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Mechanochemistry enabled highly efficient solvent-free deoxygenation of phosphine oxides in air†

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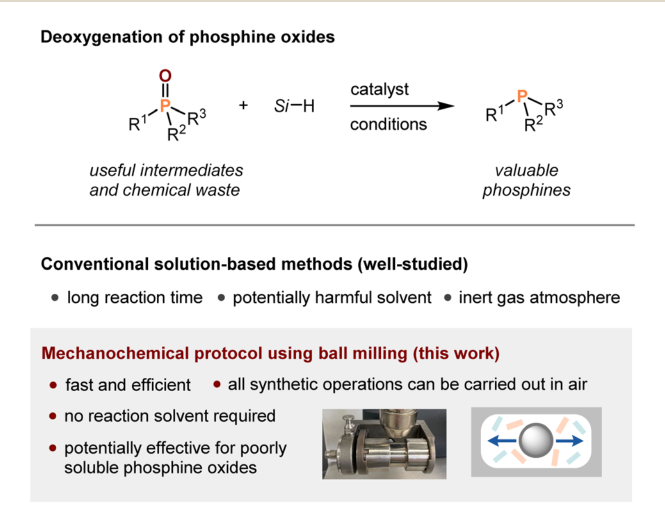
Deoxygenation of phosphine oxides is an important method for the synthesis of valuable organophosphine compounds and recycling of phosphorus resources. However, existing solution-based deoxygenation protocols usually require long reaction times, significant amounts of potentially harmful organic solvents, and inert gas atmospheres. In addition, reactions of poorly soluble phosphine oxides are challenging and often inefficient. Herein, we demonstrate that a high-temperature mechanochemical protocol enables the highly efficient solvent-free deoxygenation of phosphine oxides with hydrosilanes in the presence of a phosphoric acid additive. These reactions were rapid and completed within 30 min for most substrates. Notably, this is the first practical deoxygenation of phosphine oxides in which all synthetic operations can be carried out in air. A preliminary study on the mechanochemical catalytic Wittig reaction is also described.

Introduction

Tertiary phosphines are an essential class of compounds that are used as stoichiometric synthetic reagents, nucleophilic organocatalysts, and ligands in organometallic catalysts.[1] Therefore, the development of efficient methods for the synthesis of tertiary phosphines has attracted significant attention. Given their high chemical stability and ease of handling under atmospheric conditions, phosphine oxides serve as important synthetic intermediates that can be converted into a broad range of organic phosphine compounds through the deoxygenation of the P═O bond.[2] In addition, phosphine oxides are generated as stoichiometric chemical waste in numerous fundamental organic transformations, including the Wittig, Mitsunobu, Staudinger, Rauhut–Currier, and Appel reactions.[1] Deoxygenation of phosphine oxides to phosphines has been recognized as a prominent strategy for recycling phosphorus resources.[2] Despite the importance of organophosphine synthesis and phosphorus recycling, existing deoxygenation methods are harsh owing to the strength of the P═O bond and require long reaction times, potentially harmful organic solvents, and delicate operating conditions, which reduce their practical utility.[2–7]

Conventional deoxygenation of phosphine oxides involves the use of highly reactive metal hydrides (*e.g.*, $LiAlH_4$)[3] and low-valent metal reductants (*e.g.*, SmI_2/hexamethylphosphoramide and Cp_2TiCl_2/Mg).[4] Such conditions are affected by functional group tolerance and require special precautions. Recently, hydrosilanes have been used as reductants and many useful deoxygenation protocols that proceed under mild conditions have been developed (Scheme 1).[5] However, existing solution-based deoxygenation methods with hydrosilanes usually require significant amounts of reaction solvents and long reaction times (>24 h). Furthermore, these reactions must be



Scheme 1 Development of a mechanochemical protocol for the deoxygenation of phosphine oxides to phosphines.

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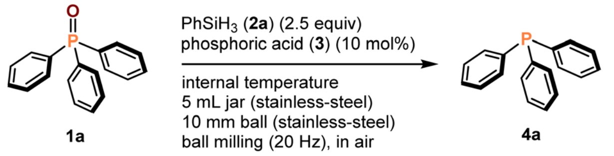
performed in an inert -gas atmosphere, which requires special training. Although the solvent-free microwave-assisted deoxygenation of phosphine oxides with hydrosilanes has also been reported,[6] an excess amount of hydrosilanes and an inert gas atmosphere are still required. Unfortunately, these requirements present major drawbacks from both environmental and economic perspectives.

Recently, mechanochemical synthesis *via* ball milling has attracted considerable attention as an efficient solvent-free synthetic technique.[8] Mechanochemical organic reactions often show much faster reaction kinetics than those under conventional solution-based conditions because of their high concentrations; moreover, the experimental operations can be carried out in air. Considering these achievements, including our recent success in solid-state ball-milling synthesis,[9] we envisioned that this mechanochemical strategy can be applied to the deoxygenation of phosphine oxides, providing a practical solution to many issues associated with conventional solution-based protocols (Scheme 1).

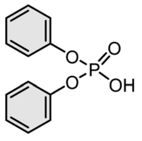
Results and discussion

All mechanochemical reactions were conducted in a Retsch MM400 mill [stainless steel milling jar (5 mL), 20 Hz; stainless steel ball (10 mm diameter)]. All experiments were performed in air. First, we investigated the deoxygenation of triphenylphosphine oxide (**1a**) with phenylsilane (**2a**), which is commonly used as a reductant in various solution-based deoxygenation reactions of phosphine oxides (Table 1).[2,5] The mechanochemical reaction at room temperature did not yield the deoxygenation product (**4a**) (<1%, entry 1). To accelerate the mechanochemical deoxygenation, we carried out the reaction at a higher temperature. We used a commercially available temperature-controllable heat gun placed directly above the ball-milling jar (see the ESI† for details).[9g] The desired product (**4a**) was obtained in good yield (80%) with the heat gun preset to 200 °C (entry 2). The internal temperature of the reaction mixture (120 °C) was confirmed by thermography immediately after opening the milling jar (see the ESI† for details). To further improve the efficiency, we added phosphoric acid (**3**) to the mixture under Beller's solution-based conditions because these additives are solid, inexpensive, and easy to handle under ambient conditions.[5c] The use of diphenyl phosphate (**3a**) (10 mol%) did not improve the reactivity (76%, entry 3). The reaction with a nitro-substituted phosphate, which is the best additive for Beller's protocol, lowered the yield of **4a** (67%, entry 4). We found that BINOL-derived phosphoric acid (**3c**), which has never been used for the deoxygenation of phosphine oxides, significantly accelerated the mechanochemical reaction to form **4a** in quantitative yield (99%, entry 5). Notably, the reaction was nearly complete within 30 min (94% yield, entry 6). A further increase in the reaction temperature decreased the yield (77%, entry 7). We also attempted the deoxygenation reaction in a test tube with efficient mixing by magnetic stirring under the optimized conditions; however, the reaction gave a much lower yield of **4a** (61%, entry 8). This result suggests that strong mechanical agitation in a ball mill is crucial for highly efficient solvent-free deoxygenation. Although further studies are required, we speculate that a strong mechanical impact could crush the solid **1a** into smaller particles with increased surface area, thereby facilitating efficient deoxygenation reactions under solvent-free conditions.

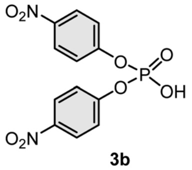
Table 1 Optimization study[a]



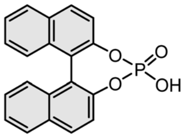
Entry	Phosphoric acid (3)	Internal temp. (°C)	Time (min)	Yield of **4a** (%)[b]
1	None	30	60	<1
2	None	120	60	80
3	**3a**	120	60	76
4	**3b**	120	60	67
5	**3c**	120	60	99
6	**3c**	120	30	94
7	**3c**	145	30	77
8[c]	**3c**	120	30	61



3a

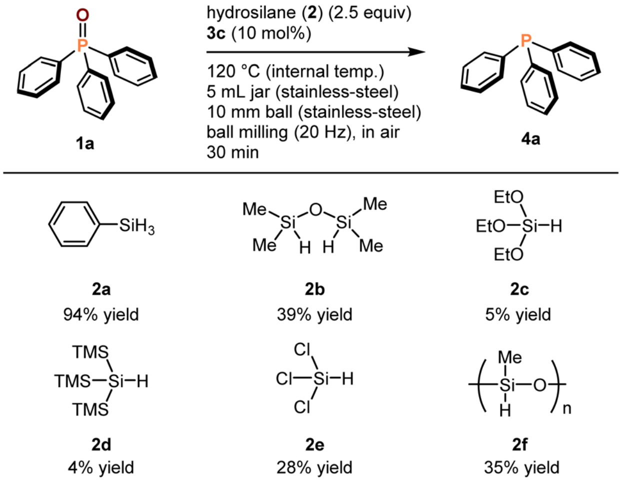


3b



3c

[a] Conditions: **1a** (0.3 mmol), **2a** (0.75 mmol), **3** (0.03 mmol) in a stainless steel milling jar (5 mL) with a stainless steel ball (10 mm). [b] Determined by GC analysis of the crude reaction mixture using an internal standard. [c] Reaction was performed in a test tube under magnetic stirring.



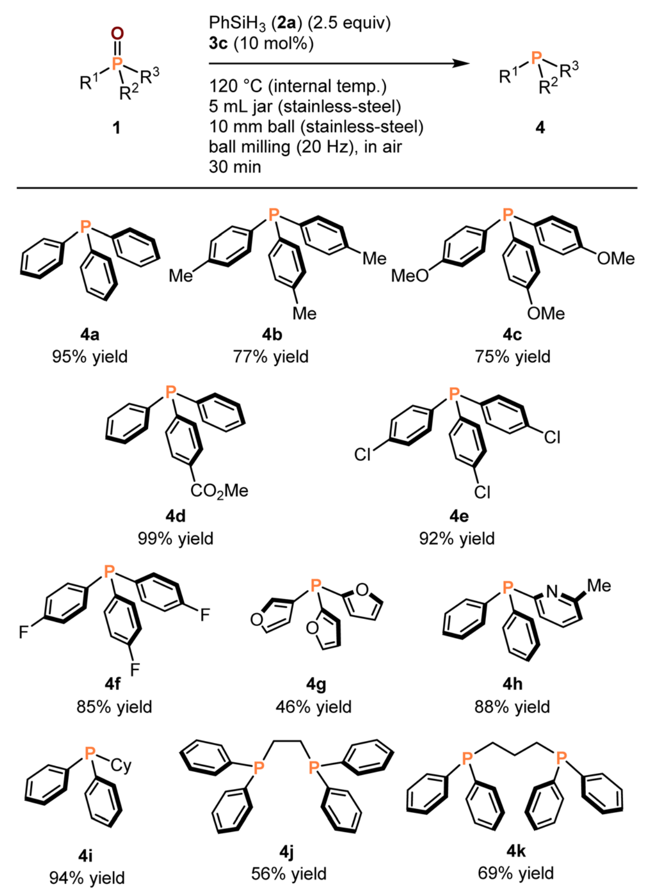
Scheme 2 Mechanochemical deoxygenation of **1a** with various silanes. [a]Conditions: **1a** (0.3 mmol), **2** (0.75 mmol), **3c** (0.03 mmol) in a stainless steel milling jar (5 mL) with a stainless steel ball (10 mm). GC yields are shown.

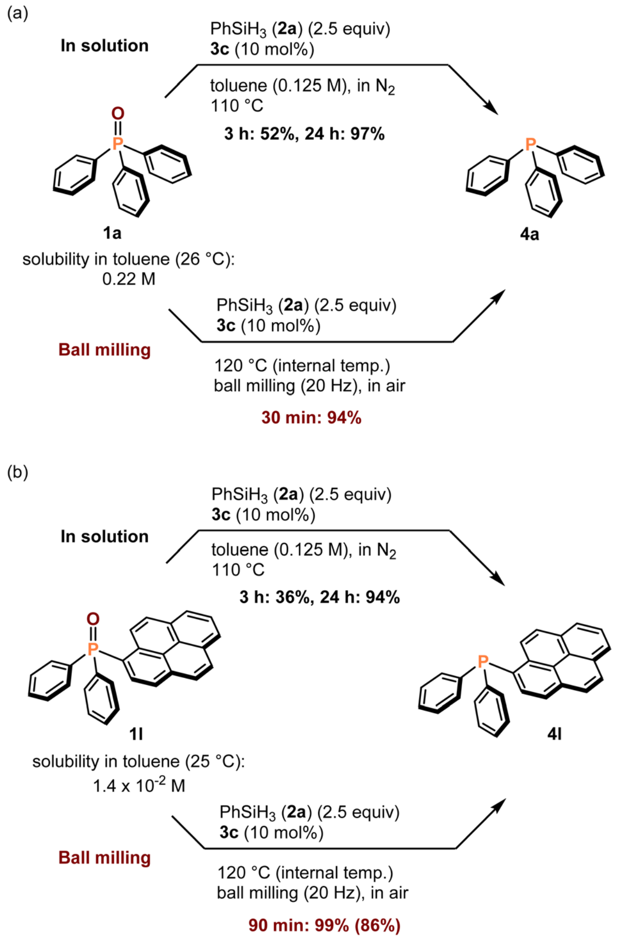
Next, we investigated mechanochemical deoxygenation reactions using different hydrosilanes (Scheme 2). The use of 1,1,3,3-tetramethyldisiloxane (**2b**) instead of **2a** resulted in a significant decrease in the yield of **4a** (39%). Using triethoxysilane (**2c**) and tris(trimethylsilyl)silane (**2d**) afforded very low yields of **4a** (5% and 4%, respectively). Trichlorosilane (**2e**), which is widely used in the deoxygenation of phosphine oxides,[2] provided **4a** in a low yield (28%). The reaction using poly(methylhydrosiloxane) [the number-average molecular weight (M_n): 1700−3200] (**2f**) was attempted, but the yield of **4a** was moderate (35%). These results suggest that **2a** is the best reductant for the mechanochemical deoxygenation of **1a**.

With the optimized conditions in hand, we explored the phosphine oxide substrate scope of mechanochemical deoxygenation. As shown in Table 2, various aromatic, heteroaromatic, and aliphatic substituted phosphine oxides were smoothly reduced to their corresponding phosphines (**4**) with full conversion for most of the substrates. The products (**4**) were isolated using flash column chromatography in air. The mechanochemical deoxygenation of aromatic phosphine oxides bearing both electron-donating and -withdrawing groups (**1a–f**) proceeded smoothy to afford the corresponding phosphines (**4a–f**) in good-to-high isolated yield (75–99%). To our delight, heteroaromatic substrates (**1g** and **1h**) were also converted into the desired products (**4g** and **4h**) in moderate-to-good yields (46% and 88%, respectively). Furthermore, the reduction of more oxidization sensitive, electron-rich alkyl substituted phosphine oxides (**1i–k**) gave the corresponding phosphines (**4i–k**) in good-to-excellent isolated yield (56–94%), despite some oxidation of the products during the purification *via* silica gel column chromatography.

To explore the practical utility of this protocol, we compared the efficiencies of solution-based and mechanochemical reactions (Scheme 3). The solution-based reaction of **1a** with **2a** in the presence of **3c** as the catalyst in toluene (0.125 M) was not complete in 3 h, requiring 24 h to afford a high yield (97%) (Scheme 3a). Such long reaction times are commonly required for the deoxygenation of **1a** using solution-based protocols. Notably, the mechanochemical deoxygenation of **1a** under the developed conditions was completed within 30 min, and a high yield (94%) was obtained, indicating the outstanding performance of the mechanical approach. The solution-based reaction of a phosphine oxide bearing a large aromatic structure, such as a pyrene moiety (**1l**), exhibited a slower kinetic profile

Table 2 Substrate scope. [a]Conditions: **1** (0.3 mmol), **2a** (0.75 mmol), **3c** (0.03 mmol) in a stainless steel milling jar (5 mL) with a stainless steel ball (10 mm). The isolated yields are shown



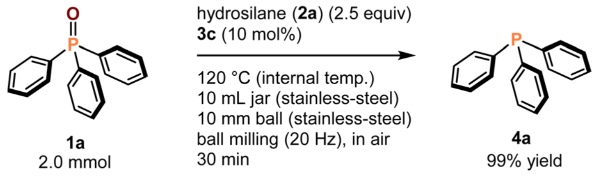


Scheme 3 Comparison to solution-based conditions. [a]For details of the reaction conditions, see the ESI.† For (3a), GC yields are shown. In (3b), NMR yields are shown, and the isolated yields are shown in parentheses.

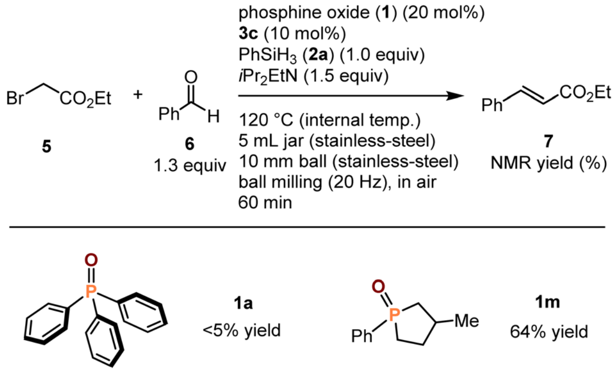
than **1a**, and a low yield (36%) of the product (**4l**) was obtained after 3 h (Scheme 3b). The observed low reactivity is probably due to the poor solubility of **1l**, which has a solubility in toluene at room temperature of 1.2×10^{-2} M, while the solubility of **1a** is 0.22 M. In contrast, **1l** was quickly converted into **4l** within 90 min, and a quantitative yield was obtained (99%) using the newly developed mechanochemical protocol (Scheme 3b). These results demonstrate the synthetic potential of our approach for the efficient deoxygenation of poorly soluble phosphine oxides, which are less reactive in solution.

To demonstrate the practical utility of this reaction, we investigated the scaled-up reaction (Scheme 4). A 2 mmol-scale reaction was conducted in a 10 mL stainless steel jar with a 10 mm stainless steel ball. The desired product **4a** was obtained in 99% yield, which was comparable to the yield obtained in the small-scale reaction. This result emphasizes the practical utility of the protocol.

The successful development of a highly efficient mechanochemical deoxygenation reaction for phosphine oxides encouraged us to investigate the catalytic Wittig reactions under mechanochemical conditions. In 2002, Pecharsky *et al.* reported the first Wittig reaction using stoichiometric amounts of triphenylphosphine (**4a**) under mechanochemical conditions.[10] Recently, Mack *et al.* developed a mechanochemical Wittig reaction using a polymer-supported triphenylphosphine.[11] There are still no reports on the development of a mechanochemical catalytic Wittig reaction in which a generated phosphine oxide is reduced to form the corresponding phosphine *in situ*; therefore, phosphine can catalyze the Wittig reaction.[12] We first examined the mechanochemical deoxygenation of ethyl bromoacetate (**5**) and benzaldehyde (**6**) in the presence of **1a** (20 mol%), BINOL-derived phosphoric acid (**3c**) (10 mol%), phenylsilane (**2a**), and diisopropylethylamine under high-temperature ball-milling conditions (Scheme 5). Unfortunately, the reaction did not proceed to completion. Given that the cyclic phosphine oxide **1m** often shows high activity in solution-based catalytic Wittig reactions, we carried out a mechanochemical Wittig reaction with **1m** (Scheme 5).[12] To our delight, desired product **7** was obtained in a promising yield (64%) even after a short reaction time (60 min). Preliminary investigation of the reaction conditions by varying the mechanochemical parameters, reductants, and bases did not improve the yield of **7** (for details, see the ESI†). Further optimization studies are currently underway.



Scheme 4 Scaled-up reaction of 1a. [a]For details of the reaction conditions, see the ESI.† The isolated yields are shown.



Scheme 5 Preliminary study on the catalytic Wittig reaction using high-temperature mechanichemistry. [a]For details of the reaction conditions, see the ESI.†

Conclusions

In summary, we demonstrated that a mechanochemical approach at high temperatures enabled the highly efficient solvent-free deoxygenation of phosphine oxides to afford the corresponding phosphines in high yields. The developed conditions enable much faster reaction kinetics than those of solution methods and require only 30 min to complete the reactions for most substrates. Importantly, this is the first practical deoxygenation protocol for phosphine oxides in which all synthetic procedures can be carried out in air; therefore, a complicated reaction setup and special synthetic techniques are not required. The synthetic utility of this protocol was demonstrated by the highly efficient deoxygenation of poorly soluble phosphine oxides, which are less reactive in solution. The advantages of the newly developed deoxygenation protocol suggest that this mechanochemical strategy will inspire the development of efficient synthetic routes to valuable organophosphine compounds and an attractive recycling method for phosphorus resources in a practical and environmentally friendly manner.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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