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The conversion of alcohols to halides using a filterable phosphine source

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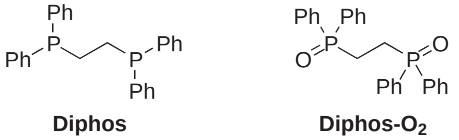
Abstract—The conversion of primary and secondary alcohols to chlorides and bromides using 1,2-bis(diphenylphosphino)ethane (diphos) is described. Use of this reagent in lieu of the typical triphenylphosphine–carbontetrahalide complex provides a facile means of purifying the desired halide from the phosphine–oxide byproduct. © 2001 Elsevier Science Ltd. All rights reserved.

The conversion of alcohols to halides is a well-studied transformation.[1] In particular, use of the triphenylphosphine–carbontetrahalide complex has become a widely used method.[2] One of the drawbacks to this phosphine reagent is the stoichiometric phosphine oxide byproduct, which can sometimes prove difficult to purify from product. One solution is the use of polymer-supported triphenyl phosphine.[3] Likewise, an alternative phosphine source whose oxide byproduct can be readily removed would also be an attractive option. During our exploration for alternative phosphines, O'Neil et al. reported the use 1,2-bis(diphenylphosphino)ethane (diphos) as a replacement for triphenylphosphine in the Staudinger and Mitsunobu reactions.[4] With methylene chloride as the solvent, the resulting phosphine oxide was readily removed by filtration. However, under the same conditions, our desired conversion of alcohol to halide did not result in the precipitation of the oxide byproduct.

Table 1. Relative solubility of diphos–O_2 as determined by LC/MS

Solvent	Rel. solubility
CH_2Cl_2	1
DCE	0.30
THF	0.05
Ph–CH_3	0.01
CCl_4	0.01



Since removal of diphos–O_2 by filtration is critical to this concept, we sought a solvent system that would

Table 2. Summary of experimental conditions

	Diphos (equiv.)	Chloride source	Solvent (concentration)	Conversion[a] (%)	Comment
1	0.5	C_2Cl_6 (1 equiv.)	CH_2Cl_2 (0.32 M)	>95	Minimal precipitate
2	0.5	None	CCl_4 (0.32 M)	45	Significant precipitate
3	0.5	C_2Cl_6 (1.7 equiv.)	Toluene (0.32 M)	80	Filtration removed 90% of phosphine oxide byproduct
4	1	C_2Cl_6 (1.7 equiv.)	Toluene (0.32 M)	>95	Gummy residue due to mixture of mono and dioxide
5	0.6	C_2Cl_6 (1.03 equiv.)	THF (0.32 M)	>95	Filtration removed 75% of phosphine oxide byproduct

[a] Conversion is based on GC analysis of reaction.

Keywords: diphos; alcohol; phosphines; phosphine oxides.

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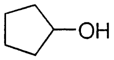
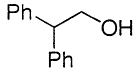
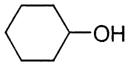
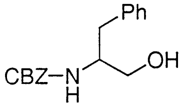
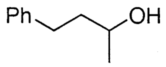
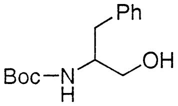
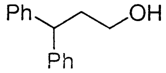
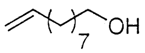
Table 3. Substrate versatility. Yields shown are isolated, with the exception of the entries denoted with *, which were determined using GC/MS

Substrate	% Yield Chloride (Bromide)#	Substrate	% Yield Chloride
	72* (73*)		40
	76* (47*)		86
	64 (67)		70
	88 (74)		76

1,2-dibromotetrachloroethane used for alcohol-bromide conversion

provide the lowest solubility of the oxidized byproduct while still promoting the desired conversion. We undertook a relative solubility study by integrating LC/MS chromatograms, and several solvents which resulted in low solubility of diphos–O_2 were identified (Table 1). The utility of these solvents for the alcohol–halide conversion was then evaluated.

The results shown in Table 2 indicate that diphos can readily facilitate the desired conversion. Using methylene chloride as the solvent, >95% conversion was achieved. However, the desired precipitation of the diphos–O_2 was not observed (entry 1). Using the significantly less polar CCl_4 resulted in precipitation of the byproduct but conversion was poor (entry 2). Near quantitative removal of diphos–O_2 by filtration was achieved when using toluene as the solvent (entry 3). However, alcohol–halide conversion was incomplete despite addition of excess hexachloroethane. Higher conversion can be achieved using a higher concentration of diphos. Unfortunately, the resulting residue was not readily removed by filtration (entry 4). The balance of high conversion and readily filterable byproduct was achieved when using THF as the solvent (entry 5).

Table 3 lists the various alcohol substrates which were examined for transformation to the corresponding chlorides and bromides. In a representative reaction, 0.5 g 4-phenyl-2-butanol (3.68 mmol, 1 equiv.) and 0.87 g hexachloroethane (3.68 mmol, 1 equiv.) was dissolved in 11 mL THF and 0.73 g diphos (1.84 mmol, 0.5 equiv.) was added. The reaction was allowed to stir at room temperature for 3 hours, at which time the suspension was filtered through Celite, the filtrate evaporated, and the resulting residue was purified by hexane elution through a short pad of silica gel. Evaporation provided 3-chloro-1-phenylbutane in 64% yield. As shown in entry 5 (Table 2) 75% of the diphos–O_2 was removed by filtration, and the remaining oxide was retained on the silica gel.

We have described an alternative method for conversion of alcohols to halides using diphos, which is converted to a readily-filtered dioxide byproduct. The reaction provides a good alternative to the standard triphenylphosphine–carbontetrahalide conversion, as well as to the polymer supported phosphine reagents.

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