J|A|C|S
COMMUNICATIONS

Published on Web 03/10/2006

Radical Phosphination of Organic Halides and Alkyl Imidazole-1-carbothioates

Akinori Sato, Hideki Yorimitsu,* and Koichiro Oshima*

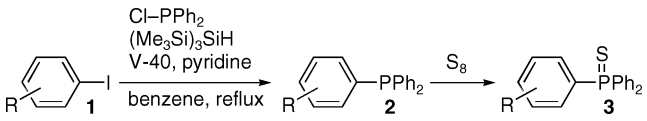
Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto-daigaku Katsura, Nishikyo-ku, Kyoto 615-8510, Japan

Received December 28, 2005; E-mail: oshima@orgrxn.mbox.media.kyoto-u.ac.jp; yori@orgrxn.mbox.media.kyoto-u.ac.jp

Organophosphines are an extremely important family of heteroatom-containing molecules that serve as synthetic reagents, ligands for transition metals, advanced materials, and building blocks of supramolecular architectures. Accordingly, development of new phosphination reactions has invaluable impacts in organic chemistry. Here we report a new phosphination reaction, taking full advantage of a chemoselective radical-based strategy.[1−4] Conventional ionic phosphination reactions often require highly basic conditions.[5] The new radical phosphination reaction can employ a variety of readily available aryl halides and alkyl imidazole-1-carbothioates as the precursors, hence offering a powerful tool for the synthesis of functionalized organophosphines.[6]

The procedure of the radical phosphination is quite simple. The transformation of iodobenzene (**1a**) to triphenylphosphine (**2a**) is representative (Table 1, entry 1). A mixture of **1a** (0.50 mmol), chlorodiphenylphosphine (2.5 mmol), tris(trimethylsilyl)silane (TTMSS, 1.5 mmol),[7] pyridine (3.0 mmol), and 1,1′-azobis(cyclohexane-1-carbonitrile) (V-40, 0.10 mmol) was heated in boiling benzene (3.0 mL) for 20 h. Since organophosphines such as **2a** are more or less sensitive to oxygen, the phosphinated product was handled as triphenylphosphine sulfide (**3a**) to clarify the efficiency of the reaction.[8,9]

Table 1. Radical Phosphination of Aryl Iodides[a]

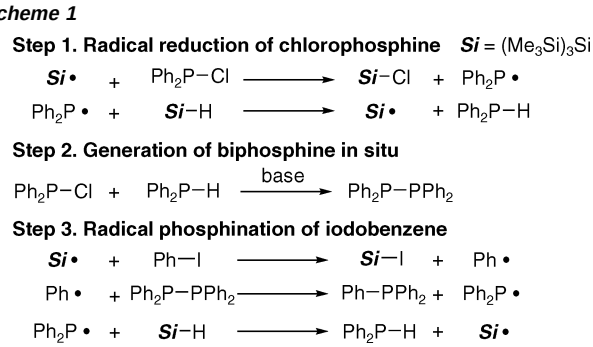


entry	R	yield/%[b]
1	H (**a**)	88 (58)
2	2-Me (**b**)	78 (52)
3	4-^{n}Bu (**c**)	81
4	2,4,6-Me_3 (**d**)	63
5	2-MeO (**e**)	65 (44)
6	3-MeO (**f**)	73
7	4-MeO (**g**)	75 (46)
8	4-CF_3 (**h**)	78
9	4-Cl (**i**)	77 (56)
10	3-EtOC(═O) (**j**)	82 (47)
11	4-Br (**k**)	66 (47)
12	4-N≡C (**l**)	69 (43)
13	4-CH_3C(═O) (**m**)	47
14	4-TfO (**n**)	68 (57)
15	4-[CH_2═$CHCH_2$OC(═O)] (**o**)	78

[a] Reaction conditions are the same as described in the second paragraph. [b] Determined by ^{31}P NMR with a sufficient first delay period. Isolated yields are in parentheses.

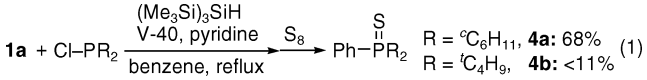
Our working hypothesis about the reaction mechanism is outlined in Scheme 1. Initially, radical reduction of chlorodiphenylphosphine with TTMSS takes place to produce diphenylphosphine (step 1).[10] The diphenylphosphine formed in situ reacts with remaining

Scheme 1

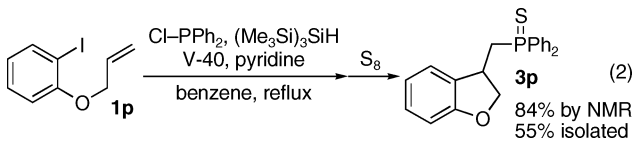


chlorodiphenylphosphine to afford tetraphenylbiphosphine (step 2). The biphosphine is responsible for the radical phosphination reaction (step 3). Tris(trimethylsilyl)silyl radical abstracts iodine from iodobenzene to furnish a phenyl radical. The S_H2 reaction of the phenyl radical with biphosphine[11] gives triphenylphosphine and diphenylphosphinyl radical.[12,13] The phosphine-centered radical abstracts the hydrogen of TTMSS to regenerate the corresponding silyl radical. The diphenylphosphine generated at the final step participates again in step 2. The in situ reduction of chlorodiphenylphosphine and the in situ formation of tetraphenylbiphosphine allow us to avoid handling air-sensitive tetraphenylbiphosphine and pyrophoric diphenylphosphine.[3]

A wide range of aryl iodides **1** were subjected to the phosphination reaction (Table 1). Sterically demanding mesityl iodide (**1d**) was also phosphinated in good yield (entry 4). Functional groups such as ester, bromo, cyano, and keto moieties were compatible under the reaction conditions (entries 10−13). The radical conditions allowed for efficient phosphination of 4-iodophenyl triflate (**1n**) and allyl 4-iodobenzoate (**1o**), the transition metal-catalyzed phosphination of which may suffer.[14] Radical phosphination with chlorodicyclohexylphosphine was also successful, whereas a similar reaction with chlorodi(*tert*-butyl)phosphine resulted in very poor yield (eq 1).

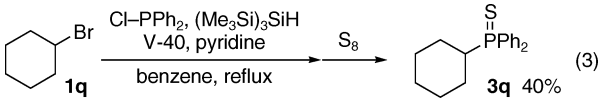


Treatment of the allyl ether of *o*-iodophenol (**1p**) led to a sequential radical cyclization/phosphination reaction, furnishing **3p** in high yield (eq 2). The cyclization reaction is highly suggestive of a radical mechanism.



10.1021/ja058783h CCC: $33.50

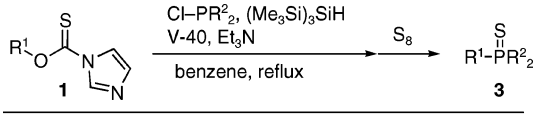
Radical phosphination of bromocyclohexane (**1q**) under the same reaction conditions led to an unsatisfactory yield of cyclohexyldiphenylphosphine sulfide (**3q**) (eq 3).

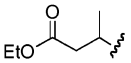
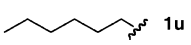


(3)

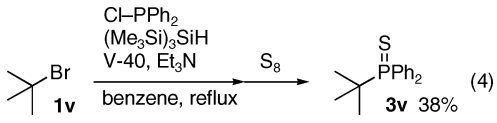
After extensive screening of reaction conditions, we found that cyclohexyl imidazole-1-carbothioate[15] (**1r**) is the best precursor for the radical phosphination (Table 2, entry 1). Phosphination of secondary alkyl groups was generally excellent. Hexyl imidazole-1-carbothioate (**1u**) was also phosphinated albeit the yield was moderate. Synthesis of *tert*-butyl imidazole-1-carbothioate resulted in failure. Instead, attempted phosphination of *tert*-butyl bromide (**1v**) afforded **3v** in 38% yield (eq 4).

Table 2. Radical Phosphination of Alkyl Imidazole-1-carbothioates[a]



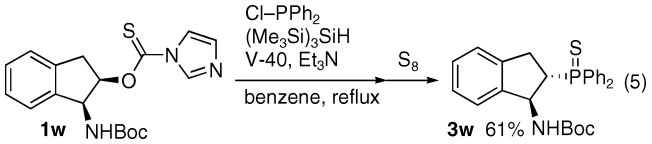
entry	R^1	R^2	yield /%[b]
1	 **1r**	Ph	**3q**, 87
2	 **1r**	$^cC_6H_{11}$	**3r**, 68
3	 **1s**	Ph	**3s**, 89 (67)[c]
4	 **1t**	Ph	**3t**, 87 (76)[c]
5	 **1u**	Ph	**3u**, 63

[a] A mixture of **1** (0.50 mmol), chlorodiphenylphosphine (1.75 mmol), TTMSS (0.75 mmol), triethylamine (1.5 mmol), and V-40 (0.60 mmol) was heated in boiling benzene (3.0 mL) for 18 h. [b] The yields were determined by ^{31}P NMR. [c] Isolated yields.



(4)

Treatment of carbothioate **1w**, derived from an optically pure amino alcohol, under the phosphination conditions provided *trans*-aminophosphine derivative **3w** exclusively (eq 5). Tetraphenylbiphosphine would approach the radical derived from **1w** from the opposite side of the amino group. Phosphine sulfides such as **3w** could be useful intermediates in the preparation of chiral aminophosphine ligands.



(5)

In conclusion, we have devised a radical phosphination reaction of organic halides and alkyl imidazole-1-carbothioate. The mild reaction conditions allow labile functional groups to survive during the reaction. The advantage of the radical-based phosphination culminated in the proof-of-principle stereoselective synthesis of a chiral organophosphine.

Acknowledgment. This work was supported by Grants-in-Aid for Scientific Research from MEXT, Japan. We thank Hokko Chemical Industry Co., Ltd. for providing $ClP(^cC_6H_{11})_2$ and $ClP(^tC_4H_9)_2$.

Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Use of phosphorus-centered radicals in organic synthesis was summarized: Leca, D.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Chem. Soc. Rev.* **2005**, *34*, 858−865.
(2) Addition reactions of phosphinyl radicals to carbon−carbon multiple bonds are the general radical-based approach to organophosphines: Stacey, F. W.; Harris, J. F., Jr. *Org. React.* **1963**, *13*, 150−376. For recent advances, see ref 1.
(3) Our radical-based approach to organophosphines: Sato, A.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1694−1696.
(4) The synthesis of phosphonic acid by the reaction of white phosphorus with carbon-centered radicals was reported: (a) Barton, D. H. R.; Zhu, J. *J. Am. Chem. Soc.* **1993**, *115*, 2071−2072. (b) Barton, D. H. R.; Vonder Embse, R. A. *Tetrahedron* **1998**, *54*, 12475−12496.
(5) (a) Elsner, G. *Methoden der Organischen Chemie (Houben-Weyl)*; Georg Thieme Verlag: Stuttgart, 1982; Vol. E1. (b) Kawashima, T. In *The Fourth Series of Experimental Chemistry*; Akiba, K., Ed.; Maruzen: Tokyo, 1992; Vol. 24, Chapter 6.1.
(6) We have developed phosphination reactions directed toward the synthesis of functionalized organophosphines: (a) Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 4873−4875. (b) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 2368−2370. Also see ref 3.
(7) Chatgilialoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* **1988**, *53*, 3641−3642. Tributyltin hydride did not serve well in the phosphination reaction. The tin hydride reacted rapidly only with chlorodiphenylphosphine to consume the tin hydride.
(8) Mild reduction of phosphine sulfide to trivalent phosphine is known: Romeo, R.; Wozniak, L. A.; Chatgilialoglu, C. *Tetrahedron Lett.* **2000**, *41*, 9899−9902.
(9) See Supporting Information for the procedure for the purification of products **3**. The purification necessitated sequential silica gel column purification and size exclusion chromatography.
(10) Separately, we confirmed that the reduction of chlorodiphenylphosphine with TTMSS took place in the presence of V-40. In the absence of V-40, the reduction did not proceed.
(11) Okazaki, R.; Hirabayashi, Y.; Tamura, K.; Inamoto, N. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1034−1036.
(12) The photoinduced reaction of alkyl iodides with tetraphenyldistibine via an S_H2 process was reported: Barrett, A. G. M.; Melcher, L. M. *J. Am. Chem. Soc.* **1991**, *113*, 8177−8178.
(13) Methods to replace halide moieties with heteroatoms via radical processes and their analogues: (a) Ollivier, C.; Renaud, P. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.: Wiley-VCH: Weinheim, 2001; Vol. 2, Chapter 2.1. (b) Braslau, R.; Anderson, M. O. in *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.: Wiley-VCH: Weinheim, 2001; Vol. 2, Chapter 2.3. (c) Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; John Wiley & Sons: Chichester, 1995; Chapter 11. (d) Nakamura, E.; Inubushi, T.; Aoki, S.; Machii, D. *J. Am. Chem. Soc.* **1991**, *113*, 8980−8982. (e) Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2001**, *123*, 4717−4727. (f) Kim, S.; Joe, G. H.; Do, J. Y. *J. Am. Chem. Soc.* **1993**, *115*, 5521−5522. (g) Barton, D. H. R.; Bridon, D.; Zard, S. Z. *Tetrahedron Lett.* **1984**, *25*, 5777−5780.
(14) (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337−2364. (b) Murata, M.; Buchwald, S. L. *Tetrahedron* **2004**, *60*, 7397−7403.
(15) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585. (b) Rasmussen, J. R.; Slinger, C. J.; Kordish, R. J.; Newman-Evans, D. D. *J. Org. Chem.* **1981**, *46*, 4843−4846.

JA058783H