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

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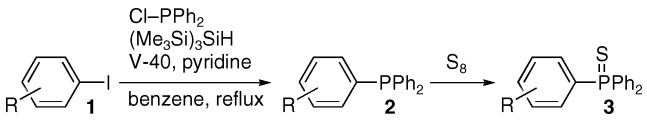
Organophosphines are an extremely important family of heteroatom-containing molecules that serve as synthetic reagents, ligands for transition metals, advanced materials, and building blocks of supramolecular architectures. Accordingly, development of new phosphination reactions has invaluable impacts 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]

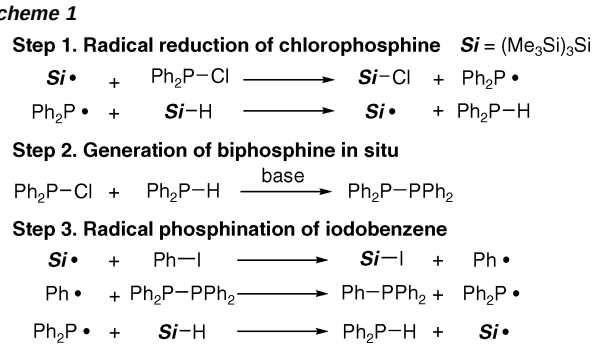


entry	R	yield/%[b]
1	H (**a**)	88 (58)
2	2-Me (**b**)	78 (52)
3	4-^{n}Bu (**c**)	81
4	2,4,6-Me_3 (**d**)	63
5	2-MeO (**e**)	65 (44)
6	3-MeO (**f**)	73
7	4-MeO (**g**)	75 (46)
8	4-CF_3 (**h**)	78
9	4-Cl (**i**)	77 (56)
10	3-EtOC(═O) (**j**)	82 (47)
11	4-Br (**k**)	66 (47)
12	4-N≡C (**l**)	69 (43)
13	4-CH_3C(═O)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

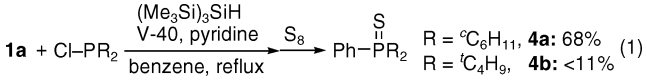
Our working hypothesis about the reaction mechanism is outlined in Scheme 1. Initially, radical reduction of chlorodiphenylphosphine with TTMSS takes place to produce diphenylphosphine (step 1).[10] The diphenylphosphine formed in situ reacts with remaining

Scheme 1

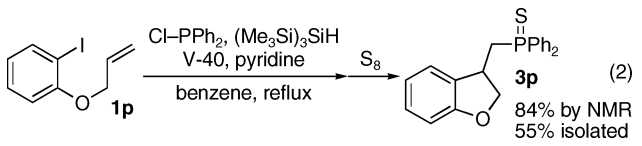


chlorodiphenylphosphine to afford tetraphenylbiphosphine (step 2). The biphosphine is responsible for the radical phosphination reaction (step 3). Tris(trimethylsilyl)silyl radical abstracts iodine from iodobenzene to furnish a phenyl radical. The S_H2 reaction of the phenyl radical with biphosphine[11] 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.



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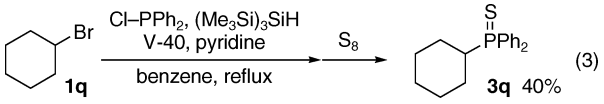
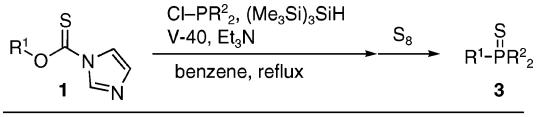
Radical phosphination of bromocyclohexane (**1q**) under the same reaction conditions led to an unsatisfactory yield of cyclohexyldiphenylphosphine sulfide (**3q**) (eq 3).

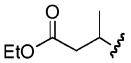
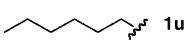


(3)

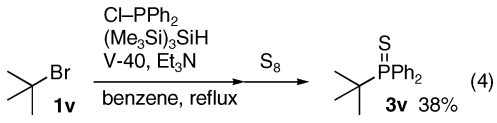
After extensive screening of reaction conditions, we found that cyclohexyl imidazole-1-carbothioate[15] (**1r**) is the best precursor for the radical phosphination (Table 2, entry 1). Phosphination of secondary alkyl groups was generally excellent. Hexyl imidazole-1-carbothioate (**1u**) was also phosphinated 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]



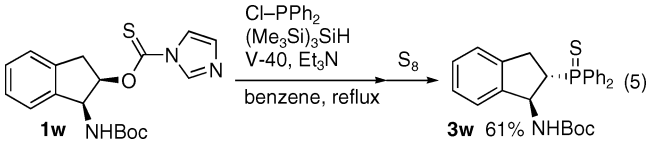
entry	R^1	R^2	yield /%[b]
1	 **1r**	Ph	**3q**, 87
2	 **1r**	$^cC_6H_{11}$	**3r**, 68
3	 **1s**	Ph	**3s**, 89 (67)[c]
4	 **1t**	Ph	**3t**, 87 (76)[c]
5	 **1u**	Ph	**3u**, 63

[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.

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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.

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