Polymethylhydrosiloxane: a versatile reducing agent for organic synthesis

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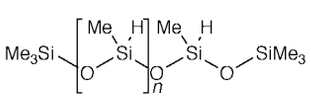
Received (in Cambridge, UK) 21st June 1999

Covering up to March 1999

1 Introduction

Reduction provides an important method for functional group interconversion in organic synthesis. The development of cleaner and safe synthetic methods and technologies for reduction to meet ever stricter environmental regulations remains an active area of organic chemical research.[1] Polymethylhydrosiloxane (PMHS) **1** is an attractive reducing reagent for environmentally benign reductive processes because it is inexpensive,[2] non-toxic[3,4] and stable to air and moisture. This is in marked contrast to commonly used reducing agents such as lithium aluminium hydride, borane and hydrogen, which are all clearly hazardous. Although polymethylhydrosiloxane has been known and readily available for the past 50 years, it has only been used sparingly as a reagent for organic synthesis. However, the increasing number of papers describing its use as a reducing agent suggest that its potential has not been fully exploited and that it will be used much more commonly in the future.



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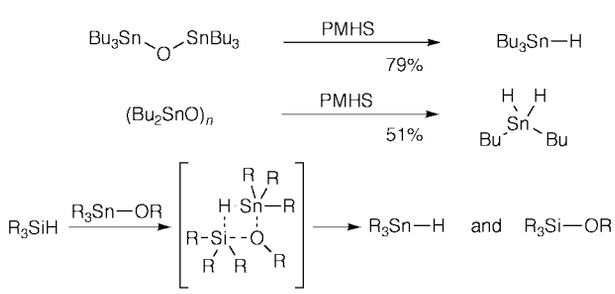
The first synthesis of PMHS was reported in 1946 by Sauer and co-workers.[5] Methyldichlorosilane is first hydrolysed in ether to yield a mixture of cyclic siloxanes, containing between 4 and 6 siloxane units. The linear polysiloxanes are prepared by equilibration of the cyclic siloxane with an excess of the 'end-capping' hexamethyldisiloxane by heating at moderate temperatures (60–150 °C). PMHS is commercially available and the reagent grade material has an effective mass per hydride of 60 g mol^{-1} and is typically a colourless free flowing liquid which is soluble in most organic solvents and is inert to air and moisture. It is this lack of reactivity in the absence of catalysts that makes PMHS such an attractive reducing agent. Numerous types of catalysts have been used in combination with PMHS to reduce a wide range of organic functional groups. The most frequently used catalysts are tin, titanium and palladium species, which mediate reduction *via* the corresponding metal hydride species. In these cases the catalysts act as sources of hydride transfer agents. Nucleophilic species, particularly fluoride ion, provide another class of catalyst which mediates reduction *via* the formation of hypervalent hydridosilicate species, thereby promoting hydride transfer directly from the silane.

In this review[6] we summarise the uses of PMHS as a reagent in organic synthesis in sections based on the type of catalyst employed.

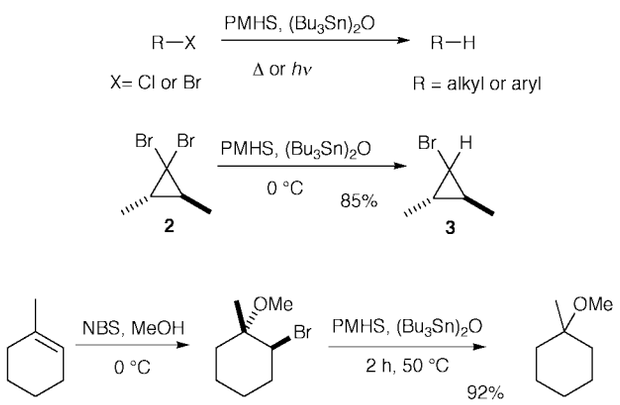
2 Tin catalysts

Many of the initial reports on the use of PMHS incorporate tin catalysts as hydride transfer reagents. In 1967 Hayashi and co-workers[7] used PMHS to prepare organotin hydrides from the corresponding tin oxide species. This represents a very useful method for the preparation of organotin hydrides and is superior to alternative methods such as reaction of an organotin halide with lithium aluminium hydride or sodium borohydride (Scheme 1). The organotin hydrides are separated from the *O*-cross-linked polymeric by-product simply by direct distillation from the reaction flask. The organotin hydride is produced *via* a σ-bond metathesis process involving silicon→tin transfer of hydride. PMHS is the best hydride donor from a series of silanes, the worst being trialkylsilanes. The best hydride acceptor was found to be dibutyldiethoxystannane; the order of reactivity is $Bu_2Sn(OEt)_2 > Bu_3SnOEt > (Bu_3Sn)_2O > (Pr_3Sn)_2O > Bu_2SnO > (Ph_3Sn)_2O > Bu_3SnOSiBu_3 > Bu_3SnOSiPh_3$. The reduction of the tin–oxygen bond in this way is a recurring theme in PMHS chemistry. PMHS compares favourably with other reducing agents (*e.g.* BH_3·THF) used to transform organotin oxides to the corresponding hydrides.[8] Significantly a wide range of potentially reducible functional groups is inert to PMHS but reactive towards BH_3·THF. It is interesting to note that the related transformations of R_3SnNMe_2,[9] R_3SnBr[10] or R_3SnCl[11]→R_3SnH are not effected by PMHS. The $(Bu_3Sn)_2O$–PMHS method has become probably the best way to make tributyltin hydride,[12] an important reducing reagent with many uses in organic synthesis.[13] The number of recent publications citing the method is testament to its efficiency. In some cases the tributyltin hydride made in this manner is superior to commercial material. For example, the reduction of certain alkyl iodides (ethanol, room temp., 2 h; 98%) can only be achieved efficiently with freshly prepared material.[14]



Scheme 1

It soon became clear that the isolation of the organotin hydride might not be necessary. Since silanes alone do not react readily with reducible functional groups, the use of an organotin oxide for the *in situ* preparation of tin hydride in the presence of PMHS was a possibility. Grady and Kuivila were first to show that this was indeed feasible.[15] They found that alkyl and aryl halides are reduced to alkanes and arenes by treatment with PMHS and tributyltin oxide (Scheme 2). The reduction of alkyl halides is as effective as the reaction employing pre-prepared organotin hydride. A comprehensive study was made of the reduction of aromatic and aliphatic chlorides and bromides. The reaction proceeds both thermally and photochemically; photochemical reactions provide improved yields at lower temperatures. Esters, nitriles, ketones and aldehydes are tolerated in these reactions. The process has also been applied to the stepwise reduction of geminal polyhalides. For example, dibromocyclopropane **2** is cleanly reduced to the monobromo derivative **3**. The method has also been used to reduce *gem*-dichlorocyclopropanes[16] and alkyl iodides[17] in a similar manner. The reduction of 1,2-bromoethers by the PMHS–$(Bu_3Sn)_2O$ combination represents a potentially useful two-step method for the preparation of ethers from alkenes.[18]



Scheme 2

The reductive cleavage of carbon–halogen bonds using tributyltin hydride generated *in situ* from PMHS has been effected on structurally complex substrates (Scheme 3). For example, Maeda and co-workers have used the reaction to prepare fluorinated steroid derivatives. The fluorobromo steroid **4** (obtained by bromofluorination of the 11,12-alkene) cleanly gives the reduced product **5** upon treatment with PMHS–$(Bu_3Sn)_2O$.[19] The adenine derivative **7** possessing a 3′-deoxyribose sugar is prepared by radical hydrodechlorination of the precursor **6** bearing a chlorine atom at the 3′ position.[20]

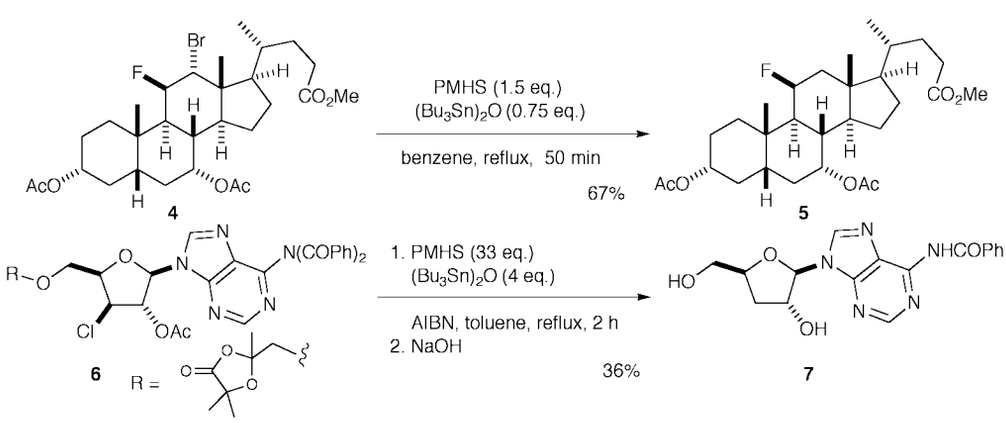
Several other applications of the PMHS–tin oxide method in carbohydrate research have appeared (Scheme 4). Stick and co-workers used the *in situ* method for generating tributyltin hydride to effect the Barton–McCombie reduction of the dithiocarbonate **8**.[21] The yield of the deoxy sugar **9** compares favourably to the 85% yield obtained by reduction with tributyltin hydride prepared *ex situ*. Prisbe and Martin have similarly prepared several 2′,3′-dideoxynucleosides, including 3′-deoxythymidine **11** *via* reduction of the corresponding methyl dithiocarbonate **10**.[22] Such reductive deoxygenation reactions are not always successful. For example, Madahavan and Martin reported that an unexpected radical mediated elimination occurs during the synthesis of the carbocyclic antibiotic aristeromycin.[23] In the attempted deoxygenation of the thiocarbonyl-imidazole derivative **12** using PMHS and $(Bu_3Sn)_2O$, only the alkene **13** is formed.

Tributyltin hydride generated *in situ* has been used in several methods involving reductive carbon–sulfur bond cleavage (Scheme 5). A phenylthio group is reduced with PMHS and tributyltin oxide in the presence of AIBN. Kawakami *et al.* used the process to prepare the 2′,3′-dideoxyadenine derivative **15** from thioether **14**.[24] The large excess of PMHS was probably used because the reaction was performed on a very small scale and the siloxane is inexpensive and not because of any great inefficiency in the process. Sekine and Satoh have developed a method for the selective synthesis of *N*-methylguanosine **17**, based on a similar reaction.[25] They found that both carbon–sulfur bonds of the 1,3-benzodithiolane derivative **16** are reductively cleaved by PMHS–$(Bu_3Sn)_2O$.

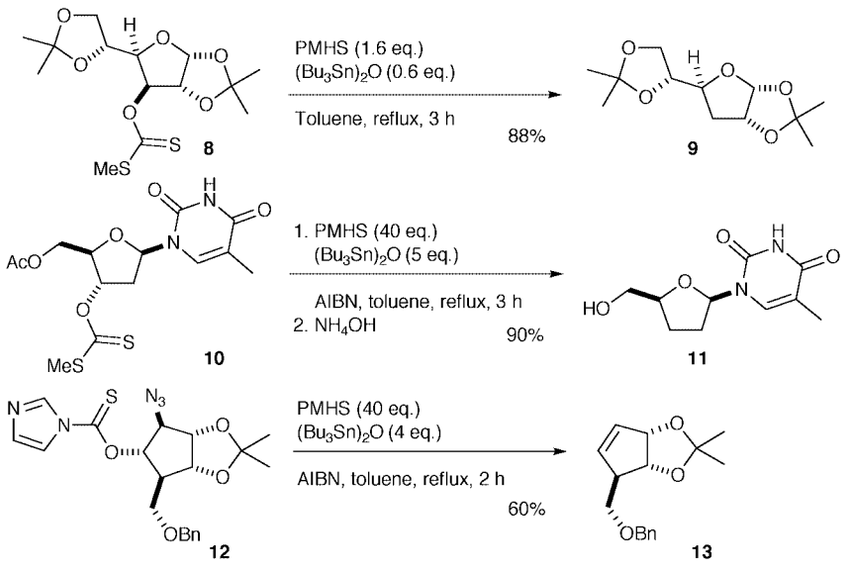
Tributyltin hydride generated *in situ* has also been used effectively to generate allenylstannanes from 2-(propargylthio)-benzothiazoles *via* a free radical process (*e.g.* **18**→**19**, Scheme 6).[26] A tributyltin radical adds to the alkyne to generate a β-stannyl-vinyl radical from which the benzothiazolylthio radical eliminates generating the allene. The yield of the reaction is the same as that using tributyltin hydride generated *ex situ*.

Tributyltin hydride has been used to reduce ketones, but the reactions are sluggish and require temperatures in excess of 140 °C in order to proceed at convenient rates.[27] Thus it is not surprising that the combination of PMHS and tributyltin oxide does not reduce ketones efficiently. However, Grady and Kuivila have demonstrated that carbonyl compounds are reduced by PMHS with dibutyltin oxide.[15] Ketones are efficiently reduced in an exothermic reaction at room temperature by dibutyltin dihydride. The reduction is accomplished in high yield by slow addition of the ketone and PMHS to a slurry of a stoichiometric amount of dibutyltin oxide in toluene at 25 °C (Scheme 7).

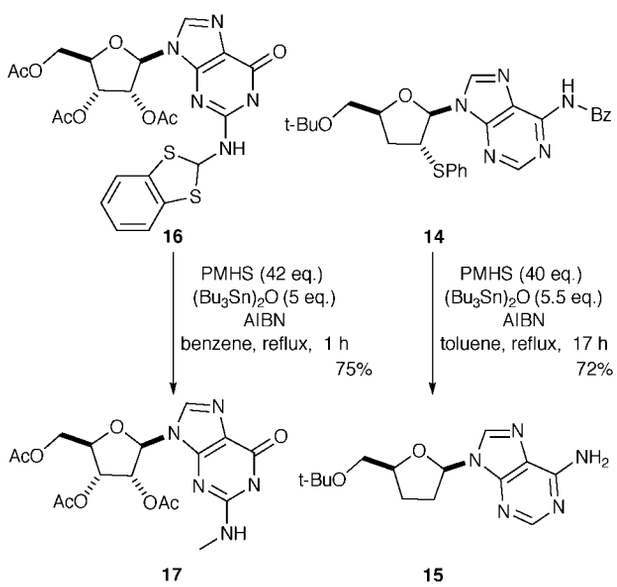
Whilst the *in situ* generated tributyltin hydride reaction clearly has advantages, it still requires at least a stoichiometric amount of the organotin oxide. In view of the toxicity of alkyltin compounds,[28] any process employing a catalytic amount of the organotin species would clearly be better. The first such process was described by Nitzsche and Wick in 1957.[29] They found that in the presence of a catalytic amount of dibutyltin dilaurate (2–5 mol%) in the presence of PMHS



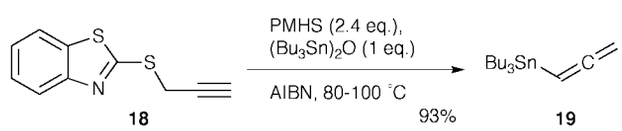
Scheme 3



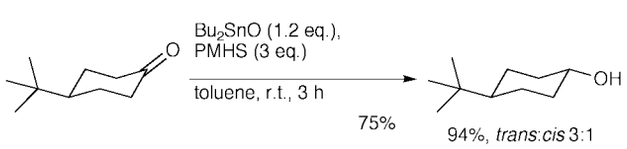
Scheme 4



Scheme 5

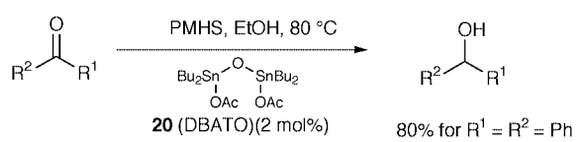


Scheme 6



Scheme 7

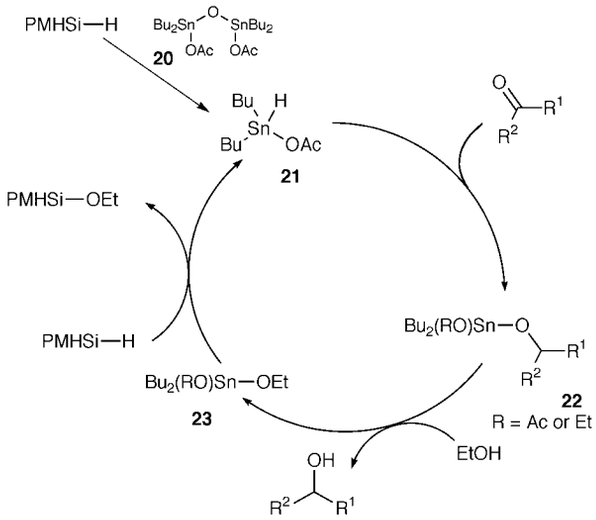
(or alternatively polyphenylhydrosiloxane) aldehydes and ketones are reduced to their corresponding alcohol.[30] The reaction proceeds rapidly at temperatures between 80 and 180 °C, but more slowly at room temperature. The key feature of the process is the use of protic solvent. The importance and basis of this finding has subsequently been described by other workers who have developed similar processes. In 1973 Lipowitz and Bowman[31] reported that bis(dibutylacetoxytin) oxide (DBATO) **20** acts in much the same way as dibutyltin dilaurate, when used with PMHS in protic solvents (Scheme 8). The reduction of aldehydes and ketones occurs in high yield. DBATO is the stable hydrolysis product of dibutyltin diacetate under neutral or mildly basic conditions[32] and is conveniently prepared by reaction of dibutyltin oxide and acetic acid. The reaction has many advantages over standard reduction protocols, namely, exclusion of air and water is unnecessary and the reaction requires no hydrolysis step.



Scheme 8

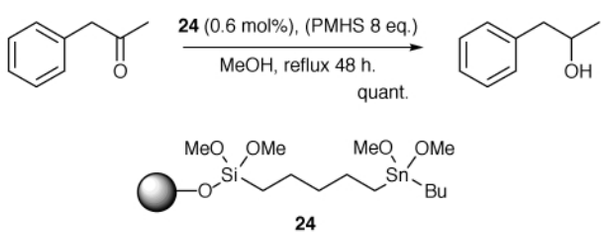
The reaction pathway proposed by Lipowitz and Bowman involves initial reaction of PMHS with DBATO **20** to form the actual reducing agent and catalyst dibutylacetoxytin hydride **21** which joins the cycle as depicted in Scheme 9. Hydrostannylation of the ketone occurs in the normal manner[33] to generate the alkoxytin species **22** *via* a pathway analogous to that of the tributyltin hydride reduction of ketones in methanol. The hydride participating in this reaction was thought to be either dibutylacetoxytin hydride **21** or dibutyltin dihydride. Although acetoxytin species are known to undergo a rapid disproportionation reaction in favour of the dihydride and the diacetate,[34] there is evidence that the actual reducing species is the acetoxytin compound **21**. For example, differences in stereoselectivity are observed in the reduction of 4-*tert*-butylcyclohexanone using dibutyltin dihydride and the DBATO–PMHS system. The PMHS–DBATO system gives exclusively *trans*-4-*tert*-butylcyclohexanol, whereas the reduction of the same substrate with dibutyltin dihydride gives a 7:1 mixture of *trans*:*cis* alcohols.[35] The next step in the catalytic cycle involves solvolysis of the alkoxytin species **22**, generating a new organotin alkoxide **23** which is reduced by PMHS regenerating dibutyltin hydride species **21**. The reduction of the more sterically encumbered tin alkoxide **22** is presumably slow; it is known that tin alkoxides derived from primary alcohols are reduced more rapidly than those derived from secondary and tertiary alcohols.[36] This type of tin alkoxide solvolysis has been used to good effect in other tin hydride mediated methodology.[37,38]

Matlin and Gandham have used a polymer-supported tin catalyst **24** in a similar fashion.[11] An organotin dialkoxide



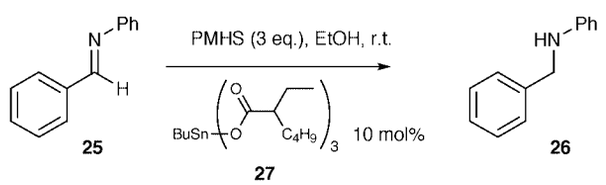
Scheme 9

species was attached to silica coated non-porous glass beads. The resulting material catalyses the PMHS reduction of aldehydes and ketones (Scheme 10). The easily recovered catalyst was cycled through four consecutive reduction sequences without any loss of activity.



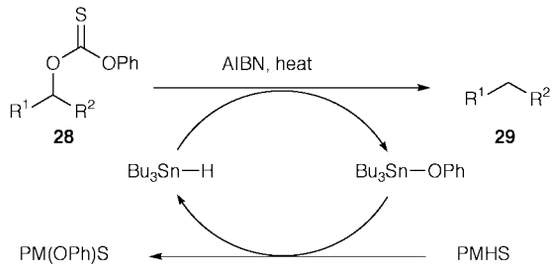
Scheme 10

Fu and Lopez[39] have used tin catalysts to reduce imines with PMHS. Imines derived from either aldehydes and ketones are reduced with PMHS in the presence of *n*-butyltin tris(2-ethylhexanoate) **27**. For example, the reduction of *N*-benzylideneaniline **25** cleanly gives *N*-phenylbenzylamine **26** in 82% yield after 7 h at room temperature (Scheme 11). The protocol is chemoselective for imine functionality in the presence of halides, esters, epoxides, nitriles, alkynes and olefins. However, aldehydes and ketones and nitro compounds are also reduced.



Scheme 11

Fu and co-workers have established several other applications of PMHS which involve the use of a catalytic amount of tributyltin hydride.[40] A striking example of this is the modified Barton–McCombie deoxygenation of alcohols **28**→**29** (Scheme 12).[41] Using PMHS they have been able to avoid the large excess of tributyltin hydride usually used for this transformation. The radical mediated reduction of the thiocarbonate by tributyltin hydride occurs in the usual fashion. The PMHS plays its role by reducing the tributyltin phenoxide and thereby regenerating the organotin hydride. The benefits of using the inexpensive, non-toxic silane as the stoichiometric



Scheme 12

reducing agent and a catalytic quantity of the toxic tin species are clear. Azides are reduced to primary amines in a similar fashion.[42] In this case the initial reduction of azide by tributyltin hydride produces a tributyltin amide, which reacts with *n*-propanol to give tributyltin propoxide which is reduced to tributyltin hydride by PMHS.

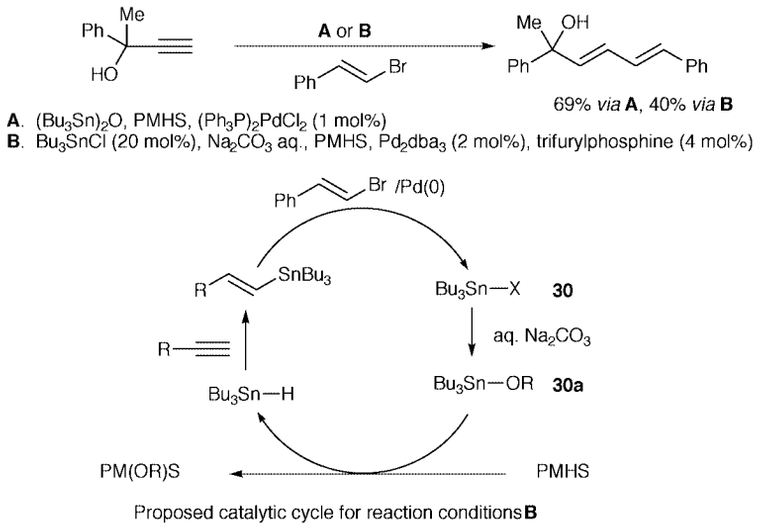
Maleczka and Terstiege have used PMHS to generate tributyltin hydride *in situ* from $(Bu_3Sn)_2O$ in an elegant synthesis of dienes from alkynes and vinyl halides.[43] The process occurs *via* the hydrostannylation of the alkyne followed by palladium catalysed Stille coupling of the resulting vinylstannane and the vinyl halide (Scheme 13). Since the process requires a stoichiometric amount of the organotin species, a protocol involving a catalytic quantity of organotin species was devised. Using tributyltin chloride (20 mol%) in the presence of aqueous sodium carbonate results in yields of the hydrostannylation–Stille coupling process approaching that of the stepwise process using a stoichiometric quantity of tributyltin chloride. According to the proposed catalytic cycle the tributyltin halide **30** produced in the Stille coupling is transformed into an organotin alkoxide **30a** which is reduced by PMHS to tributyltin hydride; the direct reduction of tributyltin halide by PMHS does not occur.

Terstiege and Maleczka have also developed another method for the generation of tributyltin hydride from Bu_3SnCl using PMHS. They found that hydride transfer from PMHS to Bu_3SnF (generated under the reaction conditions from Bu_3SnCl) could be effected by the action of potassium fluoride.[44] As noted above, PMHS alone does not reduce tin halides. It is assumed this hydride transfer occurs *via* a hypervalent silicate species. It remains to be seen whether this process will compete with Hayashi's process of H-transfer from PMHS to $(Bu_3Sn)_2O$. More importantly, the method is attractive since the tributyltin species can be used in catalytic quantities in several radical mediated processes quite successfully. For example, aryl halides are reduced to the corresponding arenes; radicals generated from alkyl halides cyclise onto alkenes efficiently (**31**→**32**, Scheme 14).

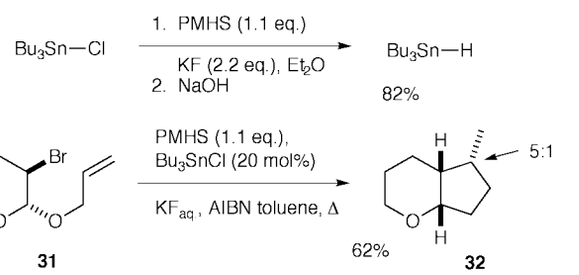
3 Titanium and zirconium based catalysts

In 1991, Buchwald and co-workers[45] reported a mild and highly efficient method for the reduction of esters by triethoxysilane and a titanocene catalyst. The catalyst is generated *in situ* from bis(cyclopentadienyl)titanium dichloride and n-BuLi (2 equiv.) (Scheme 15). Alkenes, epoxides, alkyl bromides are tolerated in the reduction. Not surprisingly, the reagent reduces ketones; methyl esters are reduced selectively in the presence of *tert*-butyl esters.

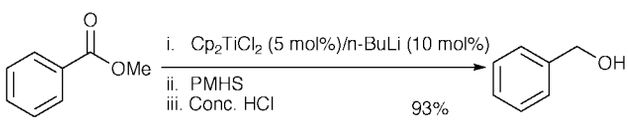
It was noted that the toxic trialkoxysilane could be substituted by PMHS. This is very important, as titanium catalysts are known to cause the disproportionation of trialkoxysilanes,[46] thereby generating pyrophoric SiH_4.[47] The use of Cp_2TiMe_2 is also known to generate $MeSiH_3$ from PMHS at room temperature;[48] methylsilane is not normally pyrophoric.[47] The proposed catalytic cycle involves reduction of the carbonyl group by a titanium hydride species **34** (Scheme 16). This is regenerated by hydride transfer from the silane to titanium *via* a σ-bond metathesis process **33**→**34** *via* **35**. Precedent for this



Scheme 13



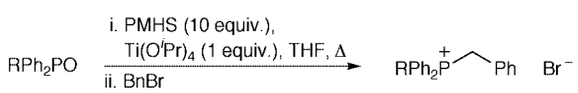
Scheme 14



Scheme 15

latter type of reaction is found in the studies of Woo and Tilley.[49] The reduction of titanium(IV) alkoxides to titanium(III) species *via* a titanium hydride has also been reported by Albizzati and co-workers.[50] The use of PMHS as a substitute for triethoxysilane in the process was reported in full in 1994. In this work the titanocene catalyst is activated by ethylmagnesium bromide (Scheme 16).[51] It should be noted that in contrast to the organotin mediated PMHS reductions, the product of the initial reaction is a silyl ether, and a separate acid or alkaline work-up is required to obtain the product alcohol.

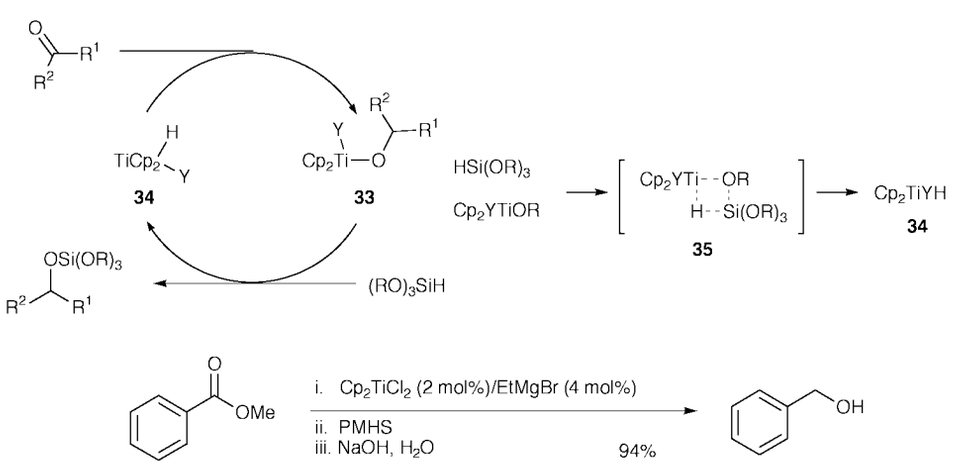
In 1992, the titanium–triethoxysilane system was refined to utilise titanium(IV) isopropoxide as the source of the catalytic species.[52] At that time we had need for an efficient synthesis of phosphines. We showed that $Ti(O^iPr)_4$–triethoxysilane system could efficiently effect the reduction of phosphine oxides.[53] At least two equivalents of triethoxysilane are essential. The reaction, which proceeds quantitatively, requires 10 mol% of $Ti(O^iPr)_4$ and is performed at 50 °C in THF. PMHS is an excellent replacement of triethoxysilane though a stoichiometric quantity of $Ti(O^iPr)_4$ is required for a convenient rate (Scheme 17). PMHS has previously been used to reduce phosphine oxides[54] and phosphonates[55] but under harsher (reaction temperatures exceeding 250 °C in the absence of a catalyst) and protic conditions.[56]



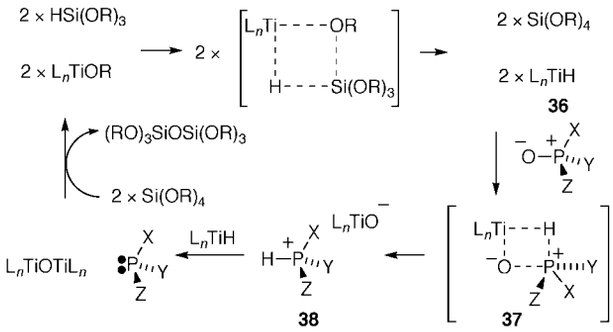
Scheme 17

The reduction of *P*-chiral phosphine oxides proceeds with retention of configuration at phosphorus. The proposed mechanism involves the reduction of the P–O bond by a titanium hydride species **36** (Scheme 18). The stereochemistry of the reduction is explained by a *syn* hydrotitanation type process giving the protonated phosphine **38** *via* **37** with overall retention of configuration.

Others have used the PMHS–$Ti(O^iPr)_4$ system to reduce

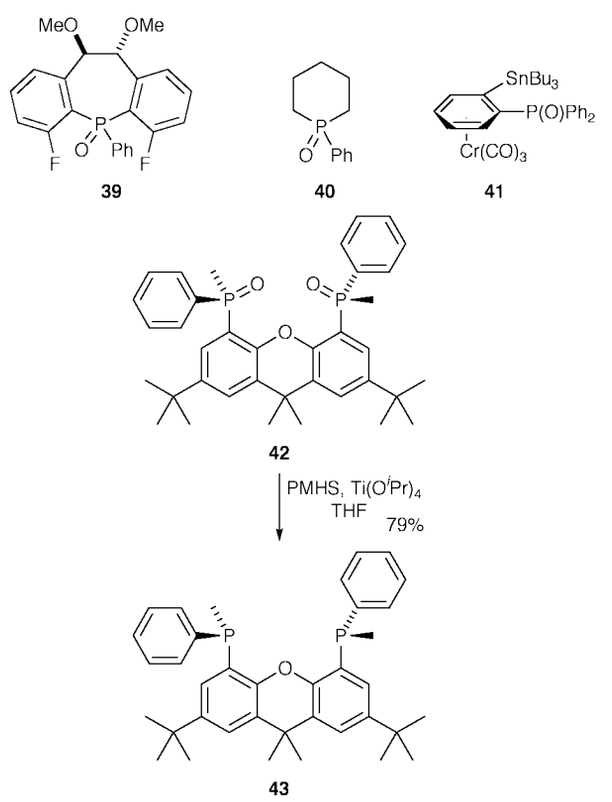


Scheme 16



Scheme 18

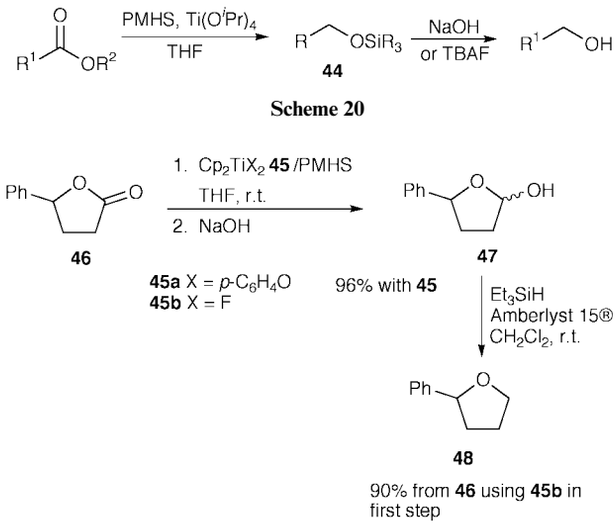
phosphine oxides (Scheme 19). For example, Warren and co-workers have reduced the phosphine oxide **39**[57,58] and triarylphosphine oxides.[59] We have used the reagent system to reduce diarylbenzylphosphine oxides[60] and 1-phenylphosphinane oxide **40**.[61] Simpkins and co-workers have also reduced the enantiomerically enriched tricarbonyl(η^6-arene)chromium complex **41**.[62] The stereoselectivity in the process has been used to good effect by Hamada and co-workers.[63] They prepared the bidentate phosphine (*S*,*S*)-**43** from its enantiomerically pure oxide (*R*,*R*)-**42** with complete retention of stereochemistry and in good yield.



Scheme 19

Our group[64] and Buchwald and co-workers[65] independently reported the Ti(O^{i}Pr)$_4$ catalysed PMHS reduction of esters (Scheme 20). The initial silyl ether **44** is hydrolysed to the corresponding alcohol with either NaOH solution or an equivalent amount of TBAF. The system is highly effective for the chemoselective reduction of carbonyl compounds. Functional groups such as bromo, chloro, nitro, olefins, alkynes, epoxides and cyclopropanes remained intact.

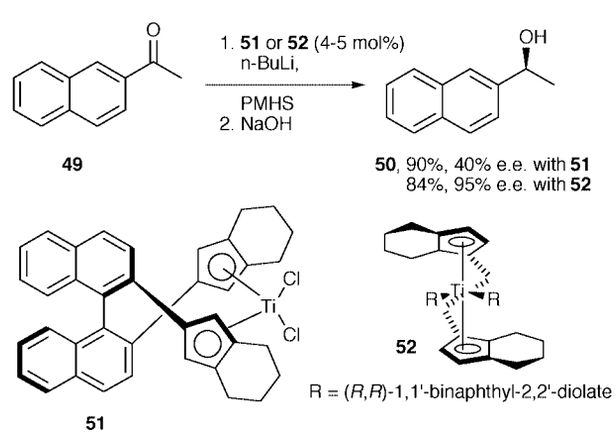
Buchwald and co-workers have found that a combination of the titanocene **45a** and PMHS effects the reduction of lactones **46** to lactols **47** (Scheme 21).[66] In the presence of a catalytic amount of TBAF on alumina the catalyst promotes the efficient room temperature hydrosilylation of lactones. The lactol is produced after a work-up consisting of treatment with hydroxide or TBAF–H_2O. The process is a useful alternative to DIBAL-H, which is commonly used to convert lactones into lactols. The titanocene difluoride **45b** is also an excellent catalyst.[67] The process has been combined with a second room temperature reaction to effect the overall conversion of lactones to cyclic ethers **48**.[68] The lactols are treated, without purification, with triethylsilane in the presence of Amberlyst 15® resin; this step does not necessitate the use of an inert atmosphere. The yields for the two-step process are good to excellent.



Scheme 20

Scheme 21

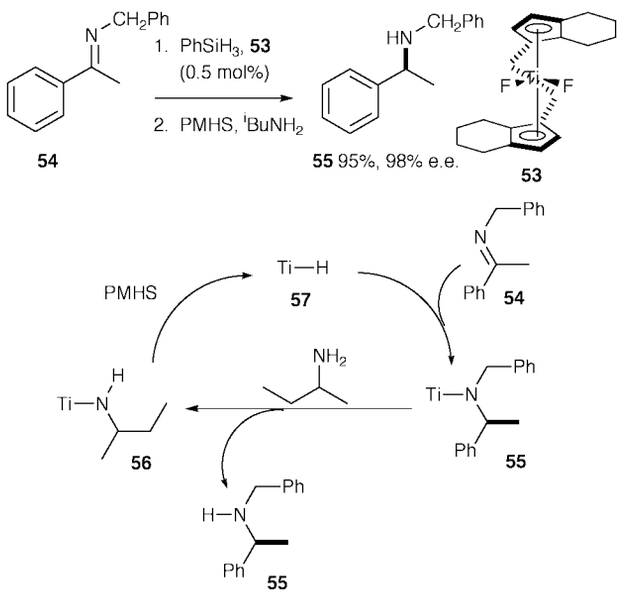
The modification of the titanium mediated hydrosilylation reaction to include enantioselective processes has also been studied. The first example was reported by Halterman and co-workers.[69] They used the enantiomerically pure titanocene derivative **51**; yields are good and accompanied with fair enantioselectivity in the best case (*e.g.* **49**→**50**) (Scheme 22). Buchwald and co-workers reported that the titanocene complex **52** is more effective for the catalytic asymmetric reduction of ketones.[70] The complex is again activated by addition of n-BuLi and promotes the enantioselective transfer of hydrogen from PMHS to prochiral ketones; a range of aryl alkyl ketones gives uniformly high enantioselectivity (typically with ees in the high 90s). Both research groups found that the enantioselectivity of the process is reduced when electron withdrawing groups are present on the aryl group.



Scheme 22

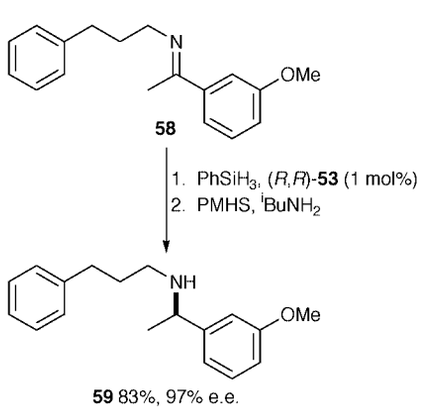
The related catalyst **53** effects the impressively efficient PMHS reduction of imines to secondary amines (**54**→**55**).[71] The titanium species is first reacted with phenylsilane to generate a titanium hydride catalyst **57**. The slow addition of *sec*-

butylamine results in exchange of amine ligands of the titanium complex to both release the amine product **55** and to give a species **56** which is reduced by PMHS to regenerate the titanium hydride species **57** as illustrated in Scheme 23. This is an effect similar to that of the alkoxy ligand exchange seen in the acceleration of several organotin mediated processes (Schemes 9 and 13). The σ-bond metathesis process must occur more rapidly for **56** than **55**.



Scheme 23

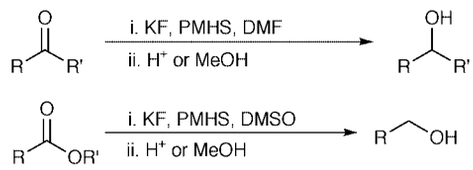
The protocol has been used in the highly efficient synthesis of the amine NPS R-568 **59**, a potently active compound for the treatment of hyperparathyroidism (Scheme 24) *via* reduction of the imine **58**.[72]



Scheme 24

4 Fluoride catalysts

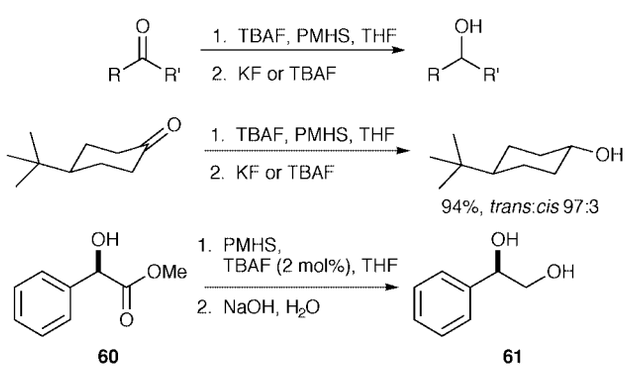
It has long been known that nucleophilic activation of silanes provides hypervalent silicate species which can act as powerful hydride donors.[73] Corriu and co-workers[74] have used potassium fluoride as a nucleophilic promoter for the reduction of carbonyl groups by PMHS (Scheme 25). In previous reports, the reaction had been achieved with the more toxic monomeric alkoxyhydrosilanes and more expensive caesium fluoride in the absence of solvent.[75,76] The rate of hydrosilylation is greatly accelerated by the use of DMF or DMSO as solvents. Using one equivalent of KF, the hydrosilylation reaction proceeds below 20 °C for aldehydes, between 30–60 °C for ketones and between 80–100 °C for esters. DMSO is used as the solvent for the reduction of esters, as at the temperature required for reaction, DMF is slowly reduced. The system is highly chemo-



Scheme 25

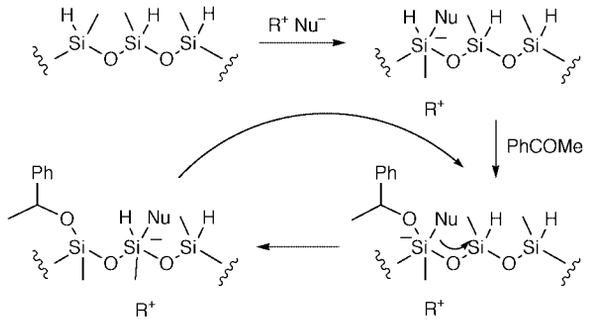
selective; the reduction of amides and acid chlorides proceeds very slowly, and imides and nitriles are unreactive. Isolated double bonds do not react under these conditions, but α,β-unsaturated substrates undergo 1,2- and 1,4-reduction (without appreciable selectivity). Due to the low solubility of potassium fluoride in the aprotic solvents used, it was proposed that the reactions proceed *via* a heterogeneous catalytic pathway. Potassium formate was also found to be an efficient catalyst for the reduction of aldehydes and ketones, but not for esters.

We have shown that tetrabutylammonium fluoride (TBAF) can be used as a fluoride source, soluble in an organic solvent, in a similar fashion.[77] We found that TBAF promotes the PMHS reduction of esters, ketones and aldehydes. At much the same time Kobayashi and co-workers[78,79] also demonstrated that aldehydes and ketones are reduced cleanly and in good yield to the corresponding alcohols with PMHS in the presence of TBAF (5 mol%) in THF (Scheme 26). The process is highly chemoselective and favours reduction of the carbonyl moiety over halide, nitrile and nitro functionality. The reduction of 4-*tert*-butylcyclohexanone occurs with axial delivery of hydride (*trans*:*cis* 97:3). The selectivity is opposite to that obtained with bulky hydride reagents such as the Selectride® family. A stereogenic centre adjacent to the carbonyl group of an ester is unaffected by the process. For example the reduction of (*R*)-methyl mandelate **60** (Scheme 26) yields the diol **61** in 90% yield (>99% ee).



Scheme 26

The TBAF catalysed reaction involving PMHS is much faster than with the corresponding monomeric silanes. This rate acceleration occurs by what we believe to be a new mode of catalysis. For example, acetophenone is reduced completely in less than 1 min using PMHS. However, when diethoxymethylsilane is used under identical conditions, the reaction is only 60% complete after one hour. This impressive rate acceleration is possibly due to the intramolecular transfer of nucleophile from the silicate to another silicon atom, as illustrated in Scheme 27 *via* a 1,3 mode of transfer; a process that is repeated over and over again as the nucleophile travels along the polymer backbone. The nucleophile involved in what we call *zipper* catalysis may, in principle, be the initial anion from NuR, or the hydride or alkoxide groups present on the polymer backbone. The intramolecular transfer need not be to the adjacent silicon atom. It is possible that 1,5- or indeed other types of intramolecular transfer are operating. The corresponding process of

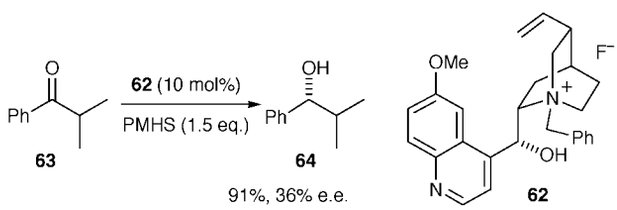


Scheme 27

nucleophile transfer in an intermolecular sense is presumably much slower.

Triton® B (benzyltrimethylammonium hydroxide) can be used as a cost-effective[80] replacement of TBAF. The reduction of acetophenone with Triton® B (2 mol%) is complete after only 3 minutes to yield 1-phenylethanol after work-up (99%). The reduction of cyclic ketones occurs with diastereoselectivity similar to the TBAF catalysed reactions. Esters and carboxylic acids are not reduced by PMHS with Triton® B but produce an amorphous gel, consistent with the PMHS having been cross-linked.

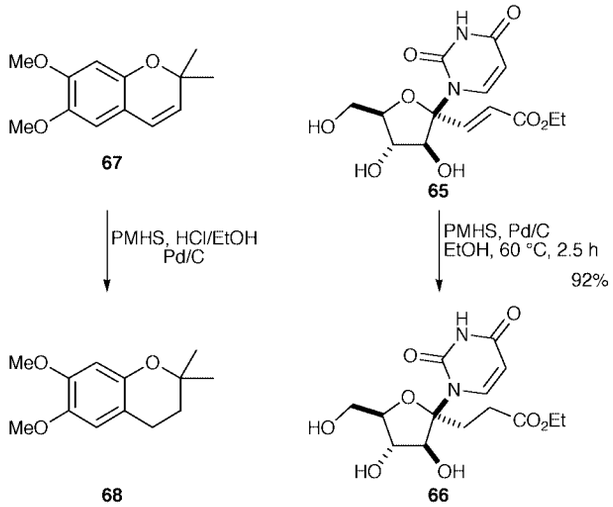
The asymmetric reduction of ketones can be achieved by the use of chiral ammonium fluoride salts (Scheme 28). For example, acetophenone is reduced with low enantioselectivity by *N*-benzylquinidinium fluoride **62** and PMHS.[81] Nevertheless, the reaction was faster than those involving alkoxysilanes, as might be expected from the zipper catalysis. The enantioselectivity of the process is governed by a weak interaction between the ketone and the chiral counter-ion.



Scheme 28

5 Palladium catalysts

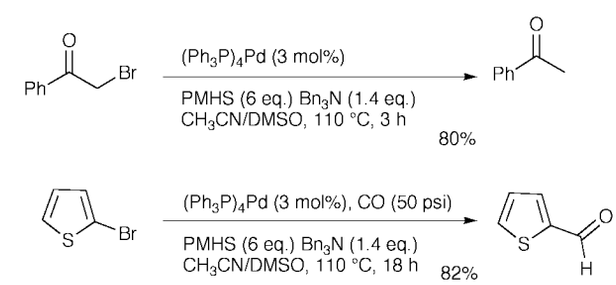
The first use of a palladium catalyst with PMHS was described by Lipowitz and Bowman.[31] The hydrogenation of terminal and *cis* olefins to alkanes, aromatic nitro compounds to anilines and aromatic aldehydes to substituted toluenes proceeds rapidly in EtOH with Pd/C. Thus PMHS is a convenient and safe replacement for hydrogen in those reactions involving low-pressure hydrogenations with Pd/C. Whilst the system behaves much like H_2 and Pd/C it should be noted that the reaction is not thought to proceed *via* formation of H_2. The lack of reactivity of *trans* alkenes enables the isolation of the pure *trans* olefin from a mixture of *cis* and *trans* isomers. For example, only the *cis* isomer of a mixture of non-2-ene (*trans*:*cis* 3:1) reacts with excess PMHS and Pd/C. However, this selectivity is not a general feature common to the reduction of all alkenes. *trans* Alkenes bearing an electron withdrawing group are reduced by PMHS and Pd/C. For example, α,β-unsaturated ketones react cleanly to give saturated ketones. The catalytic hydrogenation of the α,β-unsaturated ester **65** with PMHS and Pd/C gives the reduced product **66** in 92% yield (Scheme 29). Other hydrogen donors, such as cyclohexene, give poor yields, mainly due to competing deglycosylation.[82] The PMHS and Pd/C combination also reduces the carbon–carbon double bond of chromenes (*e.g.* **67**→**68**).[83] The conversion of aryl(perfluoro-



Scheme 29

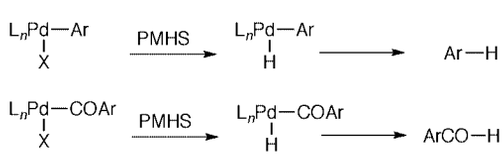
butyl)sulfones into the corresponding arene by the action of PMHS and Pd/C in ethanol–triethylamine is reported to be efficient. However, the isolation of the product is troublesome due to the formation of gels.[84]

Hydrogenolysis reactions with H_2 over heterogeneous transition metal catalysts, commonly Pd/C, is a widely applied reaction but limited to substrates lacking reducible functional groups such as nitro, olefin and carbonyl.[85] Hydrodehalogenation reactions using a soluble transition metal catalyst generally provides a more chemoselective reagent. These catalysts are not especially efficient when H_2 is used due to limited contact. Replacing the H_2 with soluble hydrogen donors overcomes this problem. Pri-Bar and Buchman[86] used PMHS and $(Ph_3P)_4Pd$ in this way to effect the dehalogenation of organobromides and iodides (Scheme 30). The PMHS–$(Ph_3P)_4Pd$ combination efficiently replaces the halogens of aryl halides, vinyl halides, α-halo ketones and acids with hydrogen. The system is highly chemoselective; the carbonyl group of aldehydes and ketones is unaffected by these conditions; carbon–carbon double bonds and nitro groups are not reduced. The reductive formylation of aromatic halides can be effected by carrying out the reaction under carbon monoxide.[87]



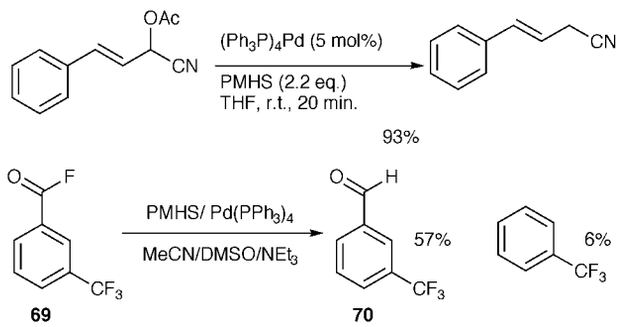
Scheme 30

The reaction is thought to proceed *via* hydrogen transfer to the complex formed by oxidative addition of the aryl halide to the $(Ph_3P)_4Pd$ catalyst (Scheme 31). The insertion of carbon monoxide into the Pd–Ar bond is presumably much more rapid than the reductive process involving the PMHS.



Scheme 31

Keinan and co-workers have investigated the reduction of the allylic acetates with PMHS and palladium(0) catalysts (Scheme 32).[88] Tributyltin hydride has also been used as the hydrogen source in similar reactions.[89,90] The hydrogen source clearly affects the selectivity of the reducing agents. For example, allylic acetates are cleanly reduced in the presence of α,β-unsaturated aldehydes by PMHS and $(Ph_3P)_4Pd$. In contrast α,β-unsaturated aldehydes are selectively reduced to saturated aldehydes with Bu_3SnH and $(Ph_3P)_4Pd$ in the presence of allylic acetates. Aromatic acyl fluorides are reduced to the corresponding aldehyde in the presence of PMHS and $(Ph_3P)_4Pd$ (Scheme 32).[91] In this case PMHS is a better reducing agent than hydrogen, giving significantly higher yields of aldehyde **70** from acyl fluoride **69**; reductive decarbonylation is a competing reaction giving a small amount of trifluoromethylbenzene.



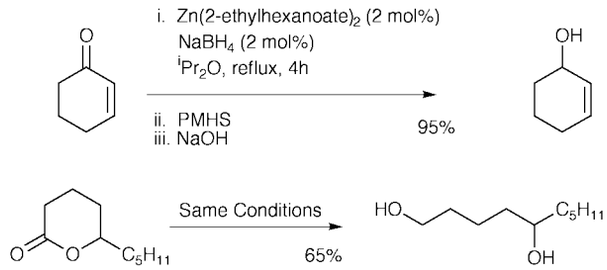
Scheme 32

PMHS in the presence of a rhodium(III) complex reduces a variety of functional groups with low conversions;[92] the catalyst can be recycled several times. Alkynes are reduced to alkenes with good *cis* selectivity; α,β-unsaturated ketones and esters are reduced in a conjugate fashion; substituted benzoyl chlorides are reduced to the corresponding substituted benzaldehyde. A similar process incorporating a $RhCl_3$–Aliquat 336 catalyst effects the transfer hydrogenation of diarylacetylenes with PMHS. For example, diphenylacetylene gives a 2:1 mixture of *Z*- and *E*-stilbene in 97% yield.[93]

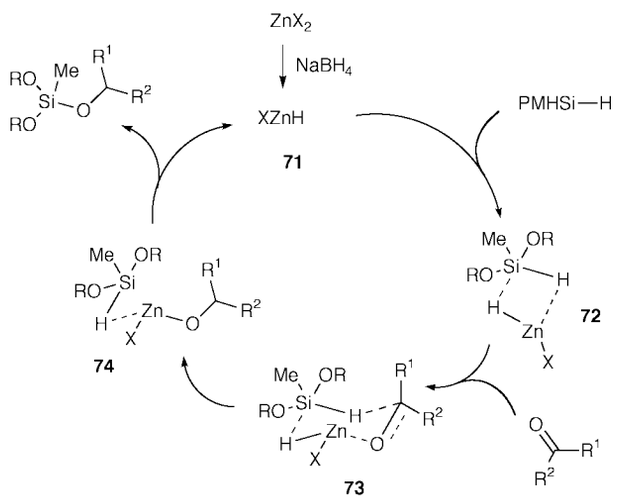
6 Miscellaneous catalysts

Mimoun has very recently described the reduction of carbonyl compounds to their corresponding alcohols using a stoichiometric quantity of PMHS in the presence of both a co-reducing agent, typically a metal hydride such as $LiAlH_4$ or $NaBH_4$ (Scheme 33), and a transition metal complex [*e.g.* Zn(II), Mn(II), Co(II), Fe(II), Cd(II) salts].[94] Unsaturated aldehydes, ketones and esters are reduced, without complication, to the corresponding unsaturated alcohols. Competing conjugate reduction of α,β-unsaturated ketones is observed when Cu(II), Ni(II), Pd(II), Ru(II) and Cr(II) salts are employed. The catalyst in the process, a zinc hydride species **71**, is first formed by reaction of sodium borohydride and the metal salt. The substrate and PMHS are then added to this zinc hydride. A mechanism involving a six-membered ring transition state has been proposed (Scheme 34). The zinc hydride species is first thought to produce the adduct **72**, from which hydride is transferred to the carbonyl compound *via* the transition state **73**. Transfer of the alkoxide from zinc to silicon in **74** both regenerates the zinc hydride species **71** and releases the silyl ether of the product alcohol. The catalyst system has also been used to produce silyl ethers from PMHS and alcohols, and secondary alcohols by reduction of epoxides of terminal alkenes. The technology for the reduction of esters to alcohols, which is particularly amenable to large scale applications, forms the basis of Morton's reagent Venpure™ ERS (Ester Reduction System).[95]

The zinc catalysed reaction has been modified, by use of a chiral diamine ligand, to enable a new approach to the efficient

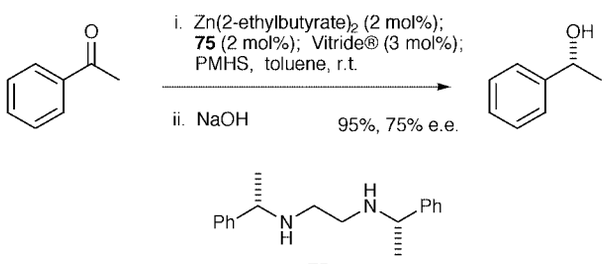


Scheme 33



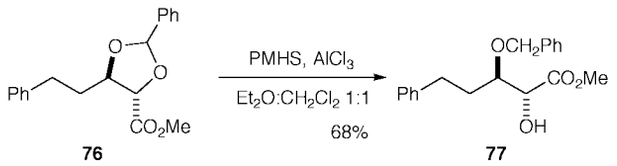
Scheme 34

asymmetric reduction of ketones.[96] The diamine **75**, prepared easily and inexpensively on a kilogram scale, in combination with PMHS and a zinc(II) compound effects the asymmetric reduction of aryl alkyl ketones in excellent yield and with good enantioselectivity (Scheme 35). The catalyst is prepared by mixing zinc(II) 2-ethylbutyrate sequentially with the diamine **75** and Vitride® [sodium bis(2-methoxyethoxy)aluminium hydride]. A similar catalyst derived from diethylzinc and the diamine was also developed and gives similar levels of enantioselectivity. The ligand **75**, albeit inexpensive, can be recovered and re-used. If the enantioselectivity of the reaction can be further improved the process will represent a safe, practical and cost effective method for the large scale asymmetric reduction of ketones.



Scheme 35

Chandrasekhar and co-workers[97] have disclosed a chemoselective reduction of carbonyl compounds with PMHS, catalysed by stoichiometric amounts of $ZnCl_2$. The reduction of a small number of functionalised aldehydes and ketones was examined at ambient temperature in ethereal solution to furnish the corresponding alcohol in satisfactory yield after purification. A report from the same laboratory outlines the use of $AlCl_3$ in combination with PMHS for the reductive ring opening of benzylidene acetals of 1,2- and 1,3-diols, thereby giving a mono-benzylated diol (Scheme 36).[98] The benzyl group is

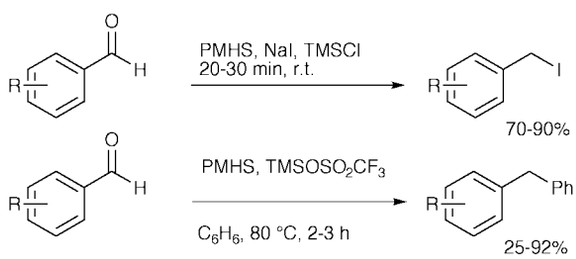


76 77

Scheme 36

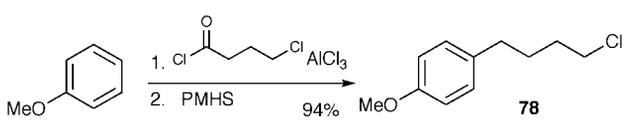
placed on the most sterically hindered of the hydroxy groups. Azide and ester groups are not reduced, and *tert*-butyldiphenylsilyl ethers of secondary alcohols are stable under these reaction conditions. The benzylidene acetal **76** is cleaved regioselectively to give the α-hydroxy ester **77**.

Palomo and co-workers have used PMHS to produce benzyl iodides from substituted benzaldehydes in the presence of iodotrimethylsilane, derived from NaI and chlorotrimethylsilane (Scheme 37).[99] The reaction, performed in the absence of solvent, is troublesome when applied to ketones and alkyl aldehydes. The related reaction of substituted benzaldehydes with PMHS and trimethylsilyl triflate in refluxing benzene, was also reported. The product diarylmethane is formed *via* a process incorporating sequential reduction and Friedel–Crafts alkylation.



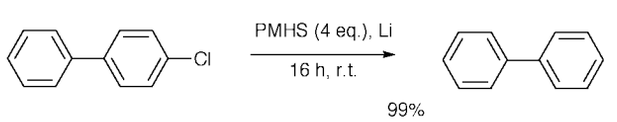
Scheme 37

A similar reaction involving the one-pot Friedel–Crafts acylation–reduction of arenes has been developed by Jaxa-Chamiec and co-workers.[100] For example, treatment of anisole with 3-chlorobutyryl chloride and $AlCl_3$ followed by addition of PMHS gives the alkylated product **78** in good yield (Scheme 38). PMHS has clear advantages over other silanes used in the process (*e.g.* triethylsilane), as an aqueous work-up is not required. The reaction mixture is simply stirred with damp silica gel and then filtered through a small silica plug.



Scheme 38

One final application nicely illustrates the potential of PMHS as an environmentally friendly reagent. PMHS and alkali metals dechlorinate toxic polychlorinated biphenyls at ambient temperature in tetrahydrofuran (Scheme 39).[101] The reaction is thought to proceed *via* the formation of an aryl radical, produced by the action of the sodium or lithium metal.[102] The aryl radical is reduced by the PMHS to generate the arene.



Scheme 39

7 Acknowledgements

We thank the EPSRC, the DTI and a consortium of chemical companies for a studentship (to M. D.) through the LINK Asymmetric Synthesis 2nd CORE Programme and to the EPSRC Catalysis and Catalytic Processes Programme for a studentship (GR/L57906 to S. B.).

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Review 9/03662H