



The reduction of tertiary and secondary phosphine oxides to phosphines

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Reduction of secondary and tertiary phosphine oxides to phosphines

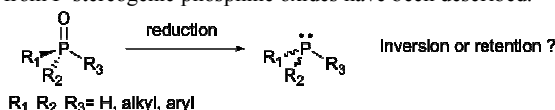
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Introduction

Convenient accesses to chiral phosphines are of paramount importance as this family of molecules is relevant in the area of organometallic catalysis and organocatalysis.ⁱ Chiral phosphines were first reported in the 60's and used in enantioselective reactions, notably in asymmetric organometallic catalysis where the ability of the phosphorus atom to bind a metal was exploited for the design of chiral catalysts. The fine tuning of the steric and electronic properties of the phosphorus atom according to the nature of its substituents represents a main feature of this type of ligand. Moreover chiral phosphines appeared to be a convenient tool to enfold metal centres with chirality. The synthesis and storage of phosphines are difficult as their oxidation is easy, spontaneous (from minutes to hours) under oxygen atmosphere. Nevertheless it is important, even challenging, to develop new methodologies aiming to form phosphines or their protected counterparts. Moreover the optical purity of P-chiral phosphines depends on the stereoselectivity of their synthesis, and is only preserved in case of low racemisation rate. If this rate is high, the chiral phosphine has to be temporarily protected (P-BH₃, P=S). Up to here, the reduction of phosphine oxides to phosphines still remains the methods of choice (Scheme 1). The essential difficulty is the high bond strength of the P=O group which involves new procedures to maintain a high chemo- and stereoselectivity. The reduction can occur with retention or inversion of the stereogenic phosphorus atom depending on the nature of the reducing agent and the presence of additive. In fact, the reactivity of phosphine oxides and the mechanism of their reductions are not always well understood. Since the first report in 1950's,ⁱⁱ numerous studies have been carried out in order to develop methodologies with new reagents and/or to understand the mechanism of the reduction of acyclicⁱⁱⁱ or cyclic phosphine oxides.^{iv} In the last decade, important progresses in this domain were reported by the groups of Beller,^v Gilheany,^{vi} Lemaire,^{vii} Pietrusiewicz,^{viii} Tanaka^{ix} and our group.^x Efficient stereoselective methodologies to optically pure phosphines from P-stereogenic phosphine oxides have been described.



Scheme 1: Stereoselective reduction of phosphine oxides

In this review, we intend to provide a comprehensive and critical overview on methodologies allowing the preparation of secondary and tertiary phosphines from their oxidized analogues. The review is divided in five parts according to the different type of reagent. In each part, the mechanistic aspects of the reduction will be discussed. We will notably highlight the influence of the catalysts, additives and phosphorus neighbouring groups (anchoring effect) on reaction stereoselectivity. We will also emphasise on examples where the structural patterns of substrates provide original reactivities or where reductions were performed under non-conventional conditions. A special attention will be paid to stereochemical aspects (racemisation, inversion or retention of the configuration of the phosphorus center).. The scope and limitations of synthetic methods will be also discussed.

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 - Catalytic reactions
 - Miscellaneous reactions
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 - Nature of boron reagents
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- Non-stereoselective reduction
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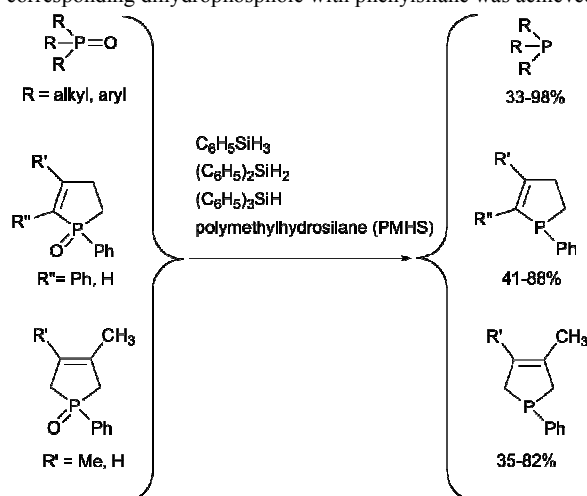
5. Other reagents and methods

- Calcium hydride
- Titanium
- Zirconium
- Samarium
- Electrochemistry
- Iodide catalysis

1. Silanes and related reagents

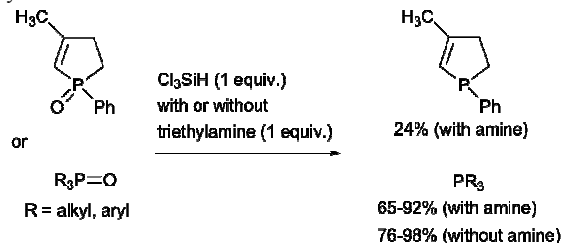
Stoichiometric reactions

Fritzsche and co-workers reported the first reduction of phosphine oxides with silanes in 1964.^{xi} Various silanes including PMHS (polymethylhydrosilane), phenylsilane, diphenylsilane and triphenylsilane were used to reduce alkyl, aryl phosphine oxides and dihydrophosphole oxides (Scheme 2). All the reactions were achieved with an excess of hydride source. Depending on the substitution on the aryl groups, the reduction occurred from low to high (33-98%) yields with respect to the electronic density at the phosphorus atom. The nature of silane does not significantly impact on the yield although PMHS leads, in some cases, to the P-C bond cleavage. Interestingly, the reduction of dihydrophosphole oxide to dihydrophosphole was chemoselective. For instance, low yield (35%) were obtained when using PMHS for the 3,4-dihydrophosphole while a higher yield (82%) was reached with phenylsilane. Reduction of its isomer namely (α -aryl)dihydrophosphole oxide, to the corresponding dihydrophosphole with phenylsilane was achieved in only 41% yield.



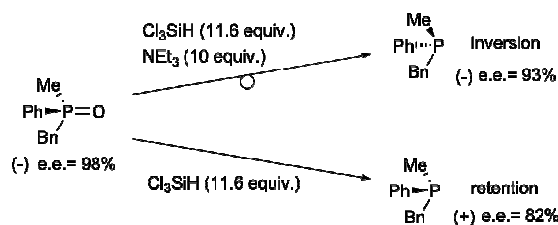
Scheme 2: Reduction of acyclic phosphine oxides and cyclic dihydrophosphole oxides with hydrosilane derivatives

Later, the same group has significantly improved the reduction reactions by employing trichlorosilane (2 equiv.) instead of the above silanes (Scheme 3). Yields were up to 98 % for the reduction of triphenylphosphine oxide. For trialkylphosphine oxides, the significant improvement was achieved when using triethylamine as additive. For instance, the tri(*n*-butyl)phosphine oxide was reduced in the presence of an equimolar mixture of trichlorosilane and triethylamine in 92% yield.^{xii}



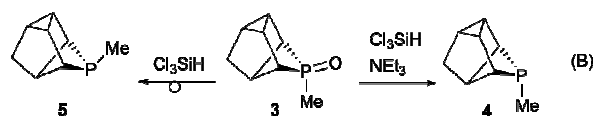
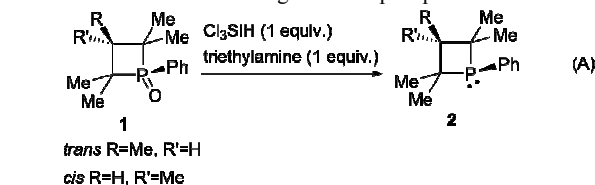
Scheme 3: Reduction of phosphine oxides with trichlorosilane

The same year, Horner and Balzer reported the first study on the reduction of P-chiral phosphine oxides (Scheme 4).^{xiii} They observed that the deoxygenation reaction of optically active P-stereogenic phosphine oxides with either HSiCl_3 , $\text{HSiCl}_3/\text{pyridine}$ or $\text{HSiCl}_3/N,N$ -diethylaniline afforded stereoselectively phosphines with retention of configuration at the phosphorus centre whereas the $\text{HSiCl}_3/\text{NEt}_3$ system gave the phosphine with inversion of configuration. A rationale based on the reactivity difference in the mode of hydride transfer from silicon to phosphorus atom (intramolecular or intermolecular) was proposed to explain the stereoselectivity divergence. The detailed mechanism will be discussed later.

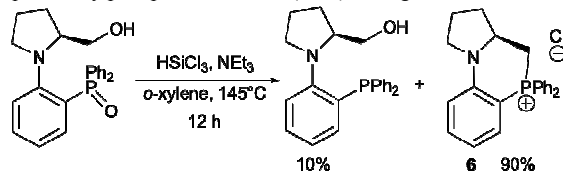


Scheme 4: Stereoselectivity divergence in the reduction of P-stereogenic phosphine oxides with silanes

In 1967, Cremer and Chorvat^{xiv} have extended the application of HSiCl_3 alone or in combination with NEt_3 to reduce four-membered ring phosphetane oxides **1** to the corresponding phosphetanes **2** (Eq. A, Scheme 5). Retention of configuration was mainly observed on either *cis* or *trans* phosphetane ring when the combined HSiCl_3 - NEt_3 mixture was used. This result contrasted with those described with acyclic phosphines. The steric hindrance of the substrates that prevents backside hydride attack accounted for these observations. Later, the retention of configuration on *trans*-phosphetane was also reported.^{xv} The reduction of polycyclic phosphetane oxides has been studied. As for **1** the reduction of **3** proceeded with retention of the configuration of the phosphorus atom to afford **4**. The reduction with sole Cl_3SiH gave **5** with inversion of configuration; epimerisation by HCl to give the thermodynamic stable isomer apparently took place (Eq. B, Scheme 5).^{xvi} More recently, Marinetti and Carmichael reviewed the preparation of phosphetanes.^{iva} Among all the reactions, they related the reduction of P-stereogenic phosphetane oxides. They gathered all the reactions conditions using silane reagents able to reduce with either retention or inversion of configuration at phosphorus atom.

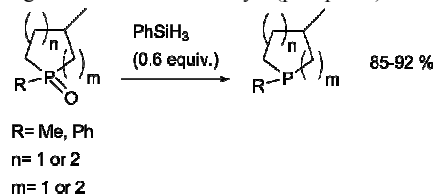
Scheme 5: Reduction of phosphetanes with HSiCl_3 and $\text{HSiCl}_3/\text{NEt}_3$ mixture^{xiv,xvi}

An interesting example on the phosphine oxides bearing a pendant free hydroxyl group was recently reported.^{xvii} Under the conditions of reduction with trichlorosilane and triethylamine, it has been observed the formation of the corresponding quaternary phosphonium salt **6** (90%) through the formation of a carbon-phosphorus bond (Scheme 6).



Scheme 6: Influence of a pendant hydroxyl group during the phosphine oxide reduction

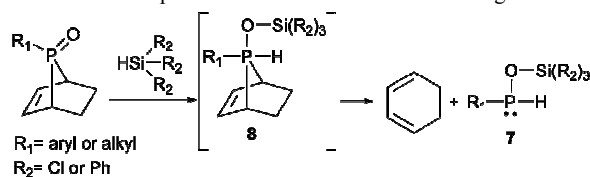
As described above, Fritzsche used for the first time in 1965 the phenylsilane as the reducing agent.^{xii} Later, Marsi^{xviii} investigated further this reagent and observed complete retention of configuration during the reduction of five and six-membered ring phosphine oxides (Scheme 7) with yields superior to 85%. In practice, this reagent can be employed to regenerate *in situ* the catalyst (phosphine) for the Appel reaction.^{xix}



Scheme 7: Deoxygenation reaction of cyclic phosphine oxides with phenylsilane

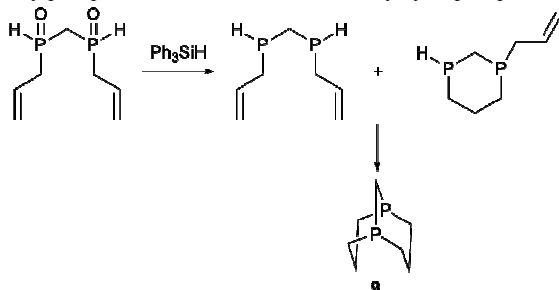
In 1984, Quin and co-workers^{xx} studied the reduction of P-bridged bicyclic phosphine oxides with HSiCl_3 or phenylsilane as reducing agent (Scheme 8). Most of the reductions occurred with the P-C bond cleavage releasing cyclohexa-1,3-diene and phosphinite **7** (retro McCormack reaction). The ring strain on the pentacoordinated intermediate **8** (C-P-C angle between equatorial groups = 100° instead of 120°) triggering the cycloreversion may account for these observations. The reactions performed in the presence of pyridine afforded exclusively the corresponding phosphines. The trichlorosilane-pyridine complex does not act as the hydride donor and the mechanism of this reduction does not involve a pentacoordinated

intermediate (See path C, Figure 2). The pyridine can serve to remove hydrogen from the complex with the phosphine oxide. This mechanism proceeded with retention of the configuration of the phosphorus atom.



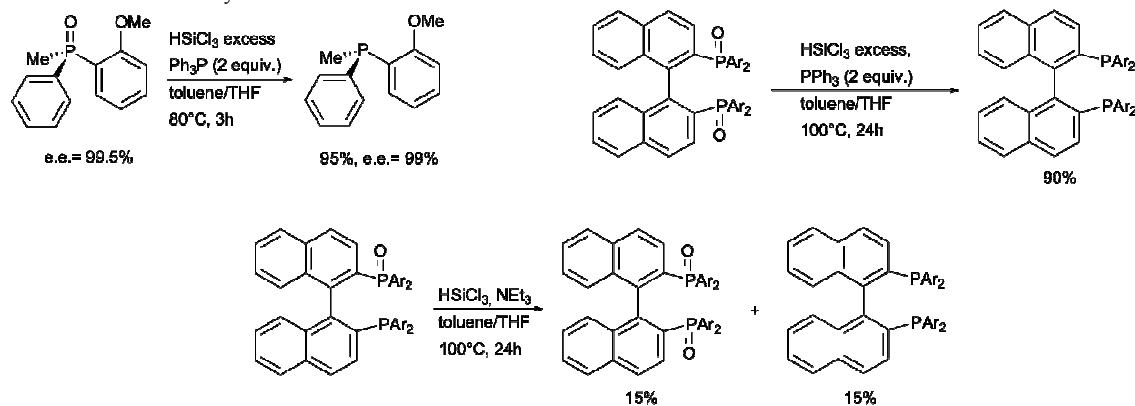
Scheme 8: Ring opening by silanes on P-bridged structure

Phenylsilane selectively reduced P=O bonds of bis secondary phosphine oxides bearing alkene functions. The resulting bis-alkylphosphine underwent intramolecularly hydrophosphination to generate the bicyclic tertiary phosphine **9** (Scheme 9).^{xxi}



Scheme 9: Reduction of bis secondary phosphine oxides followed by hydrophosphination reaction

In 2004, Spencer group reported the reduction of chiral phosphine oxides using a sacrificial phosphine such as triphenylphosphine in addition to trichlorosilane (Scheme 10).^{xxii} The oxygen atom was transferred with retention of the configuration from the chiral phosphine oxide to the sacrificial triphenylphosphine, the latter being more electron-poor than the final product. This method is complementary to the $\text{HSiCl}_3/\text{Et}_3\text{N}$ system that leads to an inversion of configuration^{xxiii}. The reduction of BINAP monoxide with the complex $\text{HSiCl}_3/\text{NET}_3$ (1 equiv.) afforded BINAP dioxide (15%) and BINAP (15%). This showed that an intermolecular reversible transfer of the oxygen atom from a phosphorus atom to another might occur. The complete reduction of BINAP dioxide to BINAP was achieved with the sacrificial triphenylphosphine (2 equiv.) and an excess of silane in 90% yield.



Scheme 10: Sacrificial electron-poor phosphine used for the capture of the oxygen atom of an electron-rich phosphine

An ^{18}O labelling study accounted for the oxygen transfer from one phosphorus atom to the sacrificial phosphine, *i.e.* the electron-poorer phosphine as labelled triphenylphosphine oxide has been detected (Figure 1). An excess of trichlorosilane is essential to further reduce triphenylphosphine oxide and thus to shift the equilibria in favor of the desired product.

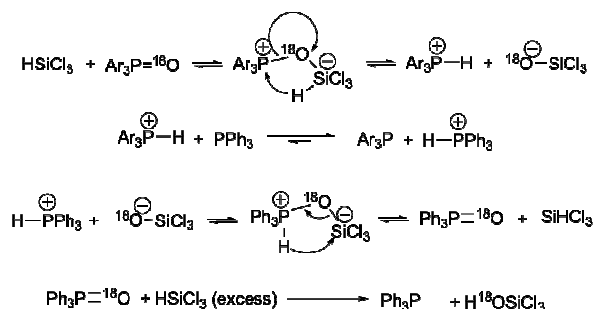
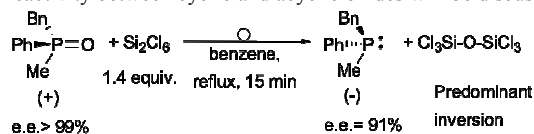


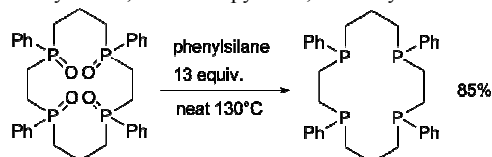
Figure 1: Proposed mechanism for the oxygen exchange between electron-rich and electron-poor phosphine

Hexachlorodisilane was also used by Mislow and co-workers in 1969 to reduce the P=O bond with high stereospecificity.^{xxiii} The reduction on acyclic phosphine oxides was achieved with inversion of configuration (Scheme 11). In contrast the reduction of phosphatane oxides substituted in position 2 was observed with retention of configuration.^{xxiv} The difference of reactivity between cyclic and acyclic oxides will be discussed later on.



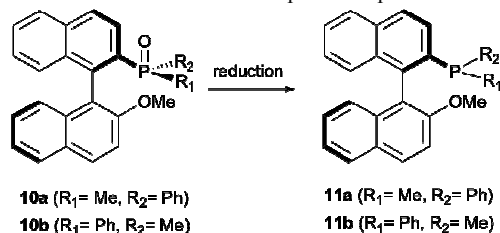
Scheme 11: Stereoselective reduction with hexachlorosilane

Other examples showed the efficiency of mono- and diphenylsilanes. Macrocyclic tetraphosphines were prepared from the corresponding phosphine oxides by reduction with phenylsilane (Scheme 12).^{xxv} Diphenylsilane was used to reduce chemoselectively phosphine oxides bearing a chiral oxazolidine group.^{xxvi} The use of trichlorosilane with an appropriate amine allows the formation of numerous phosphines. In fact the reduction of phosphine oxide derivatives have been performed with HSiCl₃ and *N,N*-diisopropylethylamine with moderate yields.^{xxvii} Other amines such as triethylamine,^{viii,xxviii,xxix} pyridine,^{xxx} tributylamine^{xxxi} or *N,N*-dimethylaniline^{xxxii} can be employed.



Scheme 12: Reduction of macrocyclic tetraphosphine oxides with phenylsilane

Gilheany and co-workers^{vii} reported that the difference of reactivity and stereoselectivity of silane reagents towards P-chiral binaphthyl monophosphine oxides **10a** (*R,R*_p) and **10b** (*R,S*_p) does exist (Scheme 13, Table 1). Hexachlorosilane reacted with diastereomer **10a** to give the corresponding phosphine **11a** with a complete diastereoselectivity. In sharp contrast, the mixture HSiCl₃/Et₃N gave the phosphine with a complete epimerisation of the phosphorus centre. It is noteworthy that the diastereoisomer **10b** was more prone to epimerisation.



Scheme 13: Reduction reaction of optically pure P-chiral binaphthyl monophosphine oxides

Table 1: Diastereoselectivity for the reduction reaction of P-chiral binaphthyl monophosphine oxides

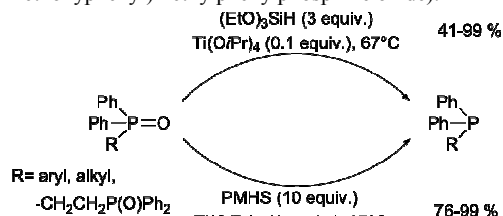
Phosphine oxide	Silane	Yield (%)	Phosphine 11a	Phosphine 11b
10a	HSiCl ₃ /Et ₃ N	65	50	50
10a	Si ₂ Cl ₆ (30 min)	60	100	0
10b	Si ₂ Cl ₆ (30 min)	70	30	70
10b	Si ₂ Cl ₆ (10 min)	36	14	86

Catalytic reactions

As related above, the reductions of phosphine oxides with silanes require an excess of reducing agent and relatively high temperatures. In order to minimize the use of dangerous and expensive reactants it has been considered to add a reagent

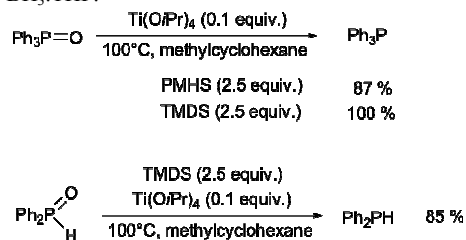
capable of activation either on the P=O bond or the Si-H bond. Considering the need of developing efficient and sustainable methods for this reaction, research groups started to study alternative reagents in the 90's.

Lawrence and co-workers developed the first catalytic reduction using silanes in 1994.^{xxxiii} Titanium (IV) was employed to reduce various (alkyl/aryl)diphenylphosphine oxides under mild conditions. For instance, triethoxysilane could efficiently reduce P=O bond in presence of 0.1 equiv. of $\text{Ti}(\text{O}i\text{Pr})_4$. However, one equivalent of Ti(IV) was necessary when the cheap and eco-friendly polymethylhydrosiloxane (PMHS) was used (Scheme 14). Moreover the reduction did not occur in the absence of the catalyst. Thus, the necessity to use an excess of silane in all cases is a major drawback. Retention of configuration at the phosphorus atom was observed with both silanes in the reduction of (*R*)-(2-methoxyphenyl)methylphenylphosphine oxide).



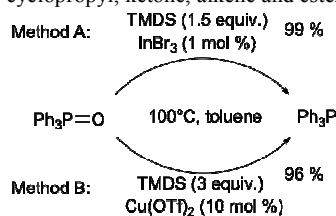
Scheme 14: Reduction catalysed by titanium complexes

In 2007, Lemaire and co-workers proposed the inexpensive tetramethyldisiloxane (TMDS) as an alternative to PMHS for the reduction of secondary and tertiary phosphine oxides in presence of $\text{Ti}(\text{O}i\text{Pr})_4$.^{viii} Both reducing agents were compared (Scheme 15). In all the cases, during the reduction of secondary or tertiary phosphine oxides, TMDS proved to be a superior reagent giving both better conversions and yields (up to 100%). Further experiments showed the beneficial effect of drying agent which improves the conversion and lowers the required temperature.^{vii} This method allows the straightforward preparation of secondary phosphine boranes by reduction of secondary phosphine oxides followed by their protection with BH_3 . THF.^{viii}



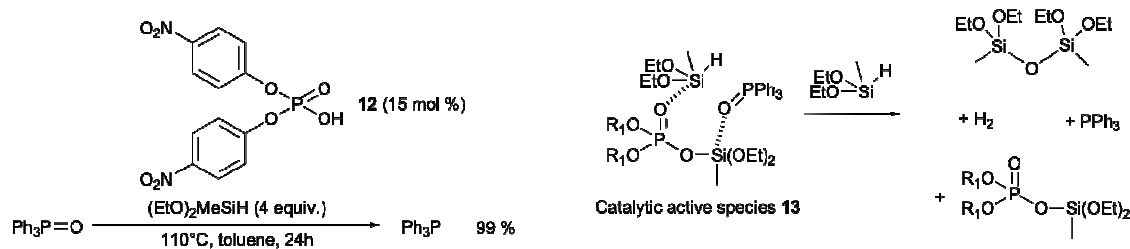
Scheme 15: Tetramethyldisiloxane as an alternative to polymethylhydrosiloxane

Recently, Lemaire's group reported the use of InBr_3 as catalyst for these reductions.^{vii} The reduction could be achieved with only 1% of catalyst and its scope includes various aliphatic, aromatic, secondary or tertiary phosphine oxides. Nevertheless, this catalyst was not chemoselective and reduced alkenes bearing the phosphorus atom in alpha or beta position (Method A, Scheme 16). Beller's group disclosed that copper (II) triflate (10% molar) catalysed efficiently and selectively the reduction of P=O bond with TMDS (3 equiv.). Interestingly, reducible functions neighbouring the phosphorus atom such as cyclopropyl, ketone, alkene and ester remained intact under these conditions (Method B).^{vb}



Scheme 16: Comparison between catalytic indium^{vii} and copper^{vb} reduction of triphenylphosphine

On the sidelines Beller's group developed a metal-free system. Thus, the first organocatalytic system for the reduction of phosphine oxides was reported.^{via} Various substrates have been reduced in the presence of aryl phosphoric acid **12** (5-15%) with diethoxymethylsilane (Scheme 17). The phosphines were obtained with yields ranging from 62 to 99%. The phosphoric silyl ester **13** was identified (³¹P NMR) as the bifunctional catalytic active species. The Lewis base-Lewis acid organocatalyst would be able to activate both silane and phosphine oxide respectively, and reacts further with the silane to afford the free phosphine and H₂. With this catalytic system, chiral phosphine oxides were reduced without racemisation.



Scheme 17: Organocatalysed-reduction reaction of phosphine oxides with silanes

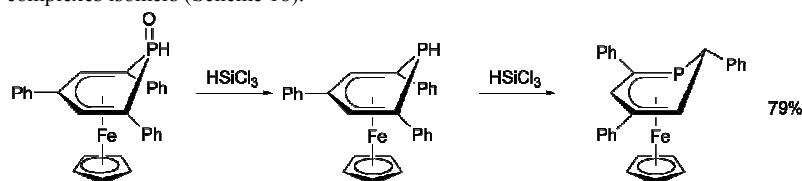
Miscellaneous reactions

In 1982, Fyfe and co-workers described the first example of reduction with trichlorosilane under heterogeneous conditions.^{xxxiv} The phosphine oxides were immobilised on silica and then converted to phosphines with good conversion. CPMAS ³¹P NMR allowed conversions determination. Later, it was reported that reduction of phosphine oxide immobilised on polystyrene resin with trichlorosilane led to corresponding phosphines in quantitative yield according to the solid state NMR.^{xxxv}

In order to prepare perfluorocarbon-soluble triarylphosphine ligand, Sinou and co-workers employed the trichlorosilane in the final step of their preparation. The reduction was performed in conventional solvents with 87% yield without triethylamine,^{xxxvi} and 96% yield when triethylamine was added.^{xxxvii} The reaction can be also carried out in fluorinated solvents,^{xxxviii} with HSiCl₃/Et₃N mixture and subsequent protection with borane.^{xxxix}

The reduction of triarylphosphine oxides by trichlorosilane (5 equiv.) and triethylamine (10 equiv.) can be assisted by microwave allowing shortening reaction time (10 minutes) and 83% yield.^{xi}

1-Hydrophosphabenzene-1-oxide iron complexes were reduced with trichlorosilane and afforded phosphadienyl iron complexes isomers (Scheme 18).^{xii}



Scheme 18: Reduction of 1-hydrophosphabenzene-1-oxide with trichlorosilane

Mechanistic aspects

Silanes as reducing agents afford phosphines with retention or inversion of configuration at the phosphorus atom depending on the presence or not of an additive (amine or catalyst). Here we will present the different pathways and attempt to rationalise the studies based on experimental observations and computational studies.

Mechanistic studies were first reported by Horner and Balzer in 1965.^{xiii} They suggested three reaction pathways that describe the reduction with trichlorosilane (Path A), trichlorosilane and triethylamine (Path B) and trichlorosilane and pyridine (Path C) (Figure 2). In the absence of amine (Path A), the P=O bond reduction occurs through the formation of the zwitterion **14** followed by an intramolecular exchange through the four-centered P-O-Si-H. The proton exchange between the resulting siloxane anion and the phosphonium gives rise to the free phosphine with retention of configuration. When triethylamine is used the zwitterion **14** reacts with the HSiCl₃-NEt₃ complex to form the inverted phosphonium **15** through an intermolecular hydride transfer (S_N2) (Path B). When pyridine is used (Path C), a stable hexacoordinated Py₂.HSiCl₃ complex **16** reacts directly with the phosphine oxide to afford the zwitterion **17**. The internal hydride delivery, similarly to the path A, releases the free phosphine with retention of configuration, poly(oxa)dichlorosilane and a pyridinium hydrochloride salt. According to Mislow and co-workers,^{xiii} the difference of basicity between triethylamine and pyridine influences the reactivity of the corresponding complexes. Strong bases (pK_b < 5) give the phosphine with predominant inversion while weak bases (pK_b > 7) afford the phosphine with predominant retention of configuration. In the case of triethylamine, the complex HSiCl₃-NEt₃ is not stable, and therefore decomposes into the ammonium **18** (evidenced by infrared spectroscopy) which further reacts with the phosphine oxide to give the phosphonium **19**. Then, a backside attack of ⁻SiCl₃ anion to the P-O bond leads to the formation of pentacoordinated trigonal bipyramide (TBP) Si-P-O species **20** with OH and SiCl₃ substituents in apical positions. The subsequent migration of the OH from the phosphorus atom to the silicon atom followed by the cleavage of the Si-P bond completes the reduction with inversion of configuration (Path D). Since the path B/D can be in competition with path A (competitive reaction between the four centres intramolecular and intermolecular proton transfer), a large amount of amine is necessary to obtain the phosphine with inversion of configuration. It is also suggested that the decomposition of HSiCl₃ in presence of base could lead to perchloropolysilanes (Si-Si bond formation).

More recently, Krenske studied the mechanism of the reduction of the trimethylphosphine oxide by quantum mechanical calculations^{xliii} and suggested a modification for the path A (Figure 2) with the formation of the pentacoordinate **21** when trichlorosilane is used alone (Figure 3). This TBP intermediate **21** with the hydrogen and OSiCl₃ in equatorial and apical positions respectively, is more stable than the initial state (Me₃P=O + HSiCl₃). The formation of the three centered transition state **22** seems more plausible as it is less energy-demanding (5.1 kcal/mol) than the formation of the ion pair **23** (15.7 kcal/mol) as described by former studies. The phosphine extrusion from **22** leaves the relative stereochemistry of the three substituents unchanged.

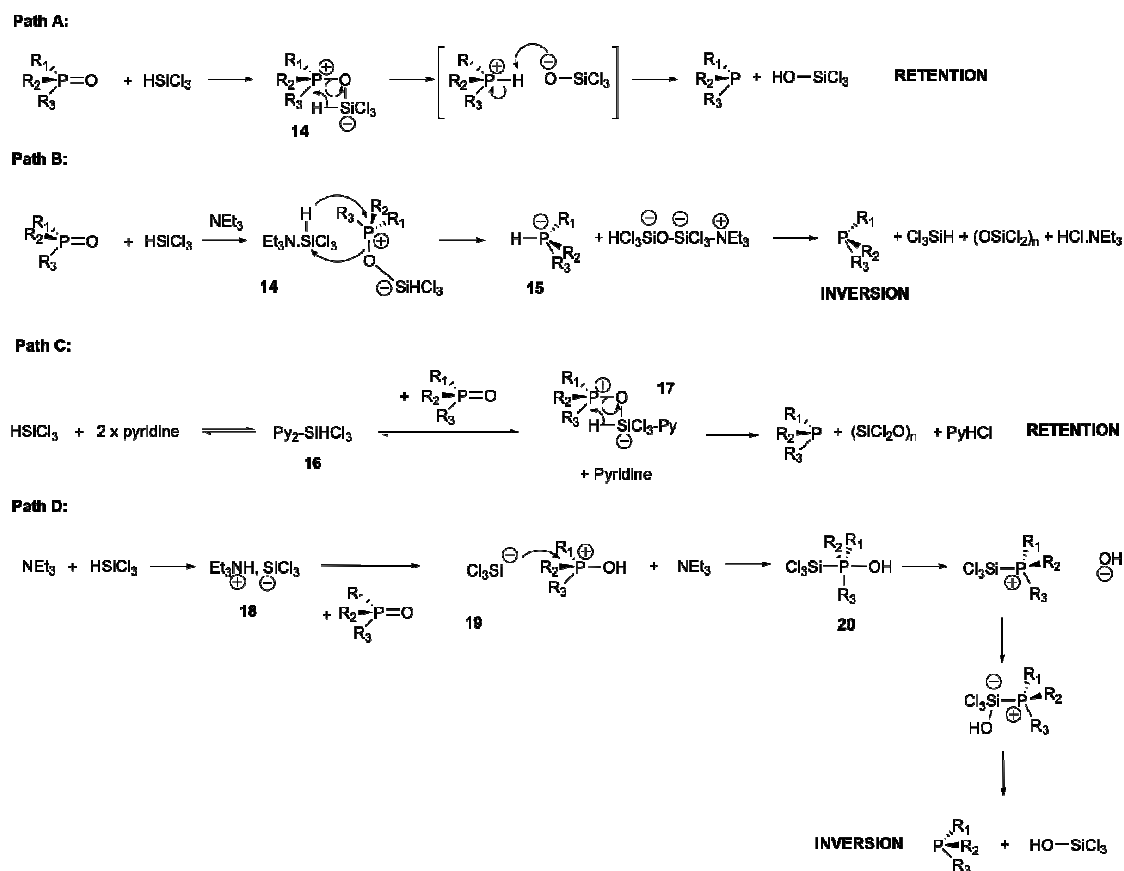


Figure 2: Proposed mechanisms for the reduction with HSiCl_3 (Path A), $\text{NEt}_3/\text{HSiCl}_3$ (Path B and D) and pyridine/ HSiCl_3 (Path C)

The mechanism of the reduction of phosphine oxides by $\text{HSiCl}_3/\text{Et}_3\text{N}$ according to path **D** (Figure 2) has been also explored according to the hypothesis that the mechanism involves a protonation of the phosphine followed by the nucleophilic attack of SiCl_3^- . Indeed, after the protonation of the phosphine oxide by the H-ammonium **18**, the favoured transition state corresponds to a backside attack of the SiCl_3^- anion on the hydroxyphosphonium **19** to generate the phosphorane **20** with the SiCl_3 and OH substituents in apical positions. The cleavage of the P-O bond is assisted by a second equivalent of the ammonium **18** and easily leads to the free phosphine with inversion of configuration.

Revisited path A:

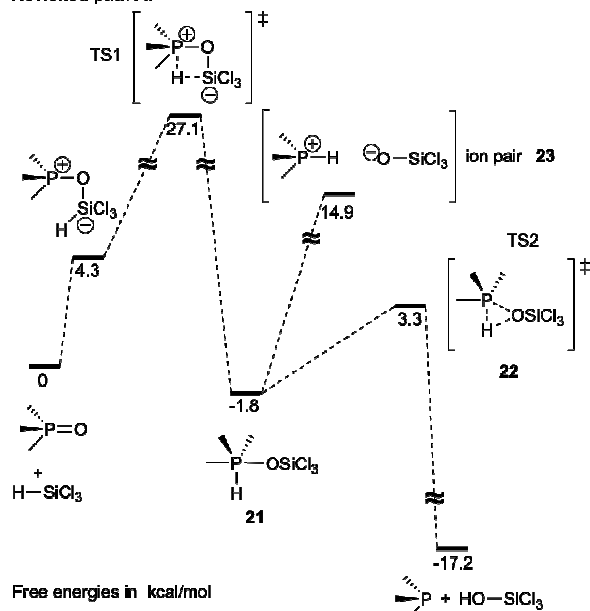


Figure 3: Mechanism of the reduction of trimethylphosphine with trichlorosilane through quantum mechanical calculations

In 1969, Mislow and co-workers described the mechanism of the reduction with hexachlorosilane, which behaves as trichlorosilane alone with inversion of configuration.^{xiii} The scission of the hexachlorosilane allows the formation of the P-O-SiCl₃ phosphonium **24** and the subsequent backside attack of the counter anion SiCl₃ to the P-O bond affords the pentacoordinated Si-P-O-Si intermediate **25** with the entry and departure of substituents in apical positions (Figure 4). The P-O cleavage releases the Si-P phosphonium **26** with inversion of configuration. Then, the free phosphine may result from an attack of OSiCl₃ anion on the silicon with the formation of Cl₃SiOSiCl₃.

Hexachlorosilane behaves differently with phosphetane oxides. In this case, the hindrance of the cycle prevents the backside attack on the phosphetanium cation. This drives the trichlorosilyl anion to react directly on the oxygen atom affording the corresponding phosphetanes with retention of the configuration at the phosphorus atom.^{xxiv}

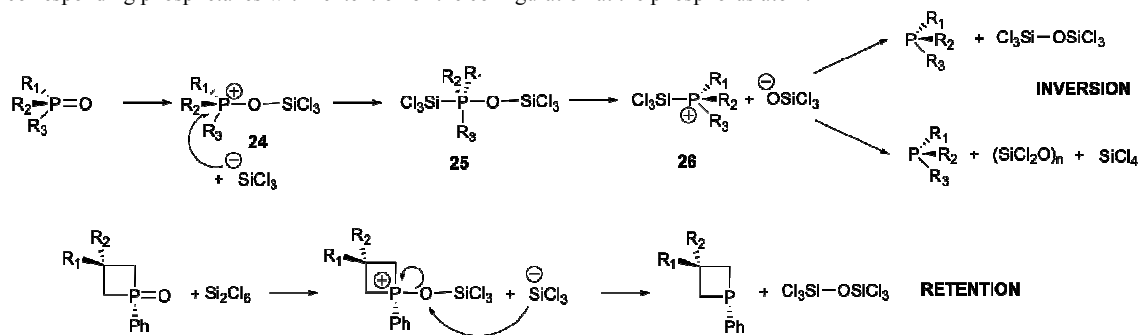


Figure 4: Proposed mechanism for the reduction of phosphine oxide with hexachlorosilane

This mechanism was corroborated recently by Krenske who studied this reaction on trimethylphosphine oxide by quantum mechanical calculations.^{xiv} The cleavage of the Si-Si bond to form the phosphonium salt is the rate-determining step of the reaction. The loss of stereoselectivity observed with this reactant was explained by the possible partial pseudorotation of the pentacoordinated phosphorane intermediate **25**.

Phenylsilane reduces the phosphine oxides with retention of configuration by addition of hydride on the P=O bond.^{xviii} The proposed mechanism is similar to the one with HSiCl₃. The four-centered intramolecular concerted rearrangement leads to the H-phosphonium **27**. The subsequent attack of siloxane anion releases the free phosphine (Figure 5).

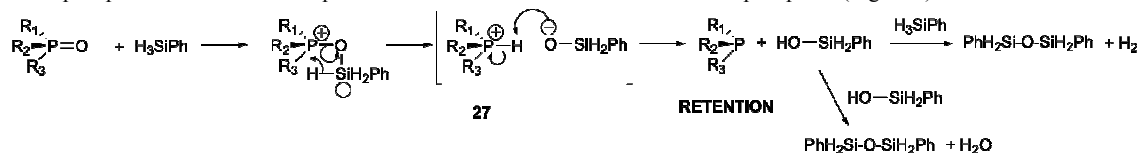


Figure 5: Proposed mechanism for the reduction with phenylsilane

Depending on the nature of the silane and/or its additives it is possible to control the stereoselectivity of the reduction of phosphine oxides. Mechanisms of these reductions have been elucidated. The pseudorotation of the pentacoordinated phosphorane intermediate could be responsible for the loss of stereoselectivity observed in some cases.

Catalysts can also enhance the reactivity of the silane. In 1994, Lawrence proposed a mechanism for the reduction with titanium (IV) and silane that occurs with retention of configuration.^{xxxiii} The catalyst precursor Ti-OR **28** is first reduced with the silane to form the active titanium hydride species **29**. The subsequent hydrotitanation of the phosphine oxide through the four-centered intermediate **30** gives the H-P phosphonium **31**. Once formed, it further reacts with **29** to release the free phosphine and H₂ (Figure 6).

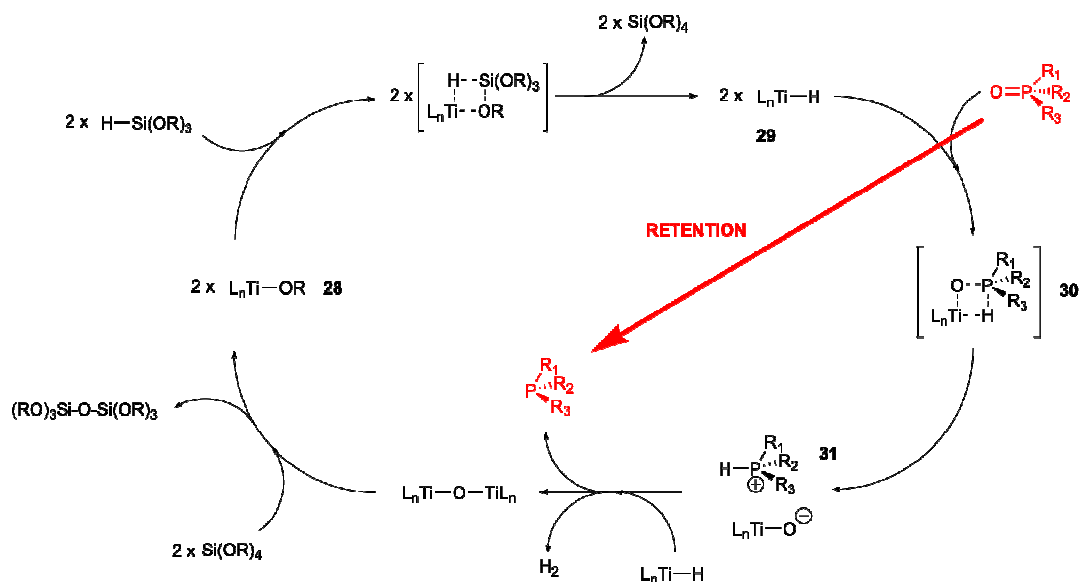


Figure 6: Proposed mechanism for the reduction catalysed by titanium complexes

Later, investigations based on EPR analysis and ^{29}Si NMR from Lemaire's group ended in a different mechanism (Figure 7).^{vii} The key point of these studies is the evidence of the presence of Ti (III) intermediate **32**, which may result through a single electron transfer mechanism. They also proposed that water is formed instead of hydrogen and that only one equivalent of Si-H reagent is necessary. Another recent study confirmed the presence of **32**.^{viii} Moreover, formed polyhydrosiloxanes and polysiloxanes were finely identified by analysis of crude reaction mixture, which accounts for the water formation during the process instead of hydrogen.

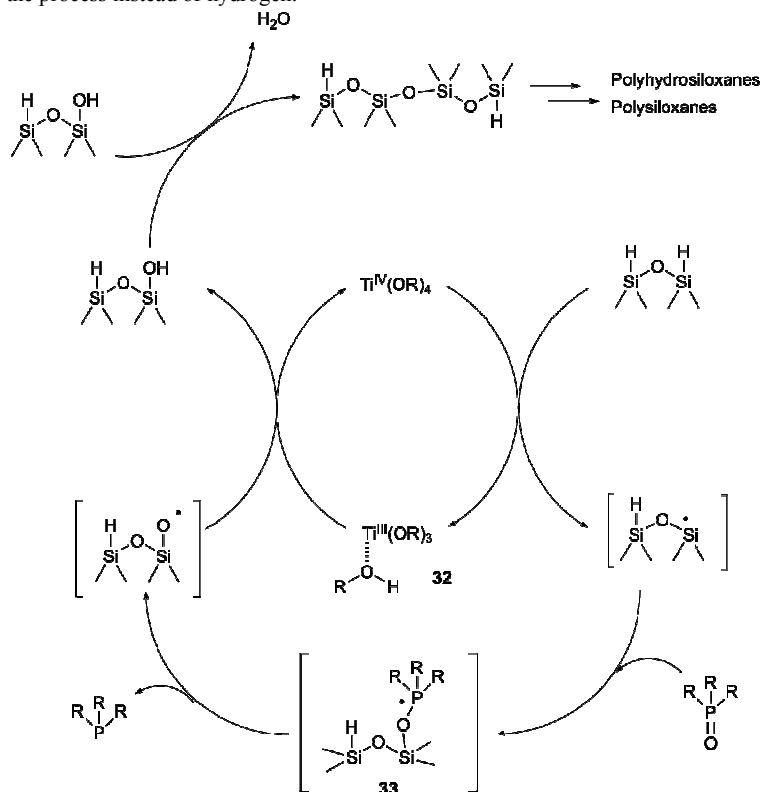
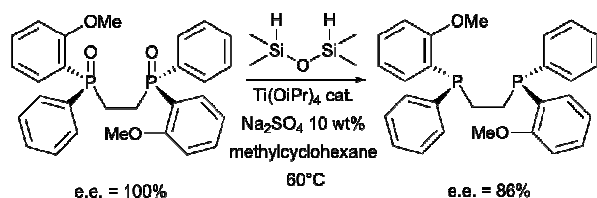


Figure 7: Alternative radical mechanism for the reduction catalysed by titanium complexes

The proposed catalytic cycle involves the formation of silyl radical intermediate which reacts with the phosphine oxide. Therefore it is not surprising to observe partial loss of the chiral information. This is probably due to the pseudorotation of radical intermediate **33**, which leads to the pseudoracemisation of the phosphorus radical species. The formation of silanol, upon dimerisation generates water from the system which can trap any formed radicals. Indeed in the presence of a drying

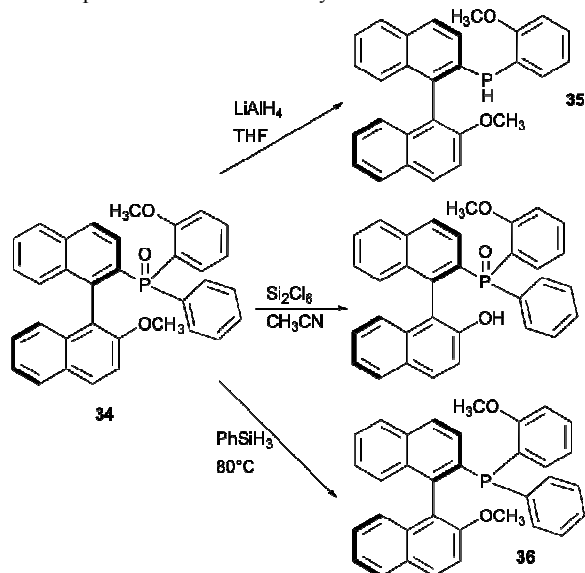
agent a high conversion was obtained at a lower temperature with less reducing agent. Under these conditions the DIPAMP was obtained in 86% e.e. from the optically pure diphosphine oxide (Scheme 19).



Scheme 19: Stereoselective reduction of optically pure bisphosphine oxides with (tetraisopropoxide)titanium complex

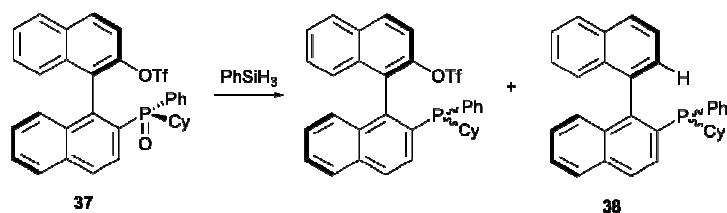
Chemoselectivity

It is noteworthy that trichlorosilane can be chemoselective when ketone and phosphine oxide are in competition. In the example described by Granoth and co-workers for the preparation of dibenzophosphorine, trichlorosilane is used to reduce selectively the P=O without reducing the keto group (90% yield).^{xiv} Another example deals with the case of a methyl ester bearing phosphine oxide. Again, in this case the reduction of the ester does not occur.^{xlvi} Similarly, the deoxygenation reaction of phosphine oxides bearing alkene functions with phenylsilane is chemoselective.^{xi,xxi,xlvii} The unsaturated cyclic phosphine oxides were reduced while alkene functions did not react. PhSiH₃ or a mixture of PhSiH₃/HSiCl₃ can also reduce secondary ethynylphosphine oxides with moderate yield (55-75%) without reduction of the alkyne function.^{xlviii} More complex molecules can also be reduced selectively. Odinets group described the reduction of a cyclopropane substituted by a nitrile and phosphine oxide groups. Only the phosphine oxide in beta-position of the nitrile function was reduced by trichlorosilane.^{xix} In 2005, Gilheany and co-workers studied the influence of the nature of the reducing agent (LiAlH₄, Si₂Cl₆ and PhSiH₃) on the chemo- and stereoselectivity during the reduction of diastereomeric 2-(anisylphenylphosphinyl)-2'-methoxy-1,1'-binaphthyl **34** (Scheme 20). The reaction of a mixture of a 1:1 diastereoisomer mixture with LiAlH₄ led to the cleavage of the P-Ph bond and the formation of diastereoisomers of the secondary phosphine **35** in the same 1:1 ratio.^{vib} This reduction to the secondary phosphine is probably not stereoselective. Moreover it was shown that epimerisation does not occur at room temperature in the absence of acid (used during the work-up). Si₂Cl₆ exclusively cleaves the ether C-O bond of MeO on the naphthyl ring and does not reduce the P=O bond. In contrast, PhSiH₃ is efficient nevertheless the reduction was not complete after 3 days at 80°C. In the case of optically pure phosphine oxide, epimerisation of the phosphorus atom of the reduced product **36** was detected by ³¹P NMR.



Scheme 20: Effect of different silane reactants on diastereomeric 2-(anisylphenylphosphinyl)-2'-methoxy-1,1'-binaphthyl

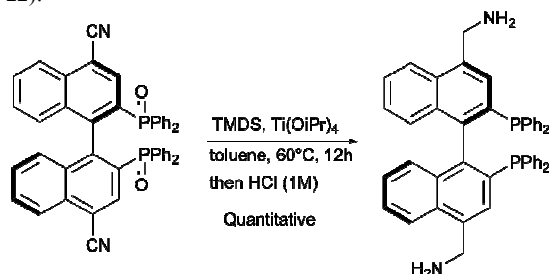
Although its efficiency was demonstrated for reductions, the use of PhSiH₃ in the case of the reduction of binaphthylphosphine oxide **37** has been proved to be ineffective in terms of chemo- and stereoselectivity.^{vic} Along with the expected phosphine, the overreduced compound **38** was also observed. In both reduced compounds, it was observed a loss of stereochemical integrity of the phosphorus centre (Scheme 21).



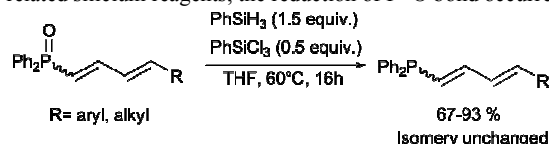
Scheme 21: Non-chemoselective reduction with phenylsilane

In an example described by Gloede and co-workers, the phenylsilane selectively reacts with the phosphine oxide group while the phosphonate function remains unchanged.ⁱ

As previously mentioned, Lemaire and co-workers introduced reductions with indium.^{viii} They studied two substrates containing alkene functions in alpha or beta position. The catalytic system displayed no chemoselectivity towards alkene functions. Thus, the reduction of both P=O and C=C bonds gave the alkyl phosphines in excellent yields (>95%). This group took advantage of the lack of chemoselectivity for the preparation of DIAMBINAP ligand. A stoichiometric amount of Ti(OiPr)₄ and TMDS allowed to reduce simultaneously nitrile and tertiary phosphine oxide in quantitative yield (Scheme 22).^{viii}

Scheme 22: Positive non-chemoselectivity towards nitrile functions of the system Ti(OiPr)₄/TMDS

In 2013, Taillefer and Gaumont related the chemoselective reduction of 1,3-butadienylphosphine oxides to 1,3-dienylphosphines in good yields (67-93%) (Scheme 23).^{li} The reduction was successfully achieved using 3/1 mixture of PhSiH₃/PhSiCl₃ which allowed the *in situ* formation of active PhSiHCl₂. Due to its better oxophilicity compared to other related silicon reagents, the reduction of P=O bond occurred without overreduction of the neighboring C=C bond.

Scheme 23: *In situ* formation of chemoselective reducing agent

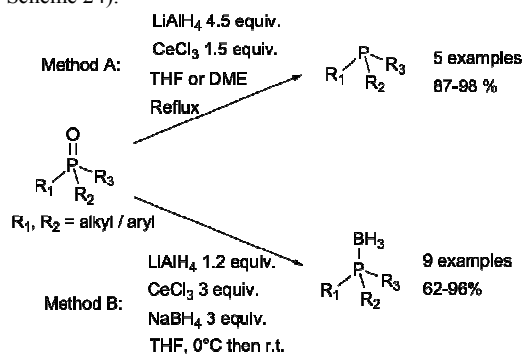
As related before, Beller and co-workers have shown that the reduction of phosphine oxides to phosphines by inexpensive silanes PMHS or (EtO)₂MeSiH was promoted by Brønsted acids such as (4-NO₂C₆H₄O)₂P(O)POH. This metal-free reduction offered an excellent chemoselectivity. Several reducible groups such as aldehyde, ketone, amide, olefin or cyclopropane were tolerated under these reduction conditions.^{va}

2. Reduction with aluminum compounds.

Stoichiometric reactions

The very first disclosure of the use of aluminum hydride as reducing agent for phosphine oxides and sulfides was reported by Hein and co-workers in 1956.ⁱⁱⁱ The reduction of trialkylphosphine oxides proceeded with yields up to 70%, but arylphosphine oxides were scarcely reduced under the conditions used. Three years later, Issleib and co-workers screened the reduction of triphenylphosphine oxide in various solvents.ⁱⁱⁱ The reaction worked well in aliphatic ethers and the authors noted the formation of diphenylphosphine in THF or dioxane, presumably through the diphenylphosphide anion intermediate. Further works in the late 60's showed that lithium aluminum hydride (LiAlH₄) was not very efficient in the reduction of P=O bonds.ⁱⁱⁱ In 1985, Imamoto and co-workers published an article, mainly based on the reduction of organic halides, that contains the first example of an efficient reduction of phosphine oxides by LiAlH₄.ⁱⁱⁱⁱ The reductive system was a mixture of LiAlH₄ and CeCl₃ (Method A, Scheme 24). The strong Lewis acid character of the cerium salt activates the P-O bond prior to the reduction. In the absence of CeCl₃, only traces of triphenylphosphine were observed. Under these conditions, the reduction of an optically active phosphine oxide proceeded with predominant racemisation at the phosphorus atom. This procedure has since been applied successfully in several occasions.^{iv} Interestingly, this LiAlH₄-CeCl₃ system, associated with NaBH₄, allowed the production of phosphine borane directly from the phosphine oxide, thus avoiding the isolation of corrosive and/or air sensitive phosphines (especially secondary and primary phosphines).^{iv} Tertiary or secondary phosphine oxides as well as phosphinic acid esters were transformed into the corresponding phosphine-borane with good to excellent yields. In these cases, the trivalent cerium was assumed to activate both the P-O bond and the NaBH₄ to allow the reduction

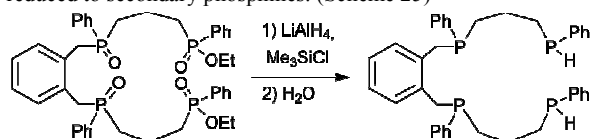
and then led to the phosphine-borane. It should be emphasised that no reaction occurred in the absence of CeCl_3 (Method B, Scheme 24).



Scheme 24: Cerium assisted reduction with LiAlH_4

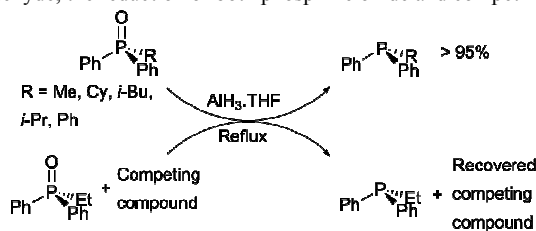
In one single case, LiAlH_4 alone proved to be efficient for the reduction of sterically hindered phosphine oxides although a cleavage of a P-Ph bond occurred during the reduction (See Scheme 20).^{vib}

For the synthesis of tetraphosphine ligand, Wong and co-workers succeeded in the reduction of a compound containing several P=O bonds by adding Me_3SiCl to LiAlH_4 .^{lvi} No chemoselectivity was observed as the phosphinates groups were also reduced to secondary phosphines. (Scheme 25)



Scheme 25: Reduction of phosphine oxides and phosphinates with $\text{LiAlH}_4/\text{Me}_3\text{SiCl}$

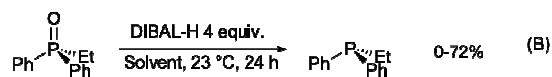
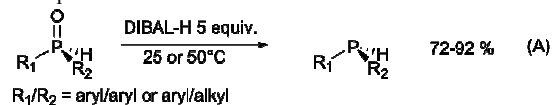
The workup required by these methods often led to, at least, a small amount of oxidized product.^{xxxiii} To overcome the formation of undesirable by-products, Wyatt and co-workers have designed a system that does not require an aqueous work-up.^{lvii} This system implies the use of alane AlH_3 generated from concentrated sulfuric acid and LiAlH_4 . This method gave excellent results for the diphenylalkylphosphine oxides (Scheme 26). Further studies showed an excellent chemoselectivity of this reagent.^{lviii} Indeed, reacting diphenylethylphosphine oxide with AlH_3 .THF in the presence of a competing compound such as sulfoxide, ester, amide and even epoxide resulted satisfactorily to the selective reduction of the phosphine oxide. Competing compounds were recovered in 90 to 96% yield. In contrast, with co-reactants such as disulfide, ketone or aldehyde, the reduction of both phosphine oxide and competing reactant was observed.



Competing compound : sulfoxide, ester, amide or epoxide

Scheme 26: Reduction of phosphine oxides with AlH_3

Diisobutylaluminumhydride (DIBAL-H) showed to be efficient in the reduction of secondary phosphine oxides.^{lix} This reagent allowed the formation of sterically hindered phosphines (di-*tert*-butyl and di-*mesityl* phosphine) (Eq. A, Scheme 27). When R_1 or R_2 contains heteroatoms (nitrogen or oxygen) the number of DIBAL-H equivalents has to be increased. Indeed these heteroatoms can inhibit the reduction by coordinating the reducing agent. Some experiments showed that ethers, amides and aryl iodides functionalities are preserved during the reduction. It was also shown that trisobutylaluminum hydride is efficient in this reduction. The same authors published later a comprehensive study aimed to the optimisation of reduction of tertiary phosphine oxides (Eq. B, Scheme 27).^{lx} It was shown that cyclopentyl methyl ether and methyl *tert*-butyl ether proved to be the best solvents.



Scheme 27: Reduction of hindered secondary (Eq. A)^{lix} and tertiary (Eq. B)^{lx} phosphine oxides with DIBAL-H.

Reduction of diphenylethylphosphine oxide was observed in an optimal 72% yield. No significant improvement was noticed after 24h of reaction time or addition of excess DIBAL-H. The proposed mechanism (Figure 8) consists in the first step by a hydroalumination of the P=O bond to form a H-phosphorane. The latter reacts with DIBAL-H to afford H₂, the corresponding phosphine and TIBAO which is formed in equimolar amount in respect to the phosphine. It was shown that TIBAO inhibited the reaction probably through a binding to the phosphine oxide (TPO) as a six-membered alane phosphine complex **39** was formed. This assumption was supported by the better results obtained when using electron-rich ethers as solvents able to displace the TPO from complex **39**. It was anticipated that the addition of a more electron-rich phosphine oxide than the substrate should improve the conversion. Indeed, adding tricyclohexylphosphine oxide to the reaction led to complete conversion and higher yield of phosphine at 72°C in cyclohexane. Under these conditions, reductions could be conducted on gram scale to give products in 89-99% yield. The DIBAL-H reduction of chiral tertiary phosphine oxides proceeded with retention of configuration but with a poor stereoselectivity. This racemisation is probably due to the pseudorotation of the H-phosphorane intermediate formed in the first reduction step.

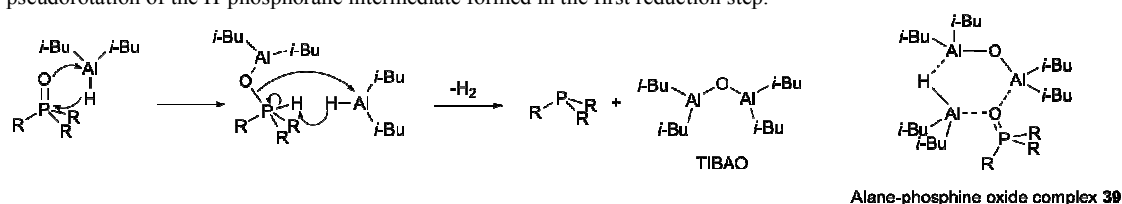
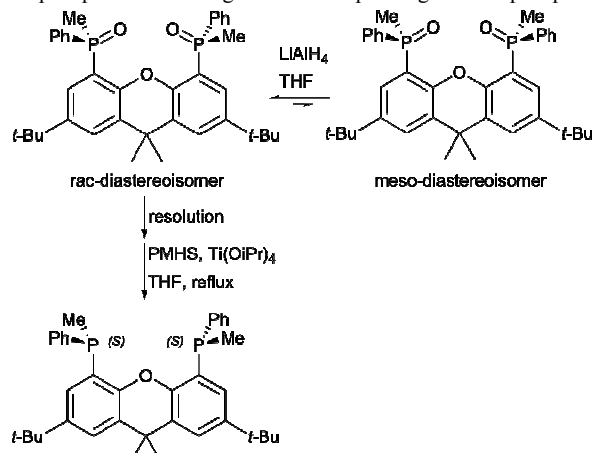


Figure 8: Proposed mechanism for the reduction with DIBAL-H

Enantioselectivity

Chiral phosphine oxides undergo rapid stereomutation in presence of LiAlH₄ prior to their reduction.^{lii, lxi} Thus mixing (+)-methylphenyl-*n*-propylphosphine oxide and LiAlH₄ in a 1:2 molar ratio led to complete racemisation of the phosphine oxide at about 10% conversion to the corresponding phosphine. It is assumed that a reversible addition of LiAlH₄ to the phosphine oxide is responsible for the racemisation through the pseudorotation of a pentacoordinated phosphorane Li[Al(OPHR₃)₄] intermediate. However, this racemisation process has found an useful application in the synthesis of the chiral bidentate phosphine, 2,7-di-*tert*-butyl-9,9-dimethyl-4,5-bis(methylphenylphosphino)xanthenes. The latter was formed from the epimerisation of the meso into racemic diphosphine oxide diastereoisomer followed by chemical resolution and complete enantioselective reduction with PMHS/Ti(OiPr)₄ system (Scheme 28). This reduction proceeded with complete retention at the phosphorus atom to give the corresponding chiral biphosphine in 79% yield.^{lxii}



Scheme 28: Synthesis of chiral bidentate phosphine

The asymmetric reduction of racemic phosphine oxides remains very challenging to access to P-stereogenic phosphines. The reduction of the cyclic phosphine oxide **40** by aluminum hydrides associated to chiral amines bearing optically active substituents **41** or **42** (R* = (*S*)-phenylethylamine; R=Me) led to some, although rather low, enantiomeric induction to afford non racemic phosphines (Figure 9).^{lxiii} It is generally admitted that, after complexation of the phosphine oxide by the alane the hydride transfer can occur through two different pathways: a unimolecular pathway leading to retention of configuration and a bimolecular pathway giving an inversion of configuration. These two competing mechanisms can be both involved under the reaction conditions and their relative predominance is determined by the experimental conditions. The best asymmetric inductions were obtained at low temperature using a 2:1 or 3:1 AlH/PO ratio. Increasing the temperature or the AlH/PO ratio, thus increasing the participation of the bimolecular mechanism, led to lower asymmetric inductions. Later (*S*)-2-(anilinomethyl)-pyrrolidone was also used to form the alane complex but the asymmetric induction was low (<7%).^{lxiv}

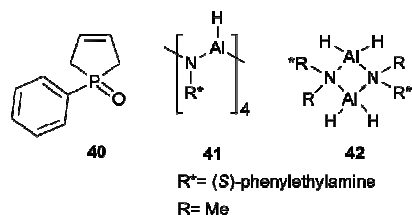
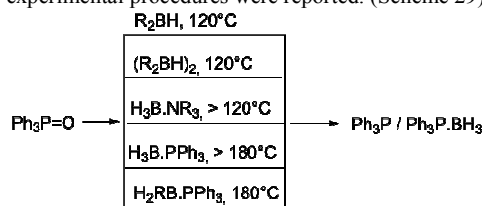


Figure 9: Chiral aminoalanes for the reduction of cyclic phosphine oxides

3. Reduction with boron compounds

Types of borane

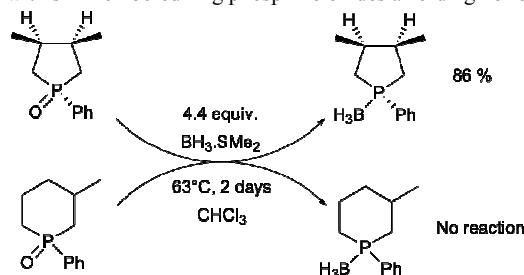
The direct reduction of phosphine oxides by borane or/and borane complexes is convenient because it allows the straightforward access to stable and easy to handle borane protected phosphine compounds. In 1965, the employment of borane derivatives as reductants to convert phosphine oxides into phosphine/phosphine-boranes was first reported by Köster and Morita.^{lxv} For instance triphenylphosphine oxide reacted with alkylboranes or their adducts such as amine-boranes and phosphine-boranes to afford triphenylphosphine under harsh conditions (120-180°C). However, no yields neither detailed experimental procedures were reported. (Scheme 29)



Scheme 29: Reduction of triphenylphosphine with different boranes

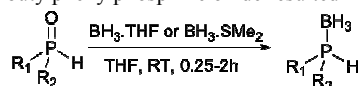
Later, the same group examined the reduction of secondary diphenyl phosphine oxide in presence of bis-(9-borabicyclo-[3,3,1]-nonane) (BBN). This reduction led to a mixture of products containing free secondary phosphine Ph_2PH and the protected $BBN\cdot Ph_2PH$.^{lxvi} More recently, Stephan and co-workers reported that tri-alkyl (ethyl and butyl) or phenyl-phosphine oxides could be selectively reduced to the corresponding phosphines by pinacolborane under refluxing conditions for 3 days in toluene but no isolated yields were reported.

In 2000, Keglevich and co-workers^{lxvii} employed the dimethyl sulfide-borane under mild conditions for the direct transformation of cyclic phosphine oxides to phosphine-boranes (Scheme 30). Five-membered ring phosphine oxides smoothly reacted with 4-5 fold equivalents of borane-dimethylsulfide complex in chloroform at 25-65°C to give phosphine-boranes in 39-92 % yields. It is noteworthy that these conditions maintain the stereochemical integrity of the phosphorus atom as supported by NMR studies and single crystal X-ray analyses. The reaction rate is very sensitive to ring strain as evidenced by the reduction of more strained five-membered ring phosphine oxide such as tetrahydrophosphole compared with six-membered ring phosphine oxides affording no reduction products under the same conditions



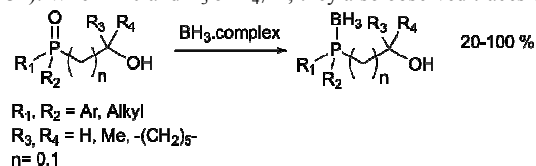
Scheme 30: Reduction of cyclic phosphine oxides with boranes

In 2003, Stankevič and Pietrusiewicz^{lxviii} found that an excess of $BH_3\cdot THF$ or $BH_3\cdot SMe_2$ (3-10 equiv.) could efficiently convert secondary phosphine oxides into secondary phosphine-boranes in moderate to good isolated yields (40-100%) (Scheme 31). In some cases, phosphinous acid-boranes were observed even in presence of large excess of reducing reagents. Surprisingly the production of phosphinous acid-boranes was suppressed by adding a small amount of water to $BH_3\cdot SMe_2$. The role of water is unclear but its presence in the medium generated other boranes such as $B(OH)_n(H)_{3-n}$ which may affect the chemoselectivity. Under these conditions, the reduction is not enantioselective, thus the reduction of optically pure *t*-butylphenylphosphine oxide resulted in the formation of (*t*-Bu)(Ph)PH with only 18 e.e. %.



Scheme 31: Formation of secondary phosphine borane from secondary phosphine oxides

Recently, Kielbasinski and co-workers^{lxviii} reported that phosphine oxides such as $(\text{Ph})(t\text{-Bu})(\text{CH}_2\text{OH})\text{P}=\text{O}$ could be reduced to $(\text{Ph})(t\text{-Bu})(\text{CH}_2\text{OH})\text{P}\cdot\text{BH}_3$ at room temperature using $\text{BH}_3\cdot\text{THF}$ complex. Under similar conditions, the phosphinate $(i\text{PrO})(\text{Ph})(\text{Me})\text{P}=\text{O}$ and $(\text{RO})(\text{Ph})(\text{CH}_2\text{OH})\text{P}=\text{O}$ ($\text{R} = \text{Me}$ or $i\text{-Pr}$) has been stereoselectively reduced to phosphinite-borane $(i\text{PrO})(\text{Ph})(\text{Me})\text{P}\cdot\text{BH}_3$ and $(\text{RO})(\text{Ph})(\text{CH}_2\text{OH})\text{P}\cdot\text{BH}_3$ respectively in 11–60% isolated yields. These low yields were due to the formation of overreduced secondary phosphine borane $(\text{Ph})(\text{R})\text{P}(\text{H})(\text{BH}_3)$ ($\text{R} = \text{Me}$, CH_2OH). The absolute configuration of the products was determined by chemical correlation as well as theoretical calculations and specific rotation $[\alpha]_{\text{D}}$ values. This reduction took place with inversion of configuration at the phosphorus center, irrespective of the substituents at phosphorus. More recently Pietrusiewicz and co-workers^{viiiid} generalised this method to a large scope of tertiary hydroxyalkylphosphines and obtained the corresponding phosphine boranes in low to excellent yields (20–100%) (Scheme 32). When $n=0$ and R_3 or $\text{R}_4 \neq \text{H}$, they also observed traces of secondary phosphine boranes and phosphinous acid boranes.



Scheme 32: Reduction and protection of hydroxyalkylphosphine oxides

Mechanistic aspects

Since the stereochemistry at the phosphorus atom of the product is preserved during the reduction, Keglevich proposed that the first step involved nucleophilic attack of the oxygen atom of $\text{P}=\text{O}$ group to the borane, followed by hydride shift to form a pentacoordinated trigonal bipyramidal phosphorus intermediate **43**. The elimination of apical BH_2O^- group leads to a phosphonium intermediate **44** which affords the phosphine after proton release (Figure 10). The last step is the complexation with excess BH_3 to form the desired product. The pentacoordinated $\text{P}(\text{V})$ involved during the addition of the borane on the $\text{P}=\text{O}$ bond relieves the ring strain of cyclic phosphine oxides specially for the five membered ring.

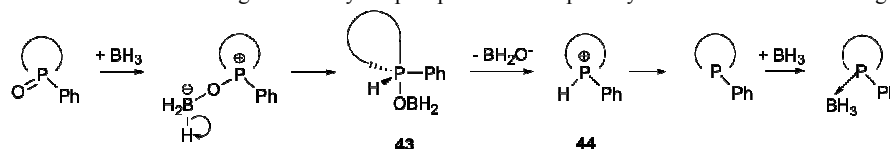


Figure 10: Proposed mechanism for the reduction of phosphine oxides with borane

According to proposed Keglevich's mechanism, Pietrusiewicz and Stankevič assumed the formation of the pentacoordinated phosphorane **45** for the borane reduction of enantiomerically pure (R) -*tert*-butylphenylphosphine oxide. The cleavage of the apical $\text{P}-\text{OBH}_2$ bond should generate a symmetrical phosphonium **46** leading to racemic *tert*-butylphenylphosphine borane complex **47**. The isolation of non-racemic *tert*-butylmethylphenylphosphine borane (18% e.e.) precludes in some extent the formation of such phosphonium to favour the formation of the secondary phosphine by a ligand-coupling (reductive elimination) (Figure 11).

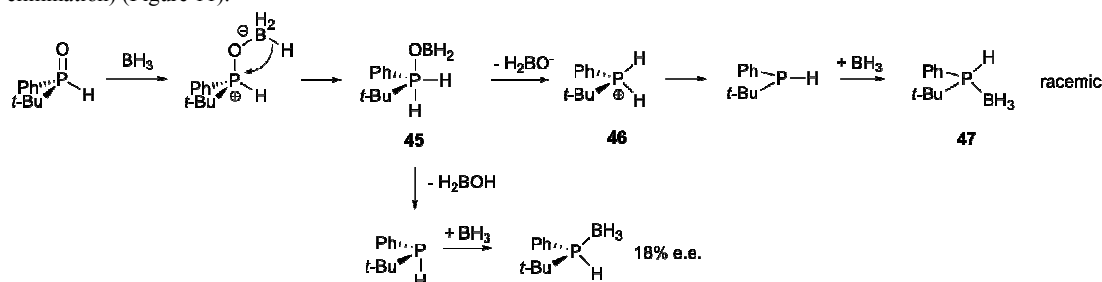


Figure 11: Alternative mechanism proposed by Pietrusiewicz

Kielbasinski observed the inversion of configuration at phosphorus centre when reducing the optically enriched acyclic alkoxy or alkyl(hydroxymethyl)phenylphosphine oxides. Therefore the above mechanism for cyclic phosphine oxides was not suitable for this transformation. The authors assumed that an intermolecular hydride attack by the $\text{BH}_3\cdot\text{THF}$ took place (Figure 12, Path A). The cleavage of phosphorus-oxygen bond followed by complexation with borane afforded the product with inversion of configuration at phosphorus atom. This alternative route looks like $\text{S}_{\text{N}}2$ mechanism where the stereo-determining step consists in an attack of a nucleophilic hydride borane to the phosphorus centre. The resulting phosphonium was produced with inversion of the configuration at phosphorus atom. Very recently, Pietrusiewicz and co-workers^{viiiid} proposed another mechanism involving the pendant $-\text{OH}$ (Figure 12, Path B). The first step consists of a reaction between BH_3 and the OH group and then the intramolecular coordination between the boron and the phosphoryl oxygen which results in the formation of a cyclic zwitterionic intermediate where the $\text{P}-\text{O}$ bond is activated. The subsequent intermolecular hydride attack by the BH_3 to the phosphorus atom leads to the formation of the phosphonium with inversion of configuration at phosphorus centre, as supported by chemical correlation and specific rotation $[\alpha]_{\text{D}}$ values.

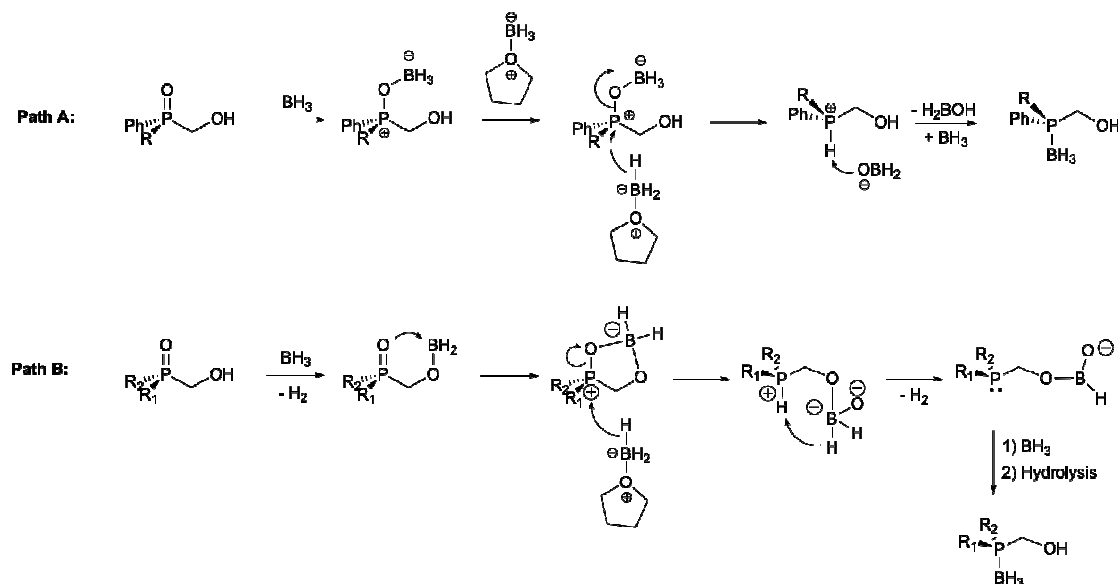


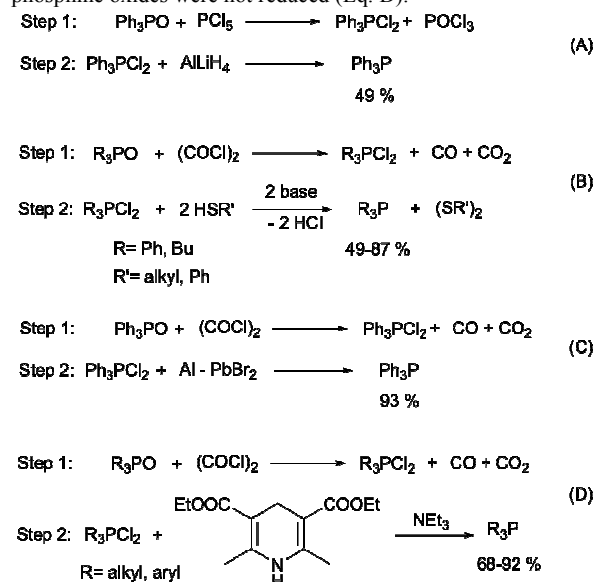
Figure 12: Proposed mechanism for the reduction of hydroxyphosphine oxide with borane

4. Two steps reduction: the phosphonium pathway promoted by halogens or alkylating agents (indirect method)

Up to here, the reduction of the $\text{P}=\text{O}$ double bond proceeded by action of a reducing agent in the presence or not of a catalyst. The general mechanism can be described as two main steps: the $\text{P}=\text{O}$ bond activation by reducing reagent $\text{X}-\text{Y}$ ($\text{X} = \text{H}$ or Si , $\text{Y} = \text{B}$, Si , Al or Ti) to form a radical or a phosphonium intermediate followed by the hydride delivery. Reducing reagents are involved both as activator and reductive agent. In this section we will focus on the cases where the phosphonium is generated by halogens or alkylating agents and subsequently reduced with common reducing agents.

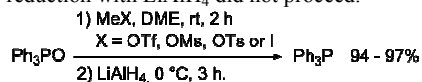
Non-stereoselective reduction

In 1958, Horner and co-workers described the formation of the triphenylphosphine dichloride Ph_3PCl_2 after reaction of triphenylphosphine oxide with PCl_5 . After its subsequent reduction with LiAlH_4 , the desired triphenylphosphine was obtained in 49% yield (Eq. A, Scheme 33).^{ib} Later, Masaki and Fukui described the formation of phosphine dichloride promoted by reaction with oxalyl chloride or trichloromethylformate. The following reduction with thiols in the presence of triethylamine afforded the corresponding phosphines in moderate to good yields (49-87%) (Eq. B).^{ix} Tanaka's group also used a modified methodology by adding a catalytic amount of Al /metal salt to a solution of phosphine dichloride (Eq. C).^{ixb} Recently, Luo and co-workers employed Hantzsch's ester in the presence of triethylamine (7 equiv.) to reduce the preformed phosphine dichlorides. The reaction was efficient on various triarylphosphine oxides (yields > 68%). Nevertheless secondary phosphine oxides were not reduced (Eq. D).^{ixc}

Scheme 33: Reduction of phosphine oxides through phosphine dichlorides intermediates (Eq. A^{ib}, B^{ix}, C^{ixb}, D^{ixc})

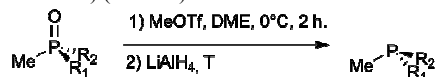
Stereoselective reduction

Imamoto and co-workers developed a two-step sequence allowing the reduction of chiral phosphine oxides with good to high enantioselectivity.^{lxxi} Phosphine oxide reacts first with MeX and the resulting *O*-methylated phosphonium salt was reduced with LiAlH₄ (Scheme 34). Among the various electrophiles screened, methyl triflate or tosylate or mesylate or iodide proved to be highly efficient giving, for instance, triphenylphosphine with a yield up to 94%. Importantly, in this case, the direct reduction with LiAlH₄ did not proceed.



Scheme 34: Reduction of triphenylphosphine oxide through formation of *O*-alkyl phosphonium salt

MeOTf was found to be the best reactant for the reduction of various chiral phosphine oxides (Scheme 35). The chiral phosphines or phosphine boranes were obtained in good to excellent enantiospecificities with inversion of configuration (88 to 98 % e.e.) (Table 2).



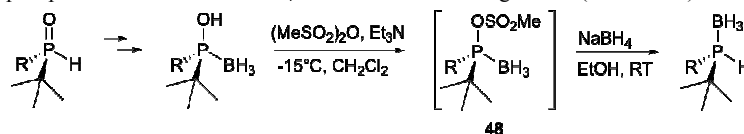
Scheme 35: Synthesis of optically pure phosphines

Table 2: Reduction of enantiomerically pure phosphine oxides

Entry	R ₁	R ₂	Temp (°C)	Yield (%) ^a	% e.e. (configuration)
1	Np ^b	Ph	-50	92	97 (<i>S</i>)
2	Np ^b	Ph	-60	90	98 (<i>S</i>)
3	Ph	<i>o</i> -MeOC ₆ H ₄	-60	85 ^c	98 (<i>R</i>)
4	<i>c</i> -C ₆ H ₁₁	<i>o</i> -MeOC ₆ H ₄	-60	74 ^c	95 (<i>R</i>)
5	<i>c</i> -C ₆ H ₁₁	Np ^b	-60	81 ^c	88 (<i>R</i>)
6	Ph	<i>o</i> -iPrC ₆ H ₄	-60	97 ^c	98 (<i>R</i>)
7	(CH ₂) ₂ Ph	<i>t</i> -Bu	-60	55 ^c	97 (<i>R</i>)
8	(CH ₂) ₂ Ph	<i>c</i> -C ₆ H ₁₁	-60	96 ^c	92 (<i>R</i>)

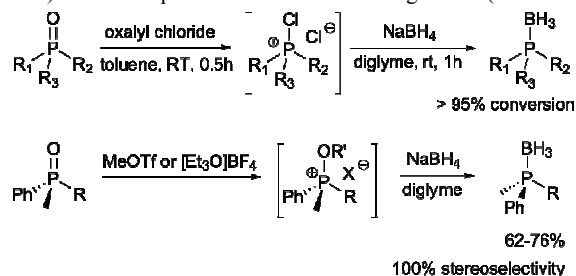
^a Isolated yield. ^b Np = 1-naphthyl. ^c Isolated as the phosphine-borane.

The safe and friendly sodium borohydride was used as both reducing and protecting reagent. Stankevič and Pietrusiewicz^{viii} and our group^x found that sulfonyloxyphosphine borane **48** isolated or formed *in situ* from reaction of optically pure phosphinous acid borane with mesyl chloride or mesyl anhydride could be stereoselectively reduced into secondary phosphine-boranes with NaBH₄ with inversion of configuration (Scheme 36).



Scheme 36: Access to optically pure secondary phosphine borane

Rajendran and Gilheany^{vid} developed a one-pot transformation that involved the treatment of various secondary and tertiary phosphine oxides with oxalyl chloride in toluene, and then addition of NaBH₄ in diglyme to form corresponding phosphine-boranes in excellent yields. In the first step, the *in situ* formation of chlorophosphonium salt was identified by ³¹P-NMR spectroscopy. Under similar conditions, the enantiomerically enriched P-stereogenic oxides gave racemic phosphine-borane compounds. The racemisation process is induced by the presence of the chlorine counter ion, which can behave as nucleophilic reagent (degenerate nucleophilic substitution^{lxxii}). Interestingly, using alkylating reagents such as methyl triflate or triethyloxonium tetrafluoroborate (Meerweim's salt) afforded stereoselectively phosphine-boranes in good yields (62-76%) with the expected inversion of P-configuration (Scheme 37).



Scheme 37: Stereoselective phosphonium formation followed by stereoselective reduction

When the reaction was carried out on P-chirogenic binaphthylphosphine **10** (MOPs) [2-(methylphenylphosphinyl)-2'-methoxy-1,1'-binaphthyl], the diastereoselectivity depends on the starting diastereomer substrate (See Scheme 13 and Table

1). For instance, phosphine oxides **10a** and **10b** formed phosphines **11a** (83% yield, 92/8 d.r.) and **11b** (70% yield, 86/14 d.r.) respectively. The anchimeric assistance of the OMe is assumed to play a role on the stereochemical outcome.^{via}

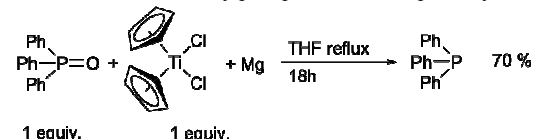
5. Other reagents and methods

- Calcium hydride

In 1964, Fritzche and co-workers^{xi} reported the reduction of triphenylphosphine oxide with calcium hydride at high temperature (350-400°C) giving benzene and triphenylphosphine in moderate to good yields (38-63%). The dismutation by cleavage of C-P bond occurred in this process.

- Titanium

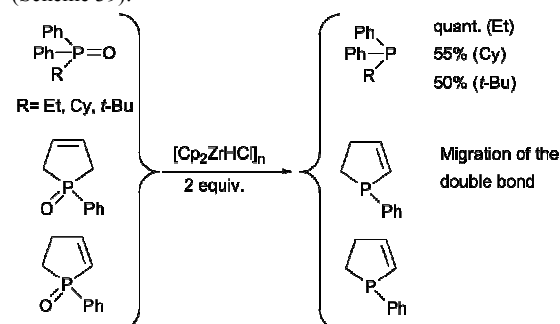
Mathey and Maillat employed a stoichiometric amount of Cp_2TiCl_2 in the presence of magnesium to reduce different aryl phosphine oxides.^{ixiii} Up to 70% yield was obtained in the case of triphenylphosphine. The titanocene amount has to be strictly stoichiometric, otherwise the yield decreased dramatically. It is noteworthy that this reducing system was not chemoselective. Notably phospholenes were partially isomerised under these conditions (Scheme 38).



Scheme 38: Reduction of triphenylphosphine oxide with dichlorotitanocene and magnesium

- Zirconium

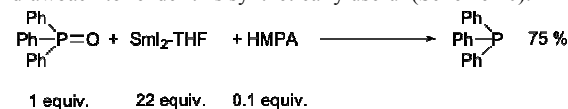
The Schwartz reagent (Cp_2ZrHCl)_n was used by Majoral and co-workers^{ixxiv} in order to reduce aryl/alkyl phosphine oxides with moderate to excellent yields (50-100%). Phospholene oxides can also be reduced but no yield was reported. In the case of the 2,3-phospholene, the reaction occurred with migration of the double bond on the corresponding dihydrophosphole (Scheme 39).



Scheme 39: Reduction of phosphine oxide with the Schwartz reagent

- Samarium

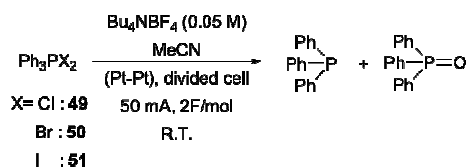
In 1989, Inanaga and co-workers^{ixxv} developed a general method for deoxygenation using samarium iodide in large excess in THF with hexamethylphosphoric acid. The triphenyl phosphine was obtained from its oxide with 75% yield after 16h. The reaction rate is very slow for this kind of substrate and the use of 22 equivalents of samarium iodide represents a major drawback to render this synthetically useful (Scheme 40).



Scheme 40: Samarium reduction of phosphine oxides

- Electrochemistry

More recently, Tanaka and co-workers proposed an indirect method using electrochemical reduction.^{ixxi} The electroreduction of triphenylphosphine dihalides was investigated according to the nature of the halogen (Cl-**49**, Br-**50** or I-**51**) (Scheme 41, Table 3 Entries 1-3). The diiodide compound **51** was found to be the most reactive giving 40% of phosphine. Only 2% of phosphine was obtained starting from the dichloride **49**. The difference of reactivity was explained according to the nature of the intermediate; between the five-coordinate phosphine dichloride **49** and the four-coordinate iodophosphonium iodide salt **51**. With the latter, the electron density on the phosphorus atom is lower compared to **49** therefore it is more reactive. In order to enhance the reactivity of **49**, addition of a Lewis acid (AlCl_3) was added and, indeed, this significantly increased the yield up to 37% (Entry 4). AlCl_3 was formed *in situ* by electrolysis of a sacrificial Al-anode. After optimisation of the concentration, the electrolytes nature, and the constant current up to 84% yield was obtained. A comprehensive study on the role of various counter anions for the phosphonium salt formation and on the electrolytes nature was reported.^{ixc} The possibility to promote the electroreduction by addition of trimethylsilylchloride, which helps to activate the oxygen atom, was also reported.^{ixd,e}



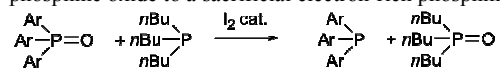
Scheme 41: Electroreduction of different halophosphonium halides

Table 3: Electroreduction of different halophosphonium halides

Entry	Phosphonium	Method	Yield of triphenyl phosphine (%) (determined by G.C)	Recovery of triphenyl phosphine oxide (%) (determined by G.C)
1	49	Divided cell	2	98
2	50	Divided cell	38	62
3	51	Divided cell	40	60
4	49	+ AlCl ₃ (1 equiv.) undivided cell	37	47

- Iodide catalysis

In 2011, Kullberg and Laven patented the use of iodide to catalyse the transfer of the oxygen atom from electron-poor phosphine oxide to a sacrificial electron-rich phosphine (Scheme 42).^{lxxvi}



Scheme 42: Oxygen transfer catalysed by iodide

Conclusions and outlook

Since 70 years, phosphines have emerged as a preeminent class of organic compounds, which hold ubiquitous applications serving as versatile ligands for transition-metal catalysed reaction and as useful reagents in a wide array of organic transformations such as Wittig, Staudinger, Mitsunobu, Baylis-Hillman and Appel reactions among others. These applications have found a growing interest in asymmetric catalysis by using chiral phosphines as ligands or organocatalysts. The chirality of these phosphines can be located either on the backbone or the phosphorus atom or both. Usually, tertiary phosphines are prepared through reduction of the corresponding phosphine oxides. As a proof of the chemists' interest, most of these protocols have been patented since the 1960's (around 30 patents). In the last decade, a renewed interest from an industrial point of view arises in this domain as illustrated by the 14 patents published notably by Gilheany's, Lemaire's, Tanaka's or Busacca's groups. This review emphasizes several reagents used successfully to reduce the P=O bond. These reagents share in common an oxophilic metal atom such as aluminium, boron, silicon, titanium, indium, copper activating the P=O bond toward a nucleophilic attack by hydrogen or silicium. Some mechanistic pathways for reduction of the phosphine oxides have been proposed from the dynamic stereochemistry and based on DFT-calculations. Starting from P-chiral phosphine oxides, silanes which represent the widest family of reducing agents, lead to phosphines with retention or inversion of configuration at phosphorus atom depending on the presence of additives (amine or catalyst). Titanium catalysed reductions of phosphine oxides by silanes have been developed allowing lower reaction temperatures and shorter reaction times. Under these safe and convenient catalytic conditions, cheap and easy to handle tetramethyldisiloxane can be efficiently used for large-scale production. We can expect that new catalytic systems will emerge in the near future as indium or copper showed recently some interesting activity. The indirect method is a two steps reduction based firstly on the formation of a phosphonium from the phosphine oxide and secondly with the reduction of this intermediate. Usually, halogens or alkylation agents promote the phosphonium pathway. In the coming years, this reduction method would be certainly considered to regenerate *in situ* the phosphine from phosphine oxide formed in several important organic reactions and thus change the use of phosphine from stoichiometric to substoichiometric amounts.

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