

Dearylation of Arylphosphine Oxides by a Sodium Hydride-Iodide Composite

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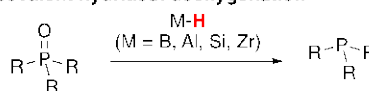
A new protocol for dearylation of arylphosphine oxides was developed using sodium hydride (NaH) in the presence of lithium iodide (LiI). The transient sodium phosphinite could be functionalized with a range of electrophiles in one-pot fashion.

Organophosphorus compounds have been utilized in various applications as reagents for chemical synthesis¹ and privileged ligands for transition metal catalysts² as well as in medicinal chemistry,³ chemical biology,⁴ and materials chemistry.⁵ Therefore, a variety of methods to construct carbon-phosphorus bonds have been developed for their synthesis.⁶

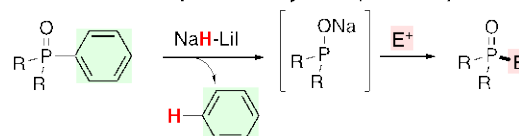
Various covalent hydrides such as boranes/borohydrides,⁷ alanes/aluminum hydrides,⁸ hydrosilanes,⁹ and zirconium hydrides (the Schwartz reagent)¹⁰ have been adopted as a reagent of choice for reduction of phosphine oxides to phosphines (Scheme 1a), whereas use of ionic hydrides has remained elusive for transformation of phosphine oxides.¹¹ We recently disclosed that unprecedented hydride donor reactivity is installed onto sodium hydride (NaH) by its solvothermal treatment with NaI or LiI in THF and the resulting NaH-iodide composites could be used for a series of hydride reduction such as hydrodeacylation, reduction of amides into aldehydes, and hydrodehalogenation of bromo- and iodoarenes.^{12,13} In this context, we wondered if the NaH-iodide composites are capable of reducing phosphine oxides in unique and unprecedented manners. Herein, we report use of the NaH-iodide composites to perform dearylation of readily

available arylphosphine oxides (Scheme 1b). Subsequent reactions of the resulting sodium phosphinites with a range of carbon-electrophiles are able to furnish functionalized phosphine oxides. The discovery, scope/limitation, and mechanistic proposal of these processes are described.

a) with covalent hydrides: deoxygenation



b) with NaH-iodide composite: dearylation (this work)



Scheme 1. Hydride reduction of phosphine oxides.

We commenced our studies with the reactions of triphenylphosphine oxide (**1a**) (Scheme 2a, see the ESI for the details on the optimization of the reaction conditions). We were surprised to find that the treatment of **1a** with NaH (2 equiv) and NaI (1 equiv) in THF at 60 °C (for 24 h) followed by aqueous work-up gave a dephenylated product, diphenylphosphine oxide (**2a**) in 88% yield.^{14,15} Use of LiI (1 equiv) instead of NaI enhanced the reaction efficiency, providing **2a** in 98% yield with the reaction time of 13 h. This hydrodephenylation of **1a** should go through formation of sodium phosphinite and its protonation. Almost no reaction was observed from the reaction with NaH only, which indicates unique feature of the NaH-iodide composites. The method could be extended for hydrodearylation of both electron-rich (for **1b** and **1c**) and sterically hindered (for **1d**) phosphine oxides to provide the corresponding diarylphosphine oxides **2b-2d** in good yields, while that of electron-deficient tris(4-trifluoromethylphenyl)phosphine oxide (**1e**) became sluggish (Scheme 2b). It should be noted that 1,3-dimethoxybenzene was also isolated in 76% yield from the reaction of **1c**.

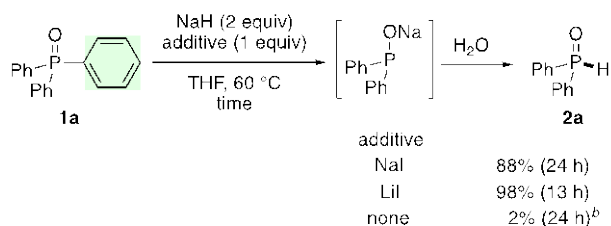
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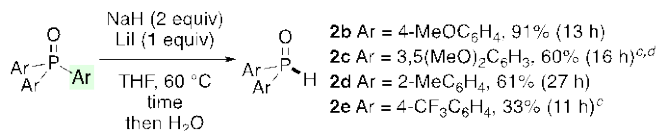
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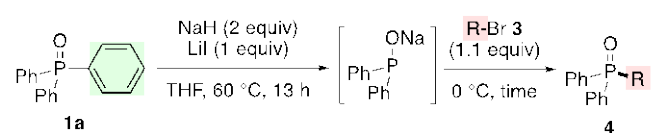
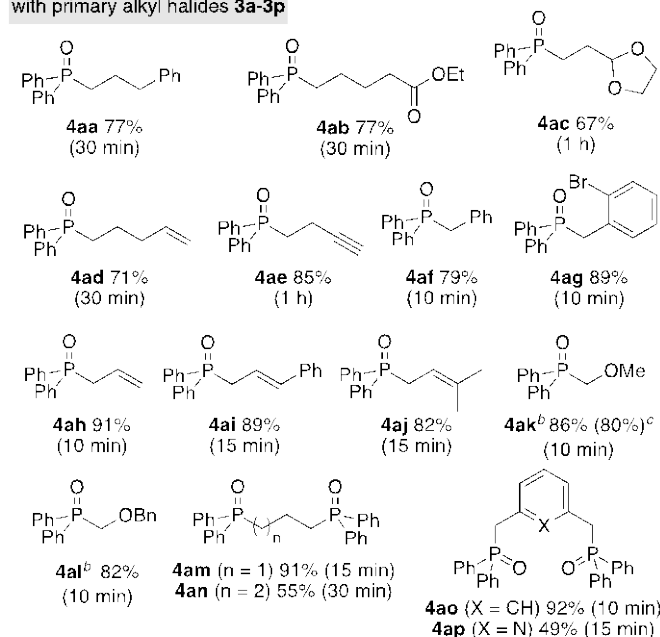
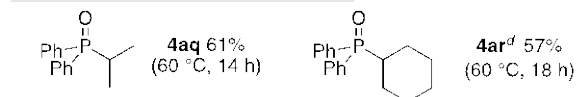
(a) reactions of triphenylphosphine oxide (1a)



(b) dearylation of triarylphosphine oxides



Scheme 2. Hydrodearylation of triarylphosphine oxides **1**. ^a The reactions were conducted using 0.5 mmol of phosphine oxides **1** in THF (2.5 mL: 0.2 M) and isolated yields of diarylphosphine oxides **2** were noted above. ^b ¹H NMR yield. **1a** was recovered in >95% yield. ^c 4 equiv of NaH and 2 equiv of Lil were used. ^d 1,3-Dimethoxybenzene was also isolated in 76% yield.

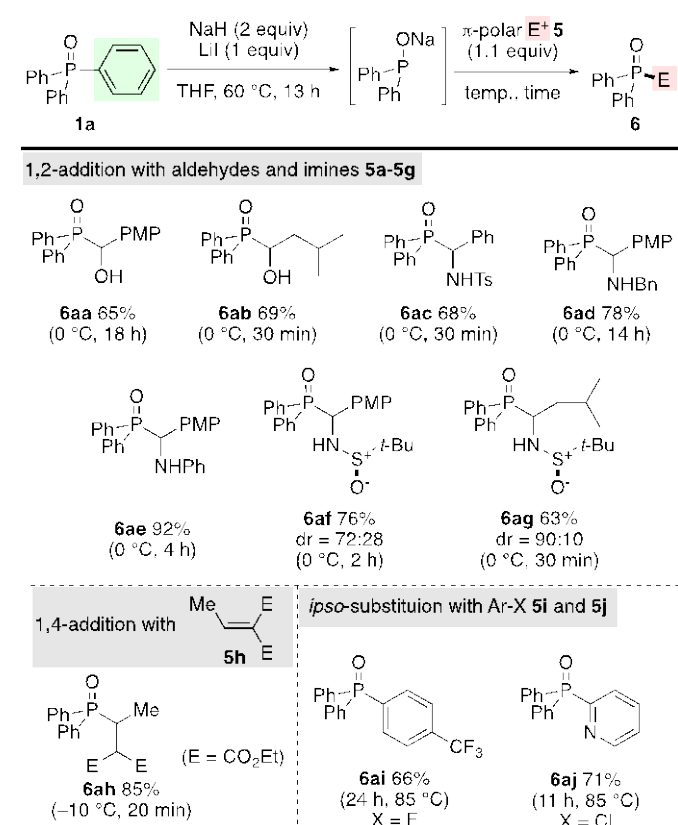
with primary alkyl halides **3a-3p**with secondary alkyl halides **3q** and **3r**

Scheme 3. Synthesis of mono-alkyl diphenylphosphine oxides **4**. ^a Unless otherwise stated, the reactions were conducted using 0.5 mmol of triphenylphosphine oxide (**1a**) with NaH (2 equiv) and Lil (1 equiv) in THF (2.5 mL: 0.2 M) at 60 °C for 13 h and then with alkyl bromides **3** (1.1 equiv). Isolated yields of the products were noted above. ^b Chlorides **3k** and **3l** were used. ^c 5 mmol of **1a** was used. ^d Iodocyclohexane (**3r**) was used.

We attempted further alkylation of the transient sodium phosphinite intermediate with alkyl halides in one-pot fashion (Scheme 3). This strategy offers a facile way to convert cheap

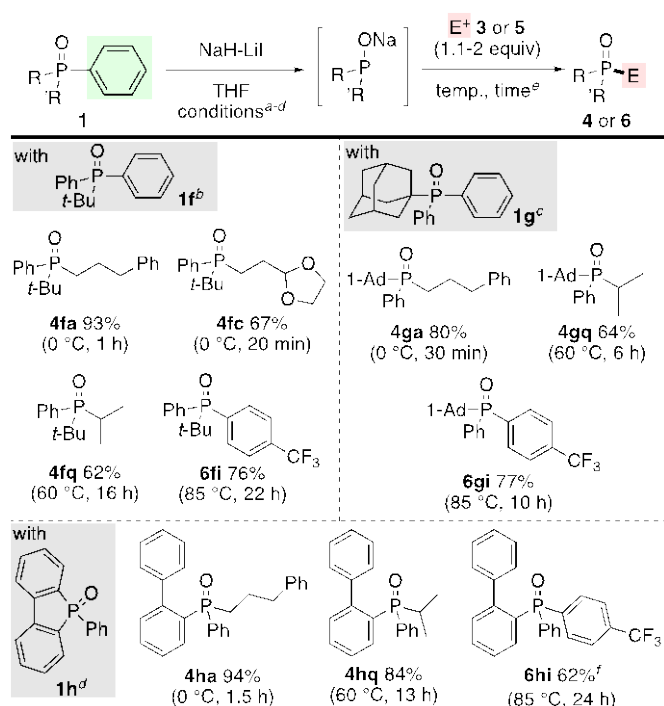
yet underutilized triphenylphosphine oxide (**1a**) to more valuable monoalkyl-diphenylphosphine oxides. We found the scope of alkyl halides to be broad and versatile. The resulting phosphinite intermediate derived from **1a** could be quickly functionalized by a series of primary alkyl bromides **3**, incorporating a wide range of functionalities such as alkoxycarbonyl, acetal, alkenyl,¹⁶ alkynyl, and alkoxymethyl¹⁷ moieties. The method is amenable to use dibromides **3m-3p** as an electrophile for synthesis of bis-phosphine oxides **4am-4ap**. Installation of secondary alkyl electrophiles required higher reaction temperature (60 °C) and/or use of more reactive iodide (for **4aq-4ar**).

We next examined use of π -polar electrophiles **5** for the functionalization of the transient sodium phosphinite derived from triphenylphosphine oxide (**1a**) (Scheme 4). 1,2-Addition onto aldehydes **5a-5b** and aldimines **5c-5e** worked well to give the corresponding alcohols **6aa-6ab** and amines **6ac-6ae**, respectively. Use of the Ellman's *t*-butanesulfinamides **5f** and **5g**¹⁸ offered diastereoselective addition of the phosphinite to afford **6af** and **6ag**, respectively. 1,4-Addition of the phosphinite proceeded efficiently onto alkylidenemalonate **5h**, whereas those onto acrylate derivatives were not successful. It is worthy to note that installation of another aromatic ring was enabled by ipso-substitution with 4-fluorobenzotrifluoride (**5i**) and 2-chloropyridine (**5j**).



Scheme 4 Reactions with π -polar electrophiles. ^a The reactions were conducted using 0.5 mmol of triphenylphosphine oxide (**1a**) with NaH (2 equiv) and Lil (1 equiv) in THF (2.5 mL: 0.2 M) at 60 °C for 13 h and then with π -polar electrophiles **5** (1.1 equiv). Isolated yields of the products were noted above. PMP = *para*-methoxyphenyl.

The present protocol with the NaH-LiI system was amenable to functionalize *t*-butyldiphenylphosphine oxide (**1f**) and adamantyldiphenylphosphine oxide (**1g**), offering a synthetic route to unsymmetrical tertiary phosphine oxides (Scheme 5).^{19,20} More fascinatingly, the reactions of dibenzophosphole oxide **1h**²¹ resulted in selective C(sp²)-P bond cleavage to break the dibenzophosphole core, leading to the formation of unsymmetrical phosphine oxides bearing a biphenyl moiety. Given that biarylphosphines have been utilized as a ligand for the transition metal catalysts in various chemical processes,²² the current method could offer an opportunity to design and supply new types of unsymmetrical tertiary biarylphosphine ligands.



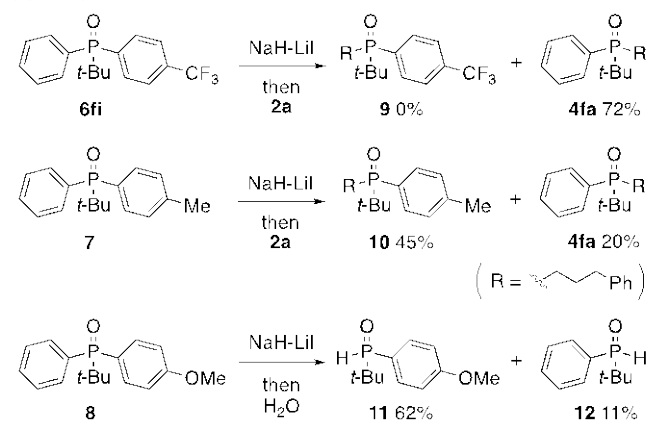
Scheme 5 Synthesis of unsymmetrical tertiary phosphine oxides. ^a The reactions were conducted using 0.5 mmol of **1** in THF (0.2 M). ^b Dephenylation was conducted using 3 equiv of NaH and 1.5 equiv of LiI at 60 °C for 16 h. ^c Dephenylation was conducted using 3 equiv of NaH and 1.5 equiv of LiI at 85 °C for 12 h. ^d Dephenylation was conducted using 2 equiv of NaH and 1 equiv of LiI at 60 °C for 6 h. ^e The reaction conditions were stated in parentheses. ^f [1,1'-biphenyl]-2-yl(phenyl)phosphine oxide (**2h**) was also isolated in 20% yield. 1-Ad = 1-adamantyl.

To investigate the reaction mechanism especially pertaining to the C(sp²)-P bond breaking process in the present dearylation, competition experiments were conducted using *t*-butyldiarylphosphine oxides **6fi**, **7**, and **8** (Scheme 6a). These experiments unambiguously indicated that the C(sp²)-P bond cleavage preferentially takes place at the more electron-deficient aryl group.

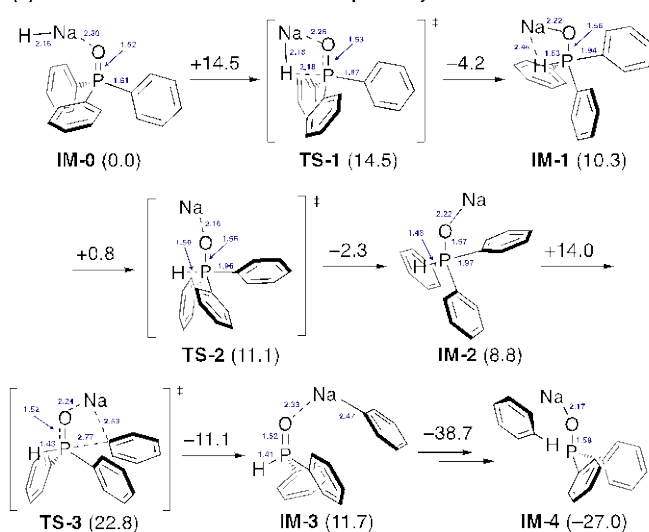
Our recent work on materials characterization of the NaH-iodide composite indicated that a smaller nanometric unit of NaH dispersed on NaI might be produced by solvothermal treatment of NaH with NaI or LiI in THF, giving rise to unique hydride donor reactivity.²³ To seek for deeper insights on the C(sp²)-P bond breaking with the formation of the sodium phosphinite intermediate, we conducted DFT calculations for a

model reaction of triphenylphosphine oxide (**1a**) with a single molecule of NaH,²⁴ at the ω B97X-D/6-31+G* (scr = pcm, THF) level of theory using Gaussian 16 software (Scheme 6b).²⁵ We found a sequential pathway, namely, nucleophilic attack of NaH on the P center, elimination of phenylsodium and diphenylphosphine oxide, and its deprotonation, as the most probable mechanism. The addition of hydride onto the P center affords a pentavalent intermediate **IM-1**, with a reasonable activation barrier ($\Delta G^\ddagger = +14.5$ kcal/mol). Through the smooth flipping of Na cation on the hydride to the opposite phenyl side (*i.e.* **IM-1**–**TS-2**–**IM-2**), the elimination of phenylsodium takes place via **TS-3**, which requires the low activation energy ($\Delta G^\ddagger = +14.0$ kcal/mol) for the single step to form diphenylphosphine (**IM-3**). Subsequent deprotonation of the P–H moiety by phenylsodium should lead to the formation of sodium phosphinite (**IM-4**).²⁶ It should be noted that the last step competes with deprotonation by co-existing NaH, which was indicated by the results of deuterium labeling experiment with NaD,²⁷ as well as the incomplete conversion in use of less than 2 equiv of NaH (see the ESI for details).²⁸

(a) competition studies



(b) DFT calculations for the reaction pathway



Scheme 6 (a) Competition studies and (b) DFT calculation results for the reaction pathway with a single molecule of NaH. Energy changes and bond lengths at the ω B97X-D/6-31+G* (scr = pcm, THF) level of theory are shown in kcal/mol and Å, respectively (see the ESI for the pathway with energy diagram).

This work demonstrates new use of the NaH-iodide composite for dearylyative functionalization of arylphosphine oxides to prepare functionalized tertiary phosphine oxides in a concise operation. Further investigation on use of the NaH-iodide composite to explore other types of reductive molecular transformations is ongoing in our laboratory.

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- The calculated deprotonation step by phenylsodium species is described in the ESI.
- The reaction of triarylphosphine oxide **1c** with NaD-Lil followed by treatment with H₂O gave diarylphosphine oxide **2c** in 57% yield and 1,3-dimethoxybenzene in 80% yield with 39% D-incorporation (see the ESI).
- Another reaction pathway via nucleophilic aromatic substitution, despite the higher energy barrier, was also estimated by the DFT calculation. See the ESI.