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Titanium (IV) Catalysis in the Reduction of Phosphine Oxides

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Abstract: Phosphine oxides can be reduced by triethoxysilane, or more conveniently polymethylhydrosiloxane, and catalytic titanium (IV) isopropoxide and provides a system for the efficient one-pot generation of phosphonium salts; the reduction occurs with retention of configuration at phosphorus.

We recently reported a novel alkene synthesis via *anti* elimination of 1,2-phosphinyl alcohols.[1] We made the phosphinyl alcohols by reduction of the corresponding phosphine oxides with Imamoto's lithium aluminium hydride/cerium (III) chloride reagent.[2] This reagent proved adequate for our needs, however we were keen to find conditions that were easier to carry out and avoid aqueous work up, which in our hands always resulted in small amounts of oxidation. This requirement seemed to rule out most of the available methods, which generally use a metal hydride [lithium aluminium hydride,[3] uranium (III) hydride,[4]] or silylhydride (Si_2Cl_6,[5] $HSiCl_3$,[6] $PhSiH_3$,[7] $Me_3SiCl/LiAlH_4$[8]) as the reducing species. We were intrigued to see whether the new reducing system, triethoxysilane/titanium (IV) isopropoxide, recently described by Berk and Buchwald[9] would meet our needs. This reagent system is described as an 'air-stable' lithium aluminium hydride equivalent that can be used to efficiently reduce esters to alcohols without requirng rigorous anhydrous and oxygen-free conditions and tolerates alkenes, alkynes, alkyl halides, epoxides and alcohols. The active reducing species is tentatively thought to be an active titanium hydride species formed via a σ-bond metathesis process. It is known that phosphine oxides are cleanly reduced by lithium aluminium hydride/titanium (IV) chloride,[10] and by magnesium and dicyclopentadienyltitanium dichloride;[11] the active species in both cases was again thought to be a titanium hydride species. The Buchwald catalyst system therefore seemed a good candidate for the reduction of phosphine oxides. In addition, the system presents an intriguing combination of the two most commonly used reducing systems i.e. silanes and metal hydrides/Lewis acids.

Our first attempt to reduce a phosphine oxide under the standard conditions described by Buchwald, involved reaction of triphenylphosphine oxide with of triethoxysilane (300 mol%) and titanium (IV) isopropoxide (10 mol%) in the absence of additional solvent and under an inert atmosphere (nitrogen) at 50 °C. The reaction, which appears to be heterogeneous, proceeded rapidly and with vigorous generation of a gas which we believe to be hydrogen, to give the phosphine (85% recryst.) essentially quantitatively as judged by tlc. We checked that the reaction does not occur in the absence of the titanium (IV) isopropoxide. The reaction can be carried out in tetrahydrofuran, and proceeds slowly at room temperature but again is essentially quantitative after one hour at 67 °C. When only one equivalent of silane was used the reaction was incomplete; two equivalents or more are needed for successful conversion; the stoichiometry is given in Equation 1.

$$R_3PO + 2 \times HSi(OEt)_3 \xrightarrow{Ti(O^iPr)_4} R_3P + (EtO)_3SiOSi(OEt)_3 + H_2\uparrow \qquad \text{Eqn 1}$$

We used the reagent system to reduce a range of phosphine oxides to their corresponding phosphines (Table 1). In some cases we isolated the phosphines directly by addition of hexane to the mixture after completion of the reaction. In other cases we illustrate that the reduction is very efficient by isolation of corresponding phosphonium salts by addition of the appropriate alkyl halide directly to the reaction mixture. In these cases it was obvious that the phosphine had been produced quantitatively (tlc) prior to quaternisation.

$$RPh_2PO \xrightarrow[Ti(O^iPr)_4\ (0.1\ eq.),\ 67\ ^\circ C]{(EtO)_3SiH\ (3\ eq.)} RPh_2P$$

Table 1. Reductions with triethoxysilane

R	yield (%)
Ph	85
$CH_2CH_2P(O)Ph_2$	90[a]
Me	99[b]
Et	95[b]
^iPr	81[b]
^tBu	41[b]
CH_2Ph	98[b]
CH_2CH_2Ph	83[b]

a. isolated as the bisphosphine ; b. isolated as the benzylphosphoniuim bromide salt

$$RPh_2PO \xrightarrow[Ti(O^iPr)_4\ (1\ eq.),\ 67\ ^\circ C]{PMHS\ (10\ eq.)} RPh_2P$$

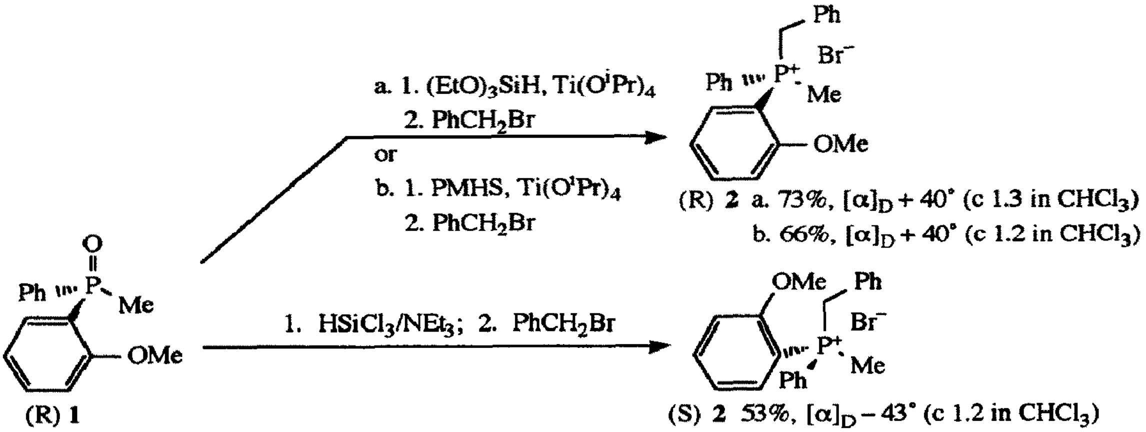
Table 2. Reductions with PMHS

R	yield (%)
Ph	93[a]
$CH_2CH_2P(O)Ph_2$	76[b]
Me	98[a]
Me	82[c]
Et	99[a]
^iPr	91[a]
^iPr	86[d]
CH_2Ph	76[c]

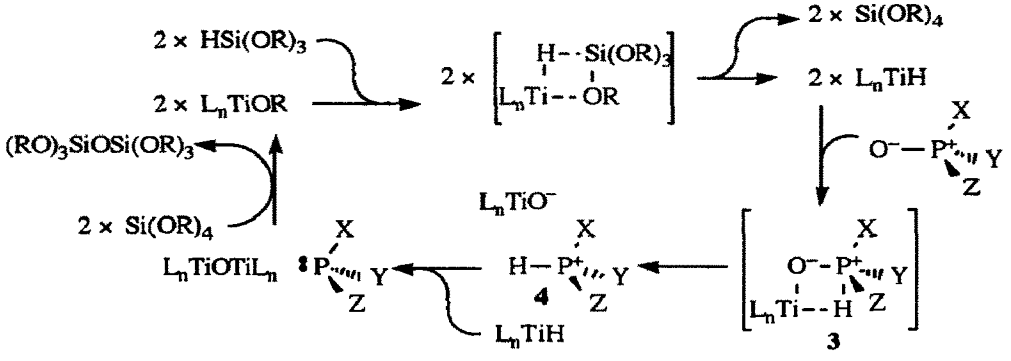
a. isolated as the benzylphosphoniuim bromide salt; b. isolated as the bis(benzylphosphoniuim bromide) salt; c. isolated as the methylphosphonium iodide salt;d. isolated as the allylphosphonium bromide salt

The use of triethoxysilane is not ideal since it is toxic (possibly causing blindness), and although it is commercially available it is not cheap. We therefore looked for an alternative silane and found that polymethylhydrosiloxane (PMHS), $Me_3SiO[(CH_3)HSiO]_nSiMe_3$, was a suitable substitute. PMHS has previously been used to reduce phosphine oxides, but under protic conditions.[12,13] It can be used to reduce carbonyl compounds in the presence of bis(dibutylacetoxytin) oxide in ethanol.[14] It is cheap (about thirty times cheaper than triethoxysilane mole for mole of Si–H) and is non-volatile and apparently does not share the toxicity of triethoxysilane. Polymethylhydrosiloxane is an extremely efficient reagent for the reduction of phosphine oxides, though it was now necessary to use a larger quantity of titanium (IV) isopropoxide (100 mol%). The reaction does not occur in the absence of titanium (IV) isopropoxide nor in the presence of bis(dibutylacetoxytin) oxide (10 mol%). The results are shown in table 2. This is now our favoured method for the reduction of phosphine oxides.

We next turned our attention to the stereochemistry of the reduction. We synthesised (R) (2-methoxyphenyl)methylphenylphosphine oxide[15] **1** by the method of Brown and co-workers.[16] When **1** is reduced by both the triethoxysilane and polymethylhydrosiloxane methods and quaternised we obtained the (R) phosphonium salt **2** with $[\alpha]_D$ of + 40° (c 1.3 in $CHCl_3$) and + 40° (c 1.2 in $CHCl_3$) respectively. When **1** is reduced with $HSiCl_3/NEt_3$, which is known to proceed with inversion of phosphorus configuration,[17,5] and quaternised the (S) benzylphosphonium bromide **2** was isolated $[\alpha]_D$ - 43° (c 1.2 in $CHCl_3$). The silane/titanium method is evidently proceeding predominantly with retention of configuration of phosphorus,[18] providing an alternative to the phenylsilane and trichlorosilane (in the absence of an amine) methods which both proceed with retention.



If the reaction is occurring by way of a titanium hydride species the stereochemistry can be explained by a *syn* hydrotitanation type process **3** as the key step to give the protonated phosphine **4** with retention of stereochemistry.



In conclusion, we have shown that the titanium (IV) catalysed reduction of phosphine oxides by triethoxysilane and PMHS provides an efficient method for the practical synthesis of phosphines and phosphonium salts with retention of stereochemistry at phosphorus. We are currently investigating asymmetric variants of this reducing system and will report our results in due course.

Standard procedures: To a stirred mixture of phosphine oxide (1 mmol) and triethoxysilane (3 mmol)(**CAUTION**, may cause blindness) in tetrahydrofuran (AR grade)(2 ml) was added titanium (IV) isopropoxide (0.1 mmol). The mixture was heated under reflux with an outlet to a nitrogen line until complete by tlc. The benzylphosphonium salt was isolated by addition of benzyl bromide (2 mmol) and the mixture heated for a further 30 min. The mixture was cooled and filtered to give microanalytically pure phosphonium salt. When polymethylhydrosiloxane is used as the reducing agent the same procedure is followed except that PMHS (10 mmol of H equivalent) and titanium (IV) isopropoxide (1 mmol) are used.

Safety Note: Buchwald reports that in the absence of substrate the system generates highly dangerous silane, SiH_4. Although they had no problems with the system, like ourselves, there has been a report of an explosion using the reagent system.[19] We therefore advise that appropriate precautions be taken to avoid build-up of large quantities of silane, when using this protocol.

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15 $[\alpha]_D + 21.7°$ (c 2.5 in MeOH); lit.[17] $[\alpha]_D + 25.9°$ (c 1 in MeOH). We therefore estimate the e.e of **1** to be approximately 88%.

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18 Reduction ($HSiCl_3/NEt_3$) of another batch of (R) **1** $\{[\alpha]_D + 16.7°$ (c 0.9 in MeOH)$\}$ followed by oxidation (*tert*-BuOOH : which results in retention of configuration, c.f. ref. 17) of the crude product gave (S) **1** $\{[\alpha]_D - 12.6°$ (c 1.8 in MeOH)$\}$. Similarly reduction with $(EtO)_3SiH$ followed by oxidation gave (R) **1** $\{[\alpha]_D + 18.9°$ (c 1.5 in MeOH)$\}$.

19 Berk, S. C.; Buchwald, S. L. *J. Org. Chem.*, **1993**, 58, 3221; an addition to reference 9.

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