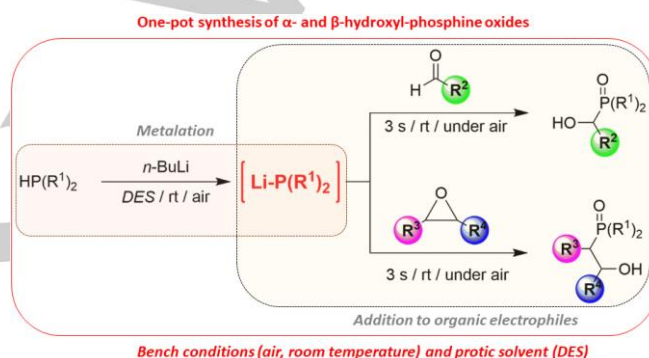


Figure 1. Representative examples of phosphine oxide containing molecules in synthetic and medicinal chemistry.

Bearing this idea in mind and trying to take the aforementioned aerobic organolithium-Deep Eutectic Solvents (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 ($LiPR_2$) to either aldehydes or epoxides (Scheme 1), under air and at room temperature (bench conditions), using *DESS* as environmentally responsible reaction media. This new *one-pot* methodology: *i*) allows the straightforward utilization of *in-situ* formed highly-reactive lithium phosphides, thus minimizing 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 (R_2PH), eventually leading to the incorporation of the phosphine oxide functional group ($R_2P=O$) into different organic electrophiles by selective C–P bond formation reactions. The resulting α -hydroxy- and β -hydroxy phosphine oxides (Scheme 1), in which the hydroxy functional group is responsible for the hydrophilicity of the molecule, are attractive candidates for designing phase-transfer catalysts.^[27] α -Hydroxy phosphine oxides are also useful precursors of phosphorylated vinyl ethers, which are interesting monomers to prepare phosphorus-containing polymers.^[28]



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.

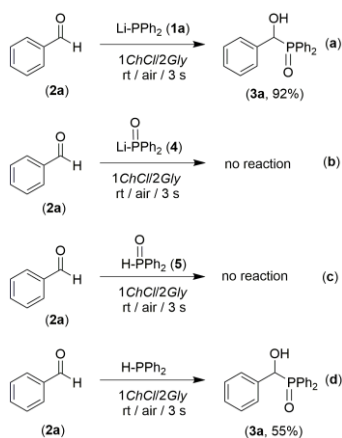
Results and Discussion

We firstly examined the operationally simple direct addition of an equimolecular amount of a preformed $LiPPh_2$ (**1a**) to benzaldehyde (**2a**), at room temperature and in the presence of air (see Experimental Section), using the prototypical eutectic mixture 1*ChCl*/2*Gly* (Scheme 2a). The formation of α -hydroxy phosphine oxide **3a** occurred in high yield (92%) 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 $Ph_2P-C(OH)Ph_2$. 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*”.^[29] Thus, it comes as no surprise that, following this methodology, α -hydroxy phosphine oxides are obtained as sole reaction products.

In light on this result, we decided to investigate whether the oxidized lithium phosphide $LiP(=O)Ph_2$ (**4**) could also undergo addition to **2a** to produce directly the expected phosphine oxide **3a** (Scheme 2b). Under the aforementioned conditions, however, the reaction lead to unreacted **2a** and the protonated phosphine oxide $HP(=O)Ph_2$ (**5**), likely generated by a spontaneous acid/base reaction between **4** and the protic

eutectic mixture 1*ChCl*/2*Gly* (i.e., quenching of LiP(=O)PPh_2 (**4**) by the protic eutectic mixture is faster than the addition reaction to **2a**). In a subsequent experiment, we observed that phosphine oxide **5** did not react with **2a** in the eutectic mixture to produce **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 $\text{Ph}_2\text{P-C(OH)Ph}_2$.

Finally, by directly reacting the secondary phosphine HPPH_2 with **2a**, adduct **3a** could be isolated, but only in a 55% yield (Scheme 2d). This observation is consistent with the fact that LiPPh_2 is essential to synthesize α -hydroxy phosphine oxide **3a** in high yields. $^{31}\text{P}\{^1\text{H}\}$ NMR analysis also disclosed the presence in the crude of a mixture of **3a** ($\delta_{\text{P}} = 28$ ppm) and **5** ($\delta_{\text{P}} = 22$ ppm). Relative integration of both peaks revealed a **3a**:**5** ratio of 1:1.



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

At this point, we explored the feasibility of developing a straightforward, one-pot protocol in which lithium phosphide could be directly generated *in-situ* by deprotonating the secondary phosphine HPPH_2 with *n*-BuLi in the eutectic mixture 1*ChCl*/2*Gly* (see Table 1). The direct addition of *n*-BuLi to a solution of the secondary phosphine in the 1*ChCl*/2*Gly*, under air and at room temperature, produced an instantaneous change of color (from colorless to orange) in the reaction vessel, while the subsequent addition of **2a** resulted in the instantaneous disappearance of the orange color and the almost quantitative formation of **3a** (95% yield, ^1H -NMR analysis; entry 1, Table 1). These results are consistent with an *in DES* formation of the lithium phosphide **1a**. A higher amount of the putative LiPPh_2 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 ($^{31}\text{P}\{^1\text{H}\}$ NMR analysis). We then explored the effect of the *s*-block alkaline metal on the outcome of the reaction. By performing the deprotonation of HPPH_2 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 remarkable 85–91% yields (entries 4,5, Table 1).^[30] Although similar yields were attained compared to *n*-BuLi, we decided to employ the latter in the further optimization of protocol design, especially

because of the easier handle of stock solutions of this commercially available reagent.

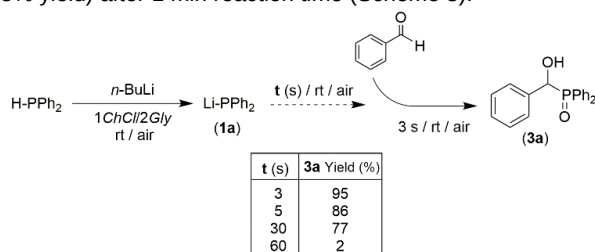
Table 1. Direct conversion of secondary phosphines (HPR_2) into the corresponding anionic phosphides (M-PR_2) through *in-situ* deprotonation with *s*-block reagents (M-R') and concomitant chemoselective and fast addition to benzaldehyde (**2a**) in different sustainable solvents.^[a]

Entry	Solvent	R	M-R'	M-PR ₂ (equiv.)	Yield (%) ^[b]
1	1 <i>ChCl</i> /2 <i>Gly</i>	Ph	<i>n</i> -BuLi ^[c]	Li-PPh ₂ (1)	3a : 95 ^[d]
2	1 <i>ChCl</i> /2 <i>Gly</i>	Ph	<i>n</i> -BuLi ^[c]	Li-PPh ₂ (2)	3a : 72
3	1 <i>ChCl</i> /2 <i>Gly</i>	Ph	<i>n</i> -BuLi ^[c]	Li-PPh ₂ (3)	3a : 65
4	1 <i>ChCl</i> /2 <i>Gly</i>	Ph	NaH	Na-PPh ₂ (1)	3a : 91
5	1 <i>ChCl</i> /2 <i>Gly</i>	Ph	KH	K-PPh ₂ (1)	3a : 85
6	1 <i>ChCl</i> /2 <i>Urea</i>	Ph	<i>n</i> -BuLi ^[c]	Li-PPh ₂ (1)	3a : 90
7	1 <i>ChCl</i> /2 <i>Fru</i> ^[e]	Ph	<i>n</i> -BuLi ^[c]	Li-PPh ₂ (1)	3a : 28
8	1 <i>ChCl</i> /2 <i>Sor</i> ^[f]	Ph	<i>n</i> -BuLi ^[c]	Li-PPh ₂ (1)	3a : 52
9	2 <i>Pro</i> /5 <i>Gly</i> ^[g]	Ph	<i>n</i> -BuLi ^[c]	Li-PPh ₂ (1)	3a : 26
10	H ₂ O	Ph	<i>n</i> -BuLi ^[c]	Li-PPh ₂ (1)	3a : 65
11	<i>Gly</i>	Ph	<i>n</i> -BuLi ^[c]	Li-PPh ₂ (1)	3a : 93
12	1 <i>ChCl</i> /2 <i>Gly</i>	<i>i</i> -Pr	<i>n</i> -BuLi ^[c]	Li-P(<i>i</i> -Pr) ₂ (1)	3b : 72
13	1 <i>ChCl</i> /2 <i>Gly</i>	<i>t</i> -Bu	<i>n</i> -BuLi ^[c]	Li-P(<i>t</i> -Bu) ₂ (1)	3c : 76

^[a] General conditions: reactions performed under air, at room temperature, using 1.62 mmol of H-PR_2 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 using CH_2Br_2 as the internal standard. ^[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.

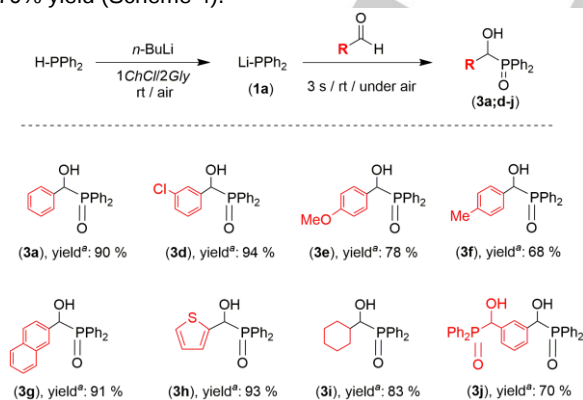
The employment of 1*ChCl*/2*Urea* as the eutectic mixture provided **3a** in 90% yield (entry 6, Table 1). On the other hand, by changing the *HBD* for sugar-based alcohols [e.g., D-fructose (*Fru*), sorbitol (*Sor*)] or the *HBA* for an amino acid like L-proline (*Pro*), the yield of **3a** dropped down to 26–52%, the remaining being only starting material (entries 7–9, Table 1). Considering the recently described successful and unprecedented addition of organolithium and Grignard reagents to organic electrophiles using water as reaction medium,^[5b,6b] we have investigated other protic solvents different from *DES*s. Thus, when bulk water or pure *Gly* were employed, although α -hydroxy phosphine **3a** was successfully prepared, no improvements in terms of yield were observed (entries 10,11, Table 1). Pleasingly, not only aromatic (HPPH_2) but also aliphatic secondary phosphines like $\text{HP}(i\text{-Pr})_2$ or $\text{HP}(t\text{-Bu})_2$ 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 studied the lifetime of the LiPPh_2 reagent in the protic eutectic mixture $1\text{ChCl}/2\text{Gly}$. By stirring the *in-situ* generated LiPPh_2 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 suppressed (<5% yield) after 1 min reaction time (Scheme 3).



Scheme 3. Lifetime of LiPPh_2 in the protic eutectic mixture $1\text{ChCl}/2\text{Gly}$.

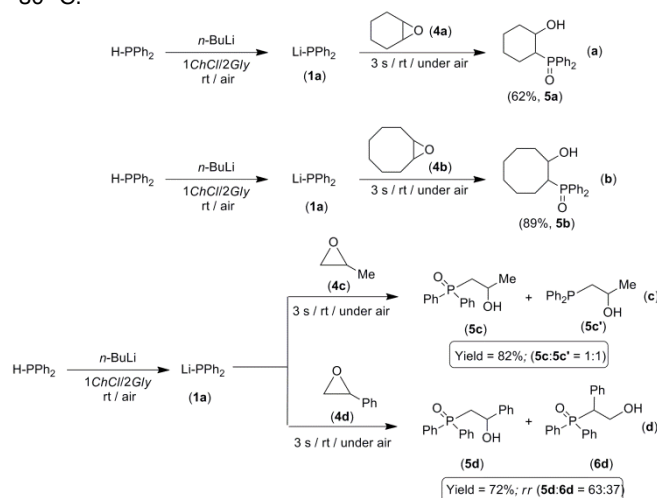
With these optimized conditions (equimolecular amounts of LiPPh_2 and aldehyde, ambient temperature, under air), we sought to capitalize on this process by exploring the scope of the reaction with a variety of aldehydes (Scheme 4). With **1a**, very good yields (68–94%) of the desired adducts (**3d–f**) 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 naphthyl 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 83–93% yield after 3 s reaction time (Scheme 4). Importantly, all the above products could be isolated by simply adding a brine aqueous solution to the eutectic mixture, which favored their precipitation. Therefore, they could be purified directly by filtration without using organic toxic VOCs. Even the addition of the solid aromatic dialdehyde isophthalaldehyde to a solution of **1a** (2 equiv) in $1\text{ChCl}/2\text{Gly}$ 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 LiPPh_2 to various aldehydes. General reaction conditions: 1.6 mL of *DES* per 1.62 mmol of HPR_2 , 1.62 mmol $n\text{-BuLi}$ 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 LiPPh_2 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). 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).^[29] In contrast, under the aforementioned reaction conditions, lithium phosphide **1a** was found to add instantaneously to symmetric cyclohexene (**4a**) or cyclooctene (**4b**) epoxides to produce the corresponding cyclic β -hydroxy 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-symmetrical 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** (^{31}P NMR at ca. 34 ppm) and **5c'** (^{31}P 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** (^{31}P NMR at 34.2 ppm) and **6d** (^{31}P 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 ^{31}P 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 LiPPh_2 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 LiPPh_2 with (*R*)- or (*S*)-propylene oxide in THF, at 0 °C, and under argon or nitrogen atmosphere,^[31] whereas *ii*) Müller *et al.*^[29] and, more recently, Vidal-Ferrán *et al.*^[32] reported that a 70:30 mixture of regioisomers formed by reacting **1a** with **4d** in THF at -30 °C.



Scheme 5. Addition of LiPPh_2 to symmetric and non-symmetrical epoxides at room temperature, under air and in $1\text{ChCl}/2\text{Gly}$. Yields of **5a** and **5b** refer to isolated products. Yield of reaction of LiPPh_2 (**1a**) with styrene oxide (**4d**) refers to the crude reaction mixture containing both

the regioisomers **5d** and **6d**. Regioisomeric ratio (*rr*) was calculated by ^1H and $^{31}\text{P}\{^1\text{H}\}$ NMR analysis of the reaction crude.

Conclusion

In summary, this work demonstrates 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 polarized lithium phosphides (LiPR_2) 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 (^{31}P), or 75.4 MHz (^{13}C) with SiMe_4 or 85% H_3PO_4 as standard. CDCl_3 , $[\text{D}_6]$ -DMSO or $[\text{D}_6]$ -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). Microanalyses were carried out with a Perkin Elmer 2400 microanalyzer.

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 HPPH_2 (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 Büchner 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–l**.

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 HPPH_2 (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 Na_2SO_4 , 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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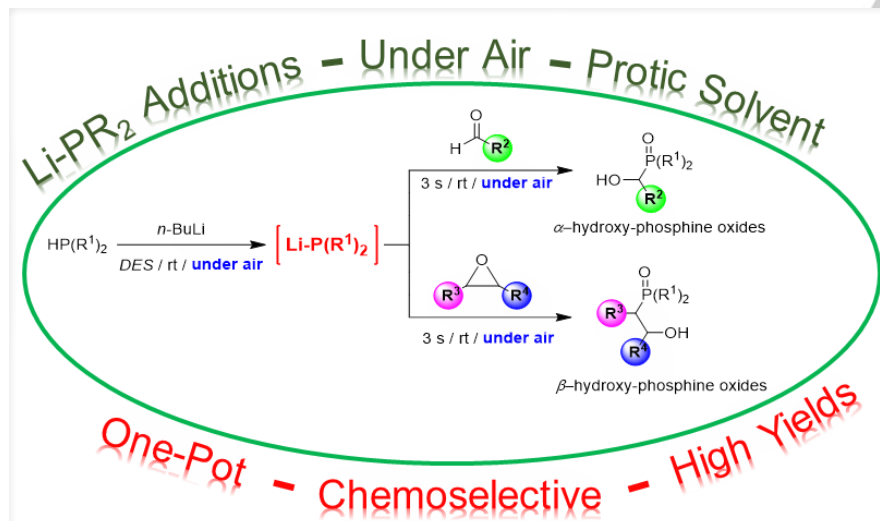
Keywords: Phosphine oxide • Organolithium • Deep Eutectic Solvent • organophosphorus • Sustainable Chemistry

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α-Hydroxy- and β-hydroxy phosphine oxides have been smoothly synthesized by a fast and chemoselective *one-pot* addition of the *in-situ* generated highly polarized lithium phosphides (LiPR₂) to both aldehydes and epoxides using eutectic mixtures as biorenewable reaction media. Despite the well-known air and moisture sensitivity of organolithium compounds, the proposed synthetic protocol allows carrying out all the reactions (preparation and reactivity of LiPR₂) at room temperature, using protic solvents, and under air atmosphere.

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