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Dearylation of Arylphosphine Oxides by a Sodium Hydride-Iodide Composite

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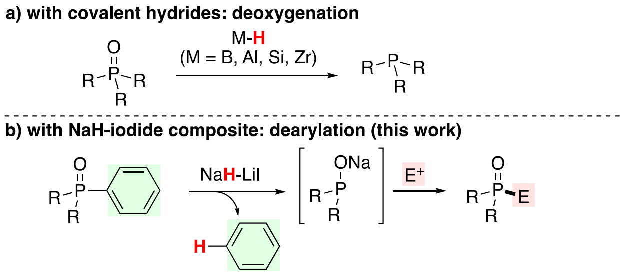
A new protocol for dearylation of arylphosphine oxides was developed using sodium hydride (NaH) in the presence of lithium iodide (LiI). The transient sodium phosphinite could be functionalized with a range of electrophiles in one-pot fashion.

Organophosphorus compounds have been utilized in various applications as reagents for chemical synthesis[1] and privileged ligands for transition metal catalysts[2] 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 hydrodecyanation, 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.



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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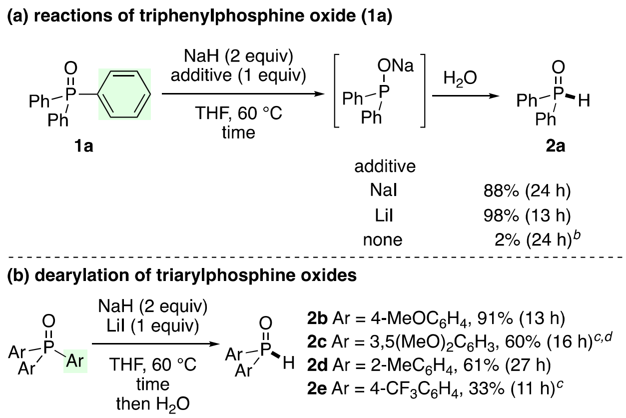
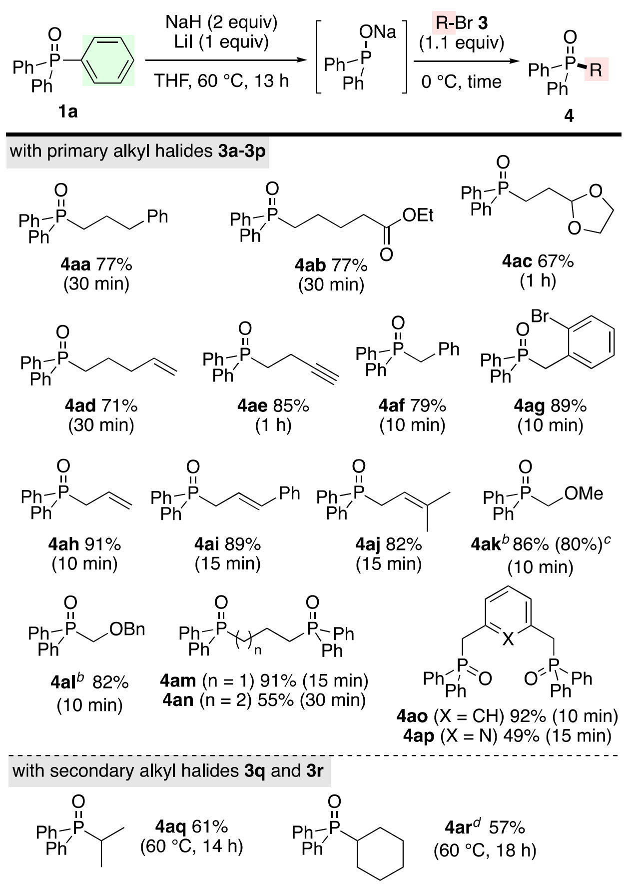


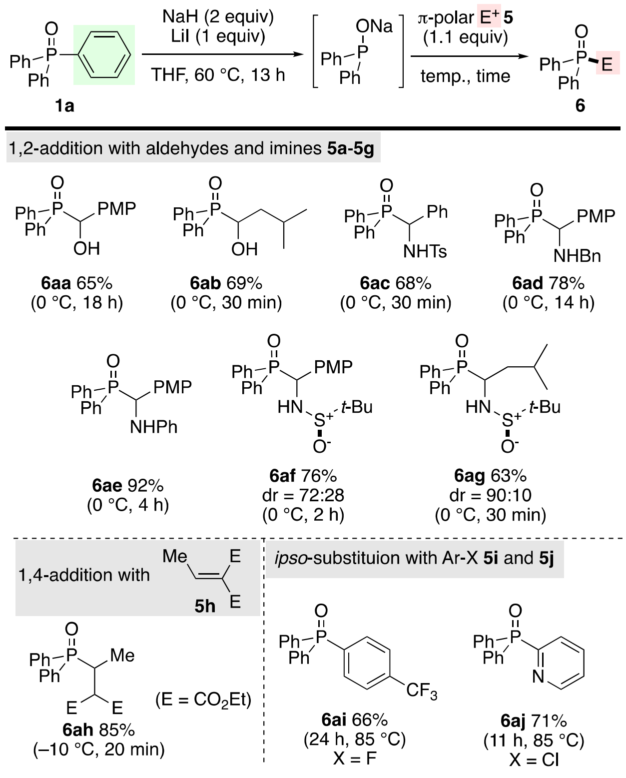
Scheme 2. Hydrodearylation of triarylphosphine oxides **1**. [a] The reactions were conducted using 0.5 mmol of phosphine oxides **1** in THF (2.5 mL: 0.2 M) and isolated yields of diarylphosphine oxides **2** were noted above. [b] ^{1}H NMR yield. **1a** was recovered in >95% yield. [c] 4 equiv of NaH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



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 LiI (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 alkoxymethyl[17] 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 LiI (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.

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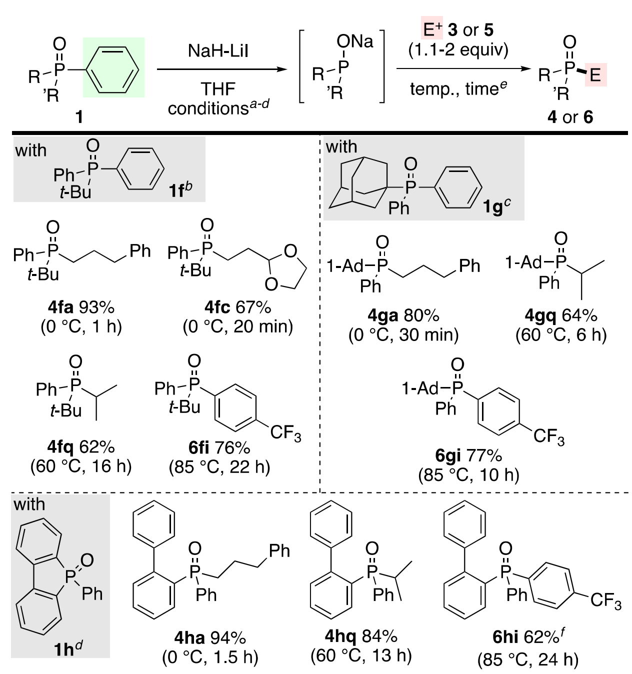
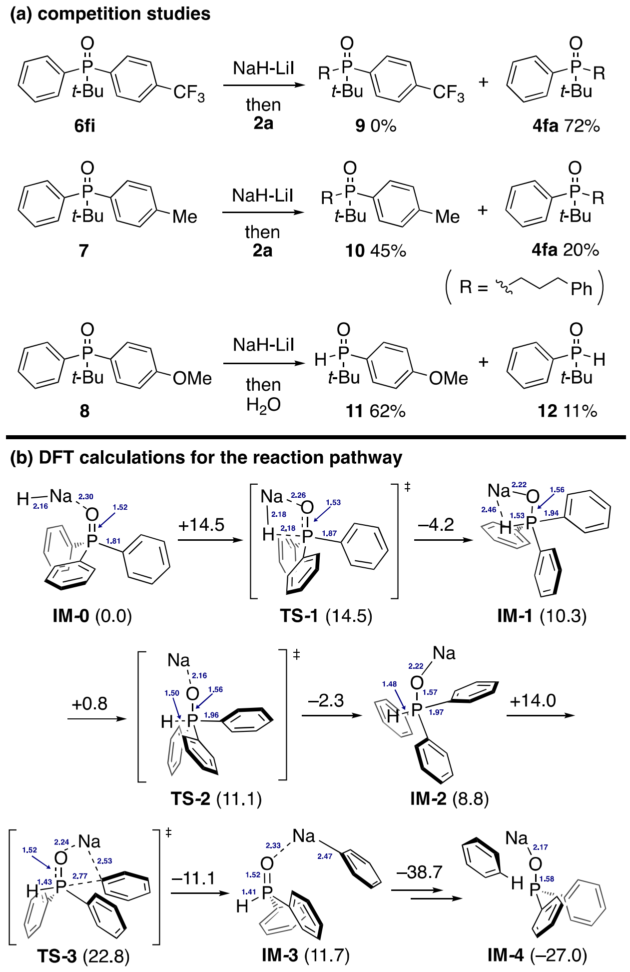
The present protocol with the NaH-LiI system was amenable to functionalize *t*-butyldiphenylphosphine oxide (**1f**) and adamantyldiphenylphosphine oxide (**1g**), offering a synthetic route to unsymmetrical tertiary phosphine oxides (Scheme 5).[19,20] More fascinatingly, the reactions of dibenzophosphole oxide **1h**[21] resulted in selective C(sp^2)-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(sp^2)-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(sp^2)-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(sp^2)-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 ωB97X-D/6-31+G* (scrf = 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 (Δ$G^‡$ = +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 (Δ$G^‡$ = +14.0 kcal/mol) for the single step to form dipnehylphosphine (**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]



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 ωB97X-D/6-31+G* (scrf = pcm, THF) level of theory are shown in kcal/mol and Å, respectively (see the ESI for the pathway with energy diagram).

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This work demonstrates new use of the NaH-iodide composite for dearylative 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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Notes and references

1 (a) L. D. Quin, *A Guide to Organophosphorus Chemistry*, Wiley, 2000; (b) P. J. Murphy, *Organophosphorus Reagents: A Practical Approach in Chemistry*, Oxford University Press, 2004.

2 (a) P. W. N. M. van Leeuwen, P. C. J. Kamer, J. N. H. Reek and P. Dierkes, *Chem. Rev.*, 2000, **100**, 2741; (b) A. Börner, *Phosphorus Ligands in Asymmetric Catalysis: Synthesis and Applications*, John Wiley & Sons, 2008; (c) A. Grabulosa, *P-stereogenic Ligands in Enantioselective Catalysis*, Royal Society of Chemistry, 2011.

3 S. Demkowicz, J. Rachon, M. Daśko, W. Kozak, *RSC Adv.*, 2016, **6**, 7101.

4 S. S. van Berkel, M. B. van Eldijk, J. C. M. van Hest, *Angew. Chem. Int. Ed.*, 2011, **50**, 8806.

5 (a) C. Queffélec, M. Petit, P. Janvier, D. A. Knight, B. Bujoli, *Chem. Rev.*, 2012, **112**, 3777; (b) T. Baumagartner, R. Réau, *Chem. Rev.,* 2006, **106**, 4681.

6 For reviews, see: (a) I. Wauters, W. Debrouwer, C. V. Stevens, *Beilstein J. Org. Chem.,* 2014, **10**, 1064; (b) H. Yorimitsu, *Beilstein J. Org. Chem.,* 2013, **9**, 1269.

7 (a) S. Sowa, M. Stankevic, A. Szmigielska, H. Maluszynska, A. E. Koziol, K. M. Pietrusiewicz, *J. Org. Chem.*, 2015, **80**, 1672; (b) S. S. Al Sulaimi, K. V. Rajendran, D. G. Gilheany, *Eur. J. Org. Chem.*, 2015, **2015**, 5959; (c) K. V. Rajendran, D. G. Gilheany, *Chem. Commun.*, 2012, **48**, 817; (d) G. Keglevich, M. Fekete, T. Chuluunbaatar, A. Dobo, V. Harmat, L. Toke, *J. Chem. Soc., Perkin Trans. 1*, 2000, 4451; (e) R. Köster, Y. Morita, *Angew. Chem.*, 1965, **77**, 589.

8 (a) C. A. Busacca, R. Raju, N. Grinberg, N. Haddad, P. James-Jones, H. Lee, J. C. Lorenz, A. Saha, C. H. Senanayake, *J. Org. Chem.*, 2008, **73**, 1524; (b) T. Imamoto, S.-i. Kikuchi, T. Miura, Y. Wada, *Org. Lett.*, 2001, **3**, 87; (c) S. Griffin, L. Heath, P. Wyatt, *Tetrahedron Lett.*, 1998, **39**, 4405; (d) T. Imamoto, T. Oshiki, T. Onozawa, T. Kusumoto, K. Sato, *J. Am. Chem. Soc.*, 1990, **112**, 5244; (e) T. Imamoto, T. Kusumoto, N. Suzuki, K. Sato, *J. Am. Chem. Soc.*, 1985, **107**, 5301; (f) P. D. Henson, K. Naumann, K. Mislow, *J. Am. Chem. Soc.*, 1969, **91**, 5645.

9 (a) A. Buonomo, C. G. Eiden, C. C. Aldrich, *Chem. Eur. J.*, 2017, **23**, 14434; (b) M. Mehta, I. Garcia de la Arada, M. Perez, D. Porwal, M. Oestreich, D. W. Stephan, *Organometallics*, 2016, **35**, 1030; (c) M.-L. Schirmer, S. Jopp, J. Holz, A. Spannenberg, T. Werner, *Adv. Synth. Catal.*, 2016, **358**, 26; (d) Y. Li, L. Q. Lu, S. Das, S. Pisiewicz, K. Junge, M. Beller, *J. Am. Chem. Soc.*, 2012, **134**, 18325; (e) H.-C. Wu, J.-Q. Yu, J. B. Spencer, *Org. Lett.*, 2004, **6**, 4675.

10 M. Zablocka, B. Delest, A. Igau, A. Skowronska, J.-P. Majoral, *Tetrahedron Lett.*, 1997, **38**, 5997.

11 For a report on use of CaH_2 at 350-400 °C, see: H. Fritzsche, U. Hasserodt, F. Korte, *Chem. Ber.*, 1964, **97**, 1988.

12 (a) D. Y. Ong, C. Tejo, K. Xu, H. Hirao, S. Chiba, *Angew. Chem. Int. Ed.,* 2017, **56**, 1840; (b) P. C. Too, G. H. Chan, Y. L. Tnay, H. Hirao, S. Chiba, *Angew. Chem. Int. Ed.*, 2016, **55**, 3719; (c) Z. Hong, D. Y. Ong, S. K. Muduli, P. C. Too, G. H. Chan, Y. L. Tnay, S. Chiba, Y. Nishiyama, H. Hirao, H. S. Soo, *Chem. Eur. J.*, 2016, **22**, 7108.

13 For use of NaH-iodide composites as the unprecedented Brønsted bases, see: (a) A. Kaga, H. Hayashi, H. Hakamata, M. Oi, M. Uchiyama, R. Takita, S. Chiba, *Angew. Chem. Int. Ed.*, 2017, **56**, 11807; (b) Y. Huang, G. H. Chan, S. Chiba, *Angew. Chem. Int. Ed.*, 2017, **56**, 6544.

14 For reports on C(sp^2)-P bond formation driven by Pd-catalyzed dephenylation from triarylphosphines, see: (a) K. Baba, M. Tobisu, N. Chatani, *Org. Lett.*, 2015, **17**, 70; (b) K. Baba, M. Tobisu, N. Chatani, *Angew. Chem. Int. Ed.*, 2013, **52**, 11892.

15 For reports on aromatic substitution reactions of arylphosphine oxides with alkyllithium or magnesium reagents, see: (a) M. Stankevič, J. Pisklak, K. Włodarczyk, *Tetrahedron*, 2016, **72**, 810; (b) T. Shimada, H. Kurushima, Y.-H. Cho, T. Hayashi, *J. Org. Chem.*, 2001, **66**, 8854; (c) N. C. Payne and D. W. Stephan, *Can. J. Chem.*, 1980, **58**, 15; (d) D. Seyferth, D. E. Welch, J. K. Heeren, *J. Am. Chem. Soc.*, 1964, **86**, 1100.

16 For use of allyl diphenylphosphineoxides for radical allylation, see: G. Ouvry, B. Quiclet-Sire, S. Z. Zard, *Angew. Chem. Int. Ed.*, 2006, **45**, 5002.

17 For use of alkoxymethylphosphine oxides such as **4ak** and **4al** for synthesis of vinyl ethers (known as the Horner-Wittig reaction), see: C. Earnshaw, C. J. Wallis, S. Warren, *J. Chem. Soc. Perkin Trans. 1*, 1979, **12**, 3099.

18 (a) M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.*, 2010, **110**, 3600; (b) J. A. Ellman, *Pure. Appl. Chem.*, 2003, **75**, 39.

19 The present protocol has thus far not proven successful with primary- or secondary-alkylphosphine oxides due to inherent Brønsted basicity of NaH.

20 For reports on synthesis of unsymmetrical tertiary phosphine oxides, see: Y. Nishiyama, Y, Hazama, S. Yoshida, T. Hosoya, *Org. Lett.*, 2017, **19**, 3899, and references therein.

21 (a) M. Onoda, Y. Koyanagi, H. Saito, M. Bhanuchandra, Y. Matano, H. Yorimitsu, *Asian J. Org. Chem.*, 2017, **6**, 257; (b) K. Nogi, H. Yorimitsu, *Chem. Commun.*, 2017, **53**, 4055.

22 (a) D. S. Surry, S. L. Buchwald, *Chem. Sci.*, 2011, **2**, 27; (b) D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.*, 2008, **47**, 6338; (c) R. Martin, S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**, 1461.

23 Our materials characterization (ref. 12c) also revealed that solvothermal treatment of NaH and LiI induces counter ion methathesis to form the activated NaH with NaI and LiH. No reaction was observed with LiH only and the LiH-LiI composite (see the ESI for details).

24 NaH has ionic character with the cubic halite crystal structure composed of sodium cations and hydride anions: a) R. E. Gawley, D. D. Hennings, *Sodium Hydride* in *the electronic Encyclopedia of Reagents for Organic Synthesis (e-EROS)* (Ed.: D. Crich), John Wiley & Sons, UK, 2006; b) S. Aldridge, A. J. Downs, *Chem. Rev.*, 2001, **101**, 3305.

25 Gaussian 16 (Revision A.03), M. J. Frisch, et al., Gaussian Inc., Wallingford CT, 2016.

26 The calculated deprotonation step by phenylsodium species is described in the ESI.

27 The reaction of triarylphosphine oxide **1c** with NaD-LiI followed by treatment with H_2O gave diarylphosphine oxide **2c** in 57% yield and 1,3-dimethoxybenzene in 80% yield with 39% D-incorporation (see the ESI).

28 Another reaction pathway via nucleophilic aromatic substitution, despite the higher energy barrier, was also estimated by the DFT calculation. See the ESI.

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TOC

A new protocol for dearylative functionalization of arylphosphine oxides was developed using NaH in the presence of LiI.