

Phosphonium ionic liquids as reaction media for strong bases

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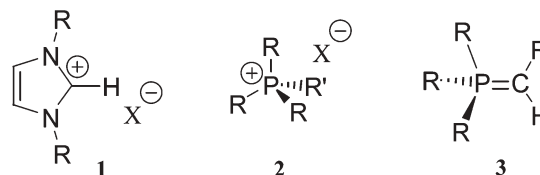
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Phosphonium ionic liquids are compatible with strong bases; for example, solutions composed of commercially available phenylmagnesium bromide in THF are persistent in tetradecyl(trihexyl)phosphonium chloride for several hours–days: their stability appears to be couched in kinetic terms.

Environmental pressure to reduce waste and re-use materials has driven studies into “Green” chemistry.^{1,2} Recent reviews have covered these emerging fields^{3–5} and it is apparent that one of the most difficult areas to make environmentally friendlier is solution phase chemistry. Solvents play key roles in chemical reactions; they serve to homogenize and mix reactants, and act as a heat sink for exothermic processes. It is clear that one of the biggest industrial concerns is replacement of volatile organic compounds (VOCs),⁶ particularly those that are toxic, such as CH₂Cl₂, and those that are hazardous to handle. Of the latter class of VOCs, the most offensive are ethers, which are volatile, flammable, and form explosive peroxides: they are, unfortunately, on the “A-list” of solvents for reactions involving strong bases. Successful attempts to replace or limit the use of VOCs have been made, and these include processes that use no solvent⁷ or new solvent systems such as supercritical H₂O,^{8–10} supercritical CO₂,¹¹ fluorosolvents,¹² and ionic liquids (ILs).^{13,14} ILs are particularly attractive because of their low volatility, high thermal capacity, and resistance to combustion. Here we report that phosphonium based ILs can support chemistry involving strong bases and we use Grignard reagents as illustrative examples.

Perhaps the most extensively studied class of ILs is based upon the imidazolium ion **1**¹⁵ and the most popular example is the ethylmethylimidazolium ion with anions such as [BF₄]⁻ and [AlCl₄]⁻. Notwithstanding the sensitivity of the anions, these ILs have garnered attention since they facilitate many unusual chemical reactions. Solutions of **1** support reactions such as alkene oligomerizations, alkylations¹⁶ and acylations.¹⁷ We note that imidazolium based solvent systems are unsuitable for reactions involving either active metals (*i.e.*, Na or K) or in reactions that involve strong bases (*i.e.* Grignards, organolithiums, and amides) since these reagents *react* with the imidazolium-based solvents. For instance, imidazolium ions react quantitatively with K_{metal} to produce imidazol-2-ylidenes (*N*-heterocyclic carbenes, NHCs),¹⁸ and treatment of imidazolium ions with bases, such as lithium di-*iso*-propylamide or potassium *tert*-butoxide, is the standard method for generation of NHCs.¹⁹ Even with weaker bases, such as NR₃, Aggarwal showed that during the Baylis–Hillman reaction in an imidazolium-based ionic liquid, the low reported yields were the result of addition of the deprotonated imidazolium cation to an aldehyde.²⁰ Finally, the other “Greener”

solvent alternatives, namely H₂O and supercritical CO₂, react with strong bases.



1 X = [AlCl₄]⁻, [BF₄]⁻

2 X = Cl⁻, Br⁻, [(CF₃)SO₂]N⁻
R = C₆H₁₃, R' = C₁₄H₂₉

We recently found that NHCs are persistent in phosphonium based ILs,¹⁸ such as tetradecyl(trihexyl)phosphonium chloride **2** (CYPHOS® IL 101).²¹ NHCs are highly basic (pK_a = 22–24)^{22,23} and we were surprised that deprotonation of the **2** to produce a phosphorane **3** did not occur. This suggested to us to examine whether stronger bases would be *persistent* and *reactive* in phosphonium based ILs. Here we report: 1. Grignard reagents are persistent in **2** and 2. a study examining the behaviour of Grignard reagents in an ionic liquid.

2 (mp = *ca.* –50 °C) can be dried by azeotropic distillation with benzene or with K_{metal} and a small amount (5%) of hexane (added to reduce viscosity and facilitate stirring). Note that the latter drying process is not feasible for **1**. The lack of reactivity of **2** with potassium portends well for the reaction of other bases in this ionic liquid since, in theory, solid potassium is a source of the strongest base, the electron.

Dry samples of **2** form clear solutions of low viscosity with commercially available PhMgBr in THF. Grignard reagents dissolved in **2** are air and moisture sensitive. These solutions show no sign of degradation after one month as shown by reactivity studies. Deprotonation of **2** to produce a phosphorane **3** was not observed. Quench of solutions composed of **2** and PhMgBr with anhydrous Br₂ resulted in the exclusive formation of PhBr, however 5% of biphenyl was detected when the one month old **2** Grignard reagent solution was quenched with Br₂.²⁴ Benzene, the product of a deprotonation reaction, was not observed. We also examined complete removal of THF from the **2** Grignard solutions, but in general this resulted in the formation of more biphenyl and hence reaction yields were reduced. Good results were obtained when the ratio of THF : **2** was 1 : 3. Unfortunately, attempts to generate the Grignard reagent in phosphonium based ionic liquids failed.

We have found that since the ionic liquids have a high heat capacity we do not need to cool the reaction solutions to the extremely low temperatures often needed for ethereal solutions. We performed a survey of reactions in **2**, and these include addition to carbonyls, benzyne reactions, halogenation and

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coupling reactions (Scheme 1). Product isolation is made easy since phosphonium ionic liquids have remarkable solvent properties. After reaction of the electrophile and the Grignard reagent, addition of water and hexane to the reaction mixture results in the formation of a three-phase system, with the organic layer on the top, ionic liquid in the middle, and the aqueous layer on the bottom. The products were isolated from the organic layer and analyzed. The low yields reported in Scheme 1 reflect the partitioning between the **IL** and organic phase, and isolated yields can be markedly improved by successive extractions. In some cases, due to the high thermal stability of the **ILs** and volatility of the products, distillation could be used to remove the product from the reaction mixtures. Analogous reactions were performed using phenyllithium, but these reactions produced a variety of products as yet unidentified. Finally, treatment of benzaldehyde with NaBH₄ in **IL 2** produces benzyl alcohol as the only detectable product. Again, this type of reaction is not feasible in **IL 1**. In all cases, **IL 2** can be washed with water and hexanes, dried, and re-used.

The inertness of **IL 2** towards reaction with bases appears to be couched in kinetic arguments. It is reasonable that deprotonation of a phosphonium ion to produce phosphorane **3** and a salt would be thermodynamically favoured, but evidence for this reaction was not observed. Contrast this with Wittig reagents, which are derived from materials analogous to **2**, but generally with significantly shorter alkyl groups. Access to the reactive protic site on **2** (Fig. 1) is difficult, and hence the Grignard reagents *dissolve* in the **IL 2** but fail to *react* with it. Further support for this kinetic argument is provided by noting that [Ph₃PCH₂CH₃][Br] is deprotonated to form a phosphorane by **IL 2**/PhMgBr solutions as shown by ³¹P{¹H} NMR studies. Addition of electrophilic reagents to the basic **IL 2** solution allows for standard organometallic chemistry to proceed. Sufficient steric protection of imidazolium ions to prevent deprotonation at the acidic C₂ site is not feasible, and thus **IL 1** can quench Grignard reagents. We note that such kinetic/thermodynamic control of solvent reactivity is common in synthetic chemistry; consider, for example, NaBH₄ reduction of an aldehyde in an ethanolic solution. Whereas reaction of NaBH₄ with ethanol to produce a borate and hydrogen gas is

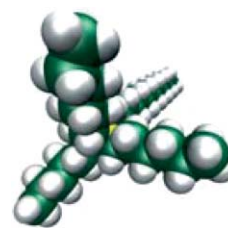


Fig. 1 MM2 minimized structure of the tetradecyl(trihexyl)phosphonium cation showing acidic C–H site surrounded by non-rigid alkyl groups.

thermodynamically favoured, reduction of the aldehyde occurs because the faster reaction involves reduction of the carbonyl.

In summary, **IL 2** is capable of supporting reactions involving strong bases such as Grignard reagents. In this light, **IL 2** complements **IL 1** by supporting reagents (*i.e.*, Grignards) that are not viable in **IL 1**. The reactions between the Grignard reagent and added reactants proceed cleanly, and there is no observed reaction between the **IL** and the strongly basic reagents. The high thermal capacity of **IL 2** limits the need to cool the samples for reaction. Use of phosphonium **ILs** also facilitates product separation due to the triphasic nature of water, ionic liquid, and hexane combinations. The identification of this chemistry opens up the possibility of limiting the use of ethereal solvents in this class of reactions thus allowing for a general “Greening” of Grignard chemistry.

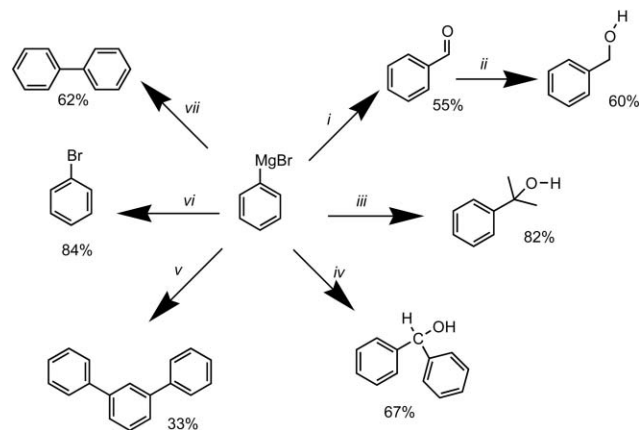
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A recent review²⁵ highlighted the non-innocence of 1,3-dialkyl imidazoliums. Our results suggest that phosphonium-based ionic liquids may be more suitable for reactions involving strong bases.

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Scheme 1 Survey of reactions explored in **IL 2**. *Reaction conditions:* i. DMF; ii. NaBH₄; iii. acetone; iv. benzaldehyde; v. 2,6-dibromiodobenzene; vi. Br₂; vii. CuCl₂. All reactions were followed by an aqueous work-up and an extraction with hexanes.

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- 24 Experimental procedure: Reactant (aldehyde, ketone, DMF, etc.) was added to a stirred solution composed of **IL 2** (15 mL) and 5 mL of commercially available C_6H_5MgBr in tetrahydrofuran. The solution was stirred under N_2 for 1–3 h. The reaction mixture was quenched with saturated aqueous ammonium chloride followed by the addition of 25 mL of water. Hexane was added to establish the three-phase system, and the products were extracted into the hexane layer. The extract was analyzed by GC-MS. Yields and extraction efficiencies were not maximized.
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