Tetramethyldisiloxane: A Practical Organosilane Reducing Agent
Jaan Pesti and Gerald L. Larson*
Gelest, Inc., Morrisville, Pennsylvania 19067, United States

ABSTRACT: The chemistry of tetramethyldisiloxane (TMDS) is largely composed of the reduction of functional groups with increasing applications for carbon−carbon bond formation. This reagent can be a safe alternative to H₂, LiAlH₄, and other reactive reagents. Notable are the amide conversion to amines and aldehydes, nitro group reductions, nitrile reductions, hydrogenolysis of aryl-chlorine bonds, reductive formation of sulfides, reductive etherification, reductive opening of ketals, reductive demethoxylation, and formation of nitriles with homologation. Selectivity can be carried out by the choice of catalysts. This review of recent chemistry will focus on synthetically applied reactions of the recent past. Displayed reactions are chosen to be representative of the referenced work but are also chosen to illustrate a new viewpoint. Finally, where applicable, the results of competing hydrosilanes are presented to compare to the results obtained with TMDS.

INTRODUCTION
The recent past has seen the rise of hydrosilane chemistry as it permits a nearly unprecedented selection of functionality reduction. They can also introduce silyl groups when the silyl group is not hydrolytically removed after the initial reaction.1 The chemistry of 1,1,3,3-tetramethyldisiloxane (trimethylhexamethyldisiloxane, TMDS) is largely composed of reductions of functional groups, with increasing applications for carbon−carbon bond formation. The transformations effected by TMDS will be presented in order of category and approximately chronologically within each category. Observations regarding scaling reactions and obstructions to increasing the scale will be added where appropriate. This review of recent chemistry will cover synthetically applied reactions of the recent past with some excursions to decades before, without being exhaustive.

The various reductions presented should be considered to be largely universal unless limitations are mentioned. Yields reported are isolated yields of purified products wherever possible. Displayed reactions are chosen to be representative of the referenced work but are also chosen to illustrate an interesting angle. Finally, where applicable, the results of competing hydrosilanes are presented to compare to the results obtained with TMDS.

GENERAL CONSIDERATIONS
Tetramethyldisiloxane, commonly referred to as TMDS, is a bifunctional organosilane and the simplest of the family of the hydride-terminated polydimethylsiloxanes (Figure 1). TMDS is prepared by the careful hydrolysis of chlorodimethylsilane. Caution for this reaction is due to the generation of HCl during the hydrolysis and the sensitivity of the Si−H bond. Thus, at higher temperatures and extended reaction times, hydrolysis of the Si−H bond can occur leading to oligomeric siloxanes and dihydrogen. The material is stable to air and to moisture at neutral or near-neutral pH values. However, the Si−H moiety of TMDS is extremely reactive to strong base and somewhat less so to acid. TMDS as a further benefit displays a safe profile beyond the propensity to generate hydrogen in acidic or basic media. It shows an autoignition temperature of 245 °C.2 In addition to its considerable utility as a reducing agent, the topic of this review, its prime industrial use is as an end-capper in the synthesis of higher molecular weight hydride-terminated polydimethylsiloxanes.

The nature of the Si−H bond is such that the hydrogen is weakly hydridic, reflected by the Pauling electronegativity values of Si (1.90) and H (2.20). This feature makes organosilanes less reactive and more selective reagents for the reduction of an extensive range of organic functional groups. Moreover, the organosilane reductants can be modified both electronically and sterically via changes in the nonreactive groups attached to the silicon. The general topic of ionic and catalyzed organosilane reductions has been extensively reviewed.3−5 Because the Si−H bond is weakly polarized and the reactivity thereby compromised, most of the ionic silane reductions are carried out in the presence of an acid catalyst to render the substrate to be reduced somewhat positive in character. Thus, groups that can generate stable carbocations are, in general, readily reduced with organosilanes under mild conditions.

In general the organosilane reducing agents are more selective than the common reducing agents such as lithium aluminum hydride, borane, dibal-h, and sodium borohydride. Among the various organosilane reducing agents, triethylsilane has proved popular due to its availability, suitable physical properties, and a benign byproduct. The related silicon-based reducing agent, polymethylhydrogen siloxane (PMHS, 1, Figure 2) has the

Figure 1. Structures of TMDS and PMHS.
advantages of a high flashpoint and being the best economical option. The principle difficulties with PMHS have to do with a precise determination of the actual hydride content and the separation of the desired product from the polysiloxane byproduct.

The current pricing at 1000 kg lots place PMHS at ~$1.00 per mole of hydride; $3.90 for TMDS; $8.60 for Et₃SiH, and >$55 for Ph₂SiH₂ or PhSiH₃. On the other hand PMHS has the disadvantage of providing a silicone gel as the silicon-based byproduct, which can make product isolation difficult. Conversely, in applications where the desired product can be extracted from the gel with an organic solvent, the gel formation can become an advantage as the silicon-based byproduct is quantitatively and readily removed in those cases. Other silanes such as phenylsilane and diphenylsilane have shown promise in selected transformations but are considerably more costly to produce.

In terms of its chemoselectivity, a rather extreme example of a selective reduction carried out with TMDS is that shown in eq 1

\[
\text{(eq 1)} \quad \begin{align*}
\text{PhCl} & \xrightarrow{\text{TMDS}, 10\% \text{ Ni/C, Ph₃P}} \text{PhCH} & \text{(96\%, 15 h)}
\end{align*}
\]

wherein the aryl chloride is reduced in the presence of a sensitive carbonyl.

A further advantage to the silane reducing agents is the benign silicon-based byproducts that are formed. For example, with triethylsilane the byproduct is hexamethyldisiloxane, an inert and volatile substance that can be removed under pump vacuum, nonpolar solvents, or by chromatography. In the case of TMDS, the typical silicon-based byproducts are cyclic siloxanes, principally octamethylcyclotetrasiloxane. These, too, can be readily removed under reduced pressure or chromatographically. It should further be noted that silicon compounds and byproducts are essentially nontoxic.

Interestingly, the similar monohydridic, but structurally similar pentamethyldisiloxane, Me₅SiOSiMe₂H, demonstrated reduced reactivity in comparison to TMDS, possibly attributable to a manifestation of the so-called dual Si–H effect. 8–10 For instance, in the reduction of an amide, Me₅SiOSiMe₂H and other monohydridic silanes showed no detectable activity for the Pt-catalyzed reaction with dihydrocinnamamide. Yet a 90% isolated yield was attained when TMDS was substituted (eq 2). 10

\[
\text{(eq 2)} \quad \begin{align*}
\text{PhCONMe}_2 & \xrightarrow{\text{Pt catalyst, 3 h}} \text{PhCONMe}_2 & \text{(90\%)}
\end{align*}
\]

To a simple approximation, the adjoining silyl hydride atom enhances the reactivity of the other. Buchmeiser and Taori derived an explanation of the positive dual Si-effect that relies solely on steric considerations. 11 Nakatani and Nagashima performed a theoretical study on the platinum-catalyzed reduction of amides with hydrosilanes that bear dual Si–H groups. 12 Nagashima further published a detailed account explaining the proximity effect of two Si–H groups. 13

## SAFETY

TMDS is a relatively safe molecule compared to many used in organic synthesis. Of note is that it will not form monosilane, SiH₄, a notoriously pyrophoric and explosive gas. The formation of monosilane is a potential problem when using triethoxysilane, HSi(OEt)₃, which can disproportionate partially to monosilane (eq 3). 14,15 Moreover, triethoxysilane is known to cause serious eye irritation including blindness. The arylsilanes, for instance phenylsilane and diphenylsilane, have shown particular selectivity in a number of reductions, though they have the potential to form pyrophoric silanes via protiodephenylation under acid conditions (eqs 4 and 5).

\[
\begin{align*}
\text{(EtO)}_3\text{SiH} \xrightarrow{\text{disproportionation}} & \quad \text{(EtO)}_2\text{SiH} + \text{(EtO)}_2\text{SiH}_2 \\
& + \text{EtOSiH}_3 + \text{SiH}_4
\end{align*}
\]

\[
\text{ClSiH}_3 \rightarrow \text{Cl}_2\text{SiH}_2 + \text{Cl}_2\text{SiH} + \text{SiCl}_4 + \text{SiH}_4
\]

Perhaps the most problematic aspect of TMDS is its low flash point of 12 °C. This renders it a flammable hazard that requires the appropriate precautions in its handling. Overall its physical properties support its being considered as a robust, selective, and relatively easily handled reagent making it an ideal silicon-based reducing agent for consideration for larger scale applications.

## THE TMDS REDUCTION OF AMIDES TO AMINES

Amines are ubiquitous in organic synthesis, particularly so in active pharmaceutical ingredients. While they may be prepared by a variety of means, the reduction of amides is generally acknowledged to be one of the most difficult and least attractive transformations, requiring the use of strong, less selective hydrides such as LiAlH₄ or borane. 16–19 The use of forcing conditions, reactive reagents, difficult workups, and nonselective reactions has presented synthetic challenges for the reduction of amides to amines. Various combinations of TMDS and an appropriate organometallic catalyst have been used for an extensive range of selective reductions as the examples to follow will illustrate.

A triruthenium cluster catalyst, [(η⁵-C₅H₄NH)₃Ru(CO)]₃, enabled the reduction of the secondary amide to the amine (eq 6). 7 The authors had previously published the

To a simple approximation, the adjoining silyl hydride atom enhances the reactivity of the other. Buchmeiser and Taori derived an explanation of the positive dual Si-effect that relies solely on steric considerations. 11 Nakatani and Nagashima performed a theoretical study on the platinum-catalyzed reduction of amides with hydrosilanes that bear dual Si–H groups. 12 Nagashima further published a detailed account explaining the proximity effect of two Si–H groups. 13
There was a brief mention of TMDS during the hydrosilane screening results for the conversion of N,N-dibenzylacetamide to N,N-dibenzylethylamine in 51% yield.\textsuperscript{21} However, Et$_3$SiH proved a better hydrosilane in this conversion. All classes of secondary amides (aliphatic, aromatic, cyclic, chiral, N-alkyl, and benzylic) were smoothly converted to the amine hydrochloride salts, which were further converted to the free amines upon treatment with sodium carbonate. This overcame the problematic isolation of secondary amines due to their high polarity and the authors list 10 examples in 34–98% yield. They developed a clever means to eliminate ruthenium residues by first precipitating the product as the HCl salt, washing the salt with ether, and following this by recrystallization from cyclopentylmethyl ether. Conversion to the free base with sodium carbonate completed the pure and high-yield transformation that required no chromatography or distillation, allowing a practical method to produce secondary amines. In this study the advantage of bifunctional hydrosilanes, in particular TMDS and similar dihydridosilane reductants, was noted. The net result of this reduction is the alkylation of an amine in the absence of an alkyl halide. However, tertiary amines were best prepared by the use of PMHS (eqs 7 and 8).\textsuperscript{9}

Further work by the Nagashima group to replace the Ru with iron carbonyl catalysis produced mixed results.\textsuperscript{22} Both Fe(CO)$_5$ and Fe$_3$(CO)$_{12}$ catalysts were applicable for the reduction of tertiary amides either under thermal reduction or irradiation. While the thermal reaction did dehalogenate a substrate containing a benzyl chloride, this undesired side reaction was completely repressed using irradiation (eq 9).

Lower temperatures, less catalyst and reduced reaction times were required if the more costly dihydridodisilane 1,2-bis(dimethylsilyl)benzene was used in place of TMDS.\textsuperscript{23} (eq 10) While increased equivalents of the iron catalyst are sometimes required, it is worth noting that Fe(CO)$_5$ is inexpensive.

An extensive report on secondary and tertiary amide reductions, including aryl, aliphatic, and lactams made use of the commercially available chloroplatinic acid H$_2$PtCl$_6$ with TMDS.\textsuperscript{10} Usually platinum-based catalysts are not useful for the reactions of carbonyls; however, this protocol produced the corresponding amines in 56–95% yields (eqs 11–13). Monohydridic silane reducing agents as well as diphenylsilane gave no reaction under the conditions of the reaction. Several otherwise reducible groups such as nitro, cyano, ester, halogen, and akenes were tolerant of the conditions. A Pt$^{IV}$ complex as a result of a double oxidative addition of Si–H to Pt was proposed.

Of further benefit, the reaction may be worked up with strong acid to convert the products to water-soluble salts. The siloxane waste is retained in the organic layer. To further demonstrate the utility of the process, several “scale-up” reactions were performed at 5 g scale.

Beller and co-workers describe the development of a Zn(OTf)$_2$/TMDS system that was used to reduce secondary amides in 50 to 86% yield (eq 14). While largely consisting of benzamides and displaying varying yields, a variety of substituents, including keto, ester, nitro, cyano, diazo, and olefin, remained unreacted by the reaction conditions. The related disilyl reductant, 1,2-bis(dimethylsilyl)benzene, gave only a 5% yield in the reduction of N-benzylbenzamide. Tertiary amides were best reduced under these conditions using (EtO)$_2$MeSiH in place of TMDS.

This initial work was followed up with one wherein aromatic, heteroaromatic, and aliphatic secondary amides were reduced in excellent yields with TMDS in the presence of Cu(OTf)$_2$ and a pybox ligand 3 (eq 15). While the ligand is expensive, ~1 mol % seems to be only required, ameliorating the expense of the reaction. As experienced for the other reductions, no reaction occurred until the catalysts were added. The bis-silyl hydride effect manifested itself again with monosilanes being only slightly active reductants.
The reduction of primary amides to the corresponding primary amine is a problematic one. Lemaire has shown that this important transformation is possible with the combination of PMHS and the inexpensive Ti(O-i-Pr)4 albeit in stoichiometric quantities (eq 16).26 TMDS was investigated as well but the results were inferior to those obtained with PMHS.

Due to the somewhat acidic hydrogen present on secondary amides, they are more difficult to reduce than tertiary amides, oftentimes requiring the more reactive organometallic reducing agents, which are less tolerant of other functional groups. Sakai and co-workers reported on the reduction of secondary amides to secondary amines using a TMDS/InI3 system (eqs 17−19).27

Preliminary studies showed that Et3SiH/InBr3, PhSiH3/InBr3, and PMHS/InBr3 among others failed to bring about useful yields of the amine. Catalysis of the TMDS reduction with InCl3, InBr3, In(OAc)3, and In(OTf)3 all failed as well. Reduction with TMDS/InI3 was successful with both secondary aryl and aliphatic amides with yields ranging from 12 to 96%. N-Aryl amides proved easiest to reduce with N-benzyl amides requiring more forcing reaction conditions.

Adronov and co-workers demonstrated the TMDS/(C6F5)3B reduction of tertiary amides and N-phenyl secondary amides under mild conditions in 65 to 98% yields (eqs 20 and 21).28

While a number of systems showed no reaction, including NH-t-Bu, NHBn, NHEt, NHal, NH2, and p-(NC)PhCO, it is interesting that the nitro, bromo, and iodo groups all survive the reaction conditions to yield the corresponding amines. Although TMDS proved to be the best silane for these reductions, PMHS was also a useful reductant though in lower yield. Diphenylsilane and diphenylmethyilsilane were also shown to be effective reductants.

Blondiaux and Cantat found that TMDS/(C6F5)3B efficiently reduced tertiary amides although PMHS/(C6F5)3B was used preferentially in their study with yields from 49 to >99% (eq 22).29 Cyano and nitro groups were not tolerated. Significantly, they found that they were able to accomplish the reduction of primary amides with TMDS/(C6F5)3B when the primary amide was first monotrtrimethylsilylated (eq 23).

Chida and co-workers reported the high-yield conversion of amides, via a reductive Mannich approach with TMDS/IrCl(CO)(PPh3)2, to β-aminoesters via trapping of the intermediate imine with a silyl ketene acetal (eqs 24 and 25).

The imine intermediate could also be reacted in good yields with other nucleophiles including TMSCN, allyl tri-n-butyltin, allenyl tri-n-butyltin, and N-methylindole.30 Peripheral electrophilic groups such as an aliphatic methyl ester, aromatic nitro, aromatic nitrile, aromatic bromide, alkene, and benzyl chloride survived the reaction conditions.

Pannell and co-workers carried out a significant mechanistic investigation on the TMDS reduction of dimethylformamide to trimethylamine under promotion with Karstedt’s platinum (bis[1,3-bis(η5-ethylene)-1,1,3,3-tetramethyldisiloxane]platinum) catalyst (eqs 26 and 27). In this work the authors identified and isolated key intermediates.31 Thus, it was shown that the initial step was the hydrosilylation of the carbonyl to form an O-silylated hemiaminal 4.

There remains a need for methodology that allows for the reduction of primary amides as well as precludes or reduces the use of toxic and suspected carcinogens, and/or environmental
hazards. In this case benzene but also the solvents ether, chloroform, dichloroethene(ethane), and other poor choices are occasionally used for various reactions and will be flagged by this review.

As the examples show, the majority of amide to amine procedures function well for the reduction of both secondary and tertiary amides. There remains a need for methodology that allows for the reduction of primary amides.

**THE TMDS REDUCTION OF AMIDES TO ENAMINES**

Enamines are versatile synthetic intermediates as they are isolable nucleophiles that are able to act as enolates. They are typically prepared via the amination of aldehydes or ketones that themselves contain α-hydrogens. In a simplified approach, the catalysis/reduction system of TMDS/Ir[Cl(CO)(PPh$_3$)$_2$] was shown by the Nagashima group to efficiently convert amides that contain an α-hydrogen to (E)-enamines with yields of >98% (eq 28). Trace amounts of the saturated amine accompanied the desired enamines. In terms of product isolation it proved superior to use the less expensive PMHS/Ir[Cl(CO)(PPh$_3$)$_2$] system, as the iridium catalyst and the silicone byproduct was found to be conveniently removed by the O-cross-linking of the PMHS to form an insoluble polymer (eq 29). An ester, ketone, and primary bromide were all shown to tolerate the reaction conditions.

This was followed with applications of the methodology to π-conjugated enamines, which have demonstrated utility from the standpoint of their hole-transport properties. Based on their successful application of Vaska’s complex to the synthesis of enamines, this was the author’s first choice for the synthesis of the π-conjugated enamines. This, however, gave no reaction for such systems even at elevated temperatures. It was subsequently found that derivatives of Vaska’s complex bearing electron-withdrawing phosphorus ligands of general structure 5 from the ligands 6–9 proved to bring about the direct conversion to a silylated hemiaminal, for example 10, proved possible.

**THE TMDS REDUCTION OF AMIDES TO ALDEHYDES**

The reductive conversion of an amide to an aldehyde is, at first glance, counterintuitive as typically the reduction of an amide is much more difficult than the reduction of an aldehyde. These reductions tend to lead to over reduction to an alcohol or amine rather than the aldehyde.

The Schwartz reagent was shown to bring about the transformation of tertiary amides to aldehydes in high yields. Although the yields are high, the conditions mild, and other functional groups are well-tolerated under this protocol, the reagent was required in greater than one equivalent, rendering it impractical for large-scale applications. Zhao and Snieckus improved on the original version of this reduction via the implementation of an in situ generated Schwartz reagent from the less expensive dichlorozirconocene and LiAlH(OBu)$_3$. Advantages that accrue are cheaper starting materials, short reaction times, and good functional group tolerance.

Buchwald and co-workers reduced tertiary amides and one example of a secondary amide to the corresponding aldehydes with diphenylsilane under Ti(O-i-Pr)$_4$ catalysis. An epoxide, olefin, alkyl, nitrile, furan, and aromatic bromide all survived the conditions of the reaction. These reductions were limited to amides with α-protons as they pass through an intermediate enamine, which is subsequently hydrolyzed to the aldehyde.

A very practical approach to this useful reduction was reported by Lemarie and co-workers wherein TMDS and a stoichiometric quantity of Ti(O(i-Pr)$_4$ as a promoter resulted in the conversion of a variety of tertiary amides and one example of a secondary amide to the aldehyde equivalents (eqs 31 and 32). An attempt to extend it to a primary aromatic amide resulted in only a 3% conversion after 24 h. The reactions were carried out at room temperature over rather extended reaction times to avoid over reduction. Nevertheless, this approach shows promise in terms of safety and scalability as only equimolar charges are used and the reagents are inexpensive.
THE TMDS REDUCTION OF NITRO GROUPS TO AMINES

The presence of the aniline subgroup in many natural products and biologically active compounds along with the ability of the nitro group to direct electrophilic aromatic substitution reactions makes the reduction of a nitro group to the primary amine a very important conversion. Typical reduction conditions for the nitro group reduction include Zn/HCl, LiAlH₄, and catalytic hydrogenation, none of which are very general or ideal.⁴⁰⁻⁴⁵

TMDS is expedient for the reduction of nitroarenes to form the corresponding anilines under the influence of an inexpensive and readily available iron catalyst.⁴⁴ From an extensive array of catalysts that were screened, tris(acetylacetonato) iron(III) (Fe(acac)₃) exhibited the highest activity (eq 33). A number of observations may be made:

- Other reducible groups including nitrile, ester, carboxylic acid, and halide survived. Strangely, methyl-4-nitrobenzoate required toluene at 90 °C for 48 h for complete reaction of the nitro group.
- Dinitro compounds tended to undergo reduction of only one of the nitro groups.
- An aldehyde was reduced to its benzyl alcohol under these conditions.
- Ortho substituents slowed the reaction and reduced the yields.

In this study, the anilines were isolated as their HCl salt. Lower conversions observed with PMHS as the reductant were explained by the formation of the insoluble silicone gel that complicated the work up and product isolation. The reduction of aliphatic nitro compounds provided synthetically unacceptable yields of the desired amines.

Alternatively, supported gold nanoparticles were used to catalyze the TMDS reduction of nitroarenes.⁴⁵ One advantage of this approach is the high chemoselectivity as compared to the more typical transition metal-catalyzed hydrogenation (eq 34).

Chloro, hydroxyl, carboxylic acid, ester, ketone, olefin, and even the readily reduced aldehyde group proved tolerant of these conditions. Thus, mesoporous gold nanoparticle assemblies (Au/MTA) acted as transfer hydrogenation agents for the reduction of nitroarenes to the analogous anilines. However, the reduction of aliphatic nitro groups yielded hydrazo and azoalkane dimers rather than amines.

Similar to this is the reported employment of magnetically separable gold nanoparticles, prepared by treating basified HAuCl₄ in an aqueous FeSO₄ solution, for the catalysis of the TMDS reduction of nitroarenes.⁴⁶ The freshly prepared catalyst resulted in Au/Fe₃O₄ nanocomposites 11, which could be dispersed in a polar solvent and could be easily removed by a small magnet for recovery postreaction (eq 35). These particles in combination with TMDS were specific for reducing nitro groups in the presence of a chloro, bromo, hydroxyl, acetyl, acetoxy, amide, cyano, vinyl, −OBen, CBZ protected amine, and pyrazole groups. The reduction was scaled to a modest 10 mmol level, and the catalyst was reused a total of 5 reaction cycles. These conditions also proved useful for the reduction of aliphatic nitro groups (eq 36).

Based on their earlier work using Et₃SiH/In(OTf)₃,⁴⁷ Sakai and co-workers demonstrated that TMDS under InI₃ promotion brought about the reduction of nitroarenes to anilines.⁴⁸ Studies showed that TMDS gave superior results to those from phenylsilane or triethylsilane. Moreover, excellent tolerance for peripheral groups such as CF₃, amino, amide, halide, ester, and lactone was noted. On the other hand, some para-substituted substrates including p-OMe, p-OH, p-COOH, p-CN, and p-acetal failed to produce useful yields of the corresponding substituted anilines (eq 37). A nitrosobenzene intermediate was found to be part of the mechanistic pathway.

Unexpectedly, the presence of a nitro group led to its TMDS reduction to the amine with survival of the amine functionality (eq 38).²² While not explained fully, these results provide an interesting and useful chemoselective TMDS reduction. Moreover, a specific reactivity was observed when TMDS/Fe₃(CO)₁₂ is compared to TMDS/Ru- or Pt-catalyzed reduction of nitro group-containing compounds.²² For various p-nitro benzenes with TMDS/Fe₃(CO)₁₂, the nitro group would be reduced to the amine. If ruthenium or platinum catalysts were used, the opposite (amide reduction, nitro survival) occurred. Groups such as halogenates and methoxy survived in high yield when TMDS/Fe₃(CO)₁₂ was used to reduce the nitro group (eq 39). To explain the specific lack of nitro group reduction with [Pt] or [Ru] catalysis, it is proposed that the amine, formed in situ, acts as a specific catalyst poison, inhibiting reduction of the other sensitive groups.

The use of a green solvent, 1,2,3-trimethoxy propane (1,2,3-TMP), which is safe, nontoxic, and can be potentially recycled, was found to be a viable medium for the TMDS reduction of nitro groups.⁹⁰ This solvent is currently not commercially available in bulk. Instead it was prepared in 78% yield in 150 g lots by the PTC alkylation of glycerol with dimethylsulfate; however, it shows promise, and the synthesis is scalable once the demand is present. It permitted the reduction of nitriles, esters, and acids,
as well as nitro groups in high yield (eq 40). Remarkably, as shown in eq 40, when there was a choice of two groups, TMDS/Fe(acac)₃ reduced the nitro group versus the nitrile in 94% yield.

### TMDS REDUCTION OF NITRILES TO AMINES

The conversion of a nitrile to an amine is an obvious transformation to prepare an aminomethylene group as it entails the double reduction of this readily available group. However, there are not many reagents or conditions that will convert this rather unreactive moiety. This functional group alteration can be effected by catalytic hydrogenation or by reactive hydride reagents such as the aluminum hydrides and boranes among other methods.

Far easier and safer is described in a pair of papers by Lemaire and co-workers that compared the reduction of nitriles to amines between TMDS or PMHS, under promotion with Ti(O-i-Pr)₄. Both systems bring about the reduction of aromatic and aliphatic nitriles in good yields with functional group tolerance that includes bromide, alkene, and nitro as well as the cyclopropyl ring (eqs 41 and 42). Thus, for example, the reduction of 4-nitrobenzonitrile under these conditions produced 4-nitrobenzylamine in 86% yield as the hydrochloride salt (eq 43). This is opposite to that obtained with the same starting material when 1,2,3-TMP was used as solvent with TMDS/Fe(acac)₃. In this case the p-cyanoaniline was isolated in 94% yield. The reduction of p-nitrobenzylamine is hypothesized to occur due to the oxophilic nature of the titanium that leads to coordination to the nitro moiety. An acidic workup enhanced the procedure as crystalline or solid amine hydrochlorides are isolated. PMHS proved to bring about the reduction about 3 times faster than TMDS under the conditions employed. The reduction of propenyl nitrile occurs with retention of the stereochemistry of the double bond (eq 44).

An interesting series of nitrogen heterocycles is possible from reduction of dinitriles, in some cases allowing for the synthesis of strained azetidine products (eqs 45–47). In general the cheaper PMHS gave better results in the formation of the azacyclics than did TMDS.

The Lemaire group further verified that the TMDS reduction of nitriles could be carried out in 1,2,3-TMP. A variety of catalysts including, Fe(acac)₃, V(O)(O-i-Pr)₃, Ni(acac)₂, and InI₃, were successful in promoting the reduction with yields from 59 to 99%, but Cu(OTf)₂ proved to be the best of the investigated catalysts (eq 48). Small amounts of the secondary amine were also produced in some cases. In addition to the reduction of nitriles to amines, this solvent was used in the reduction of esters and carboxylic acids to alcohols, as well as nitroarenes to anilines. As mentioned before, the reduction of an aromatic nitro moiety took precedent over that of the reduction of a nitrile, but curiously, similar reaction conditions were sufficient for other substituted benzonitriles to be reduced to benzyl amines.

While the reduction of nitriles to amines is possible with a variety of reagents under various conditions, the ability to avoid hazardous conditions and provide high chemoselectivity makes the protocol with TMDS/Ti(O-i-Pr)₄ an attractive addition to these methods.

### TMDS REDUCTION OF NITRILES TO ALDEHYDES

The Lemaire group was able to effect the reduction of nitriles directly to aldehydes using the TMDS/V(O)(O-i-Pr)₃ system. Aromatic as well as aliphatic nitriles could be converted to the corresponding aldehydes in modest yields (eqs 49 and 50). The reaction proceeded through the initial formation of an N-silylated imine, which upon hydrolysis provides the aldehyde final product. A side reaction occurs through the further reduction of the N-silylated imine to the N,N-bis-silylated amine, which can condense with the aldehyde during workup forming...
an imine. The reaction required a large excess of the TMDS and a full equivalent of the V(O)(O-i-Pr)₃.

## TMDS REDUCTION OF PHOSPHINE OXIDES

Aryl and alkylphosphines are very common components in many organometallic-catalyzed reactions. Their syntheses involve the utilization of organomagnesium and lithium reagents but can also involve the reduction of phosphine oxides. The phosphine oxides are usually treated as waste but have the potential of being preligands. The reduction of phosphine oxides has proven to be a somewhat difficult process with one method employing hexachlorodisilane as the reductant. Aluminum hydrides, SmI₂/HMPA, Cp₂TiCl₂/Mg, and Bi/TiO₂ have also been used. None of these address the practical scalable approaches demanded by industry.

It should be noted that triphenylphosphine oxide is a byproduct of most Wittig transformations and that expensive phosphines and diphosphines, used in numerous transition metal-catalyzed reactions, often exit the reactions as their oxides. These could be converted back to the more useful phosphines via a straightforward and scalable reduction. The reduction of phosphine oxides, including those with organosilane reductions albeit without a discussion on the scalability of the chemistry, has been recently reviewed.

The Lemaire group has reported on a practical and scalable process for the reduction of phosphine oxides to phosphines in high yields. The reaction uses TMDS as the silane reductant and a catalytic amount of Ti(O-i-Pr)₄. PMHS was shown to be an inferior reductant in this class, justifying the more expensive TMDS in all cases examined. As an illustration of the scalability of the reaction, (S)-BINAP oxide was converted to (S)-BINAP in 92% yield on a 1.44 g scale (eq 51). The reaction can also be applied to secondary phosphine oxides to give the secondary phosphine (eq 52). The mechanism of the reaction was found to proceed via silicon radicals and TiⅢ species, suggesting a single electron transfer (SET) mechanism.

They followed these efforts up with an attractive approach to this important reduction with an InBr₃-catalyzed TMDS reduction system (eqs 53 and 54). This appears to be more versatile in that aromatic, aliphatic, secondary, and tertiary phosphine oxides were reduced, but also phosphinic acids were reduced in good to excellent yields. The readily oxidized phosphines such as diphenylphosphate were isolated as their borane complexes. Substrates containing an olefin resulted in reduction of the unsaturation as well. The reaction required 1 mol % of the InBr₃ and proceeded in high yields.

The Beller group demonstrated the deoxygenation of phosphine oxides with TMDS/Cu(OTf)₂ in 68–96% yield (eq 55). This process has advantages in that the conditions are mild, and it is tolerant of several functional groups including ketones, esters, and olefins, making it complementary to the TMDS/InBr₃ procedure, which reduced olefins as well as the phosphine oxide group. PMHS was also shown to be a good reductant under the promotion with Cu(OTf)₂ but phenyl(trimethyl)silane gave no reaction. In an extension of this reaction, diphenylphosphine oxide was reduced to diphenylphosphine and without isolation cross-coupled with iodobenzene to give triphenylphosphine (eq 56). This represents a convenient nonorganometallic route to triarylphosphines.

It is interesting and useful to note at this juncture that the organosilane reduction of phosphine oxides was used in Wittig and related reactions with the use of substoichiometric amounts of the phosphine reagents. TMDS was not one of the organosilane reductants investigated in these studies. It would be useful to examine TMDS as a reductant as these protocols show great promise for scale-up to commercial levels and that would require a safe and inexpensive silane.

## TMDS REDUCTION OF CARBOXYLIC ACIDS

The general reduction of carboxylic acids to alcohols can be accomplished via a number of methods, although these methods typically show low chemoselectivity. Acids were reduced using a TMDS/Cu(OTf)₂ system in toluene (for aliphatic acids) and in 2-methyl-THF (for aromatic acids) at elevated temperatures. An extensive variety of acids were subjected to these conditions with the yields reaching 96% (eqs 57 and 58).

Cinnamic acid was reduced at both the acid and double bond providing 3-phenylpropanol (eq 59). However, another olefin-containing reactant (oleic acid) managed to react without destruction of the double bond. The reduction of benzoic acid in toluene resulted in a Friedel–Crafts benzylation of the solvent toluene consistent with carbocationic intermediates being formed in the reaction.
It was further found in this study that changing the solvent to methylcyclohexane and increasing the TMDS charge resulted in high yields of the reduction of the acid to a symmetric ether (eq 60). This reaction was extended to the conversion of aldehydes and ketones to diastereomeric mixtures of ether products in high yields using only a low charge of reagents in CH$_2$Cl$_2$ under mild conditions. Considering that this is a significant reduction, it is noteworthy that groups such as nitro, cyano, and chloride survive.

The reduction of acids in a TMDS/InBr$_3$ system produces similar results to the Cu(OTf)$_2$-catalyzed reactions (eq 61). The use of chloroform solvent and 60 °C proved to be the best at reducing aliphatic acids to alcohols and avoiding silyl ethers. TMDS/InCl$_3$ also effected the reduction of aliphatic acids but required 2 equiv of trimethylchlorosilane as a promoter (eq 62). A mechanism explaining the disparate results was proposed. The reaction was efficient for the reduction of a variety of aliphatic acids and was tolerant of alkenes, aromatic iodide, nitro groups, and thioethers.

Aryl acids were not reduced in chloroform and produced mixtures of fully reduced isomeric dimers as a result of a Friedel–Crafts benzylation when carried out in toluene (eqs 63 and 64).

An attempt to synthesize an oxetane from a 1,1-dicarboxylic acid failed suggesting the interference of ring strain. A small amount of an oxepine was observed from the reduction of a 1,4-dicarboxylic acid; however, the diol was the major product in 65% yield in this attempt.

Interestingly, the reduction of two acids, one aromatic and the other aliphatic, resulted in the formation of the benzoate ester of the aliphatic acid under the conditions of TMDS/InBr$_3$ (eq 68).

Lemaire and co-workers extended the TMDS reduction to that of esters to alcohols. In this chemistry, after an extensive investigation of a variety of conditions, they employed equimolar TMDS/MoO$_2$(acac)$_2$ or TMDS/V(O)(OiPr)$_3$ in toluene for 16–24 h with the molybdenum system being preferred. The system of PMHS/V(O)(OiPr)$_3$ worked well for this reduction as well. The addition of 2 mol % of triphenylphosphine oxide allowed for a reduction of the MoO$_2$(acac)$_2$ charge from 5 to 1 mol % with no loss in yield. As an improvement over the system of TMDS/Cu(OTf)$_2$ described earlier, olefins both aliphatic and conjugated survive the reduction. As an improvement over the system of TMDS/InBr$_3$, reduction of aromatic carboxylic acids to alcohols was possible. The presence of a nitro group resulted in its reduction to the amine; however, the ester was not affected (eq 65).

**TMDS REDUCTION OF DIACIDS TO CYCLIC ETHERS**

Cyclic ethers are present in the structure of drugs and numerous natural products. Ring systems such as substituted tetrahydrofurans and oxepines, among others, are ubiquitous in organic chemistry. It is of value to determine new means for preparing such rings with established substitution.

When the substitution of a diacid to TMDS and InBr$_3$ conditions could form either a tetrahydrofuran, tetrahydropyran, or an oxepine reductive product, cyclization was shown to occur. The pyran derivatives (17 to >98%) were formed in uniformly higher yields than the furans (26–40%) (eqs 66 and 67).

An attempt to synthesize an oxetane from a 1,1-dicarboxylic acid failed suggesting the interference of ring strain. A small amount of an oxepine was observed from the reduction of a 1,4-dicarboxylic acid; however, the diol was the major product in 65% yield in this attempt.

Interestingly, the reduction of two acids, one aromatic and the other aliphatic, resulted in the formation of the benzoate ester of the aliphatic acid under the conditions of TMDS/InBr$_3$ (eq 68).

**TMDS REDUCTIVE SUBSTITUTION OF CARBOXYLIC ACIDS AND ESTERS**

The standard sequence for the conversion of a carboxylic acid or its ester to its halide is a reduction to the alcohol and...
either reaction with an appropriate mineral acid or similar, or alternatively, mesylation followed by substitution. The Hunsdiecker reaction transposes carboxylic acids to an alkyl halide in a single step, but with loss of the carboxyl group.\(^87\) TMDS acts as a reductant in these reactions without shortening of the alkyl chain.

The Sakai group has developed a number of single-pot reductive bromination of carboxylic acids using the TMDS/InBr\(_3\) reduction/catalyst system and trimethylbromosilane as the bromide source.\(^88\) The safer and cheaper TMDS was found to be far superior to phenylsilane for these conversions. Indeed, the authors noted an explosion with phenylsilane in this work. The reaction tolerated phenolic hydroxyls and olefins, but not the nitro group (eqs 69 and 70). Mechanistic investigations using \(^13\)C NMR spectroscopy indicated a progression of intermediates from silyl ester, bis-silyl acetal, and finally silyl ether before arriving at the bromide. Other than for \(p\)-methoxybenzoic acid, the yields ranged from 80 to 97% for a range of aliphatic and aromatic acids.

In a similar study by the Sakai group, iodine or trimethyliodosilane was employed for the synthesis of alkyl iodides from carboxylic acids.\(^89\) The yields in these transformations were very high, and the corresponding alcohols were not observed (eqs 71 and 72). Olefinic acids gave complex mixtures of products. A side study utilizing triethylsilane demonstrated that the transformation proceeds via silylated carboxylic acid and silylated alcohol intermediates. It was further shown that aldehydes, acid chlorides, and esters could be converted to alkyl iodides in a similar fashion.

In this same paper the authors reported the one-pot conversion of acids to alkyl chlorides, fluorides, and amines as shown in the conversion of 3-phenylpropionic acid (eq 73). This same group showed that the direct reductive chlorination of a carboxylic acid to the alkyl chloride was possible with a TMDS/GaCl\(_3\)/CuCl\(_2\) combination wherein the GaCl\(_3\) is the catalyst and the CuCl\(_2\) the chloride source.\(^90\) Interestingly, control experiments carried out with the triethylsilylethyl intermediate showed conversion to the chloride required all three reagents; otherwise, the alcohol was formed (eqs 74–76).

Aromatic acids proved to be difficult with only strongly electron-withdrawing systems giving the chloride and then in only mediocre yields. Nitro groups and thiophenes failed to give useful results, and relatively bulky acids led to some of the alcohol in addition to the desired chloride.

In an extension of this useful chemistry, the Sakai group showed the direct, one-pot reductive substitution of a carboxylic acid to a nitrile with chain extension of one carbon.\(^91\) This again proceeded through the intermediacy of the alkyl iodide or bromide, which was then substituted with cyanide ion in a second step (eq 77). It was further shown that aldehydes, acid chlorides, and esters could be reductively converted to the nitriles as well (eq 78). This reductive homologation with cyanide, admittedly a reagent to give concern, proceeds without resorting to alkylating agents such as tosylates or halides. This avoids these safety hazards among which are mutagenic impurities. A Friedel–Crafts cyclization to produce tetralin took place with 4-phenylbutyric acid under the iodine conditions, but gave the nitrile when trimethylbromosilane was used to generate an intermediate alkyl bromide (eqs 79 and 80).

In a related approach the Sakai group employed the reductive sulfidation of esters in a manner similar to that used for the...
reductive sulfoxidation of carboxylic acids. Here again the reductant of choice turned out to be TMDS/InI₃ (eqs 81−83). The yields obtained were in the range of 29−96% for the reaction between a methyl benzoate and an aryl mercaptan and between 28 and 99% for sulfidation of an aryl aliphatic ester and aryl mercaptan. For aliphatic-aryl coupling the yields ranged from 28 to 99%. For the reductive thiolation of benzoates the more electron donating systems showed faster reaction rates supporting cationic behavior in the intermediate.

The TMDS/InBr₃ combination similarly worked well for the reductive thioetherification of aromatic acids with yields ranging from 63 to 93% (eqs 84 and 85). Triethylsilane gave a negligible yield of the thioether, but phenylsilane gave an excellent yield in a single example. Indium iodide also functioned well as the catalyst and, in fact, was the superior catalyst for the thioetherification of aliphatic acids with yields of 53−94%. The use of InBr₃ for the conversion of aliphatic acids gave the dithioacetal 14 as a significant byproduct (eq 86). When ethane dithiol was used, the cyclic dithioacetal was the principle product (eq 87). Control experiments demonstrated that the thioether was not formed from a silylated alcohol and that the dithioacetals could be reduced under the reaction conditions indicating that the dithioacetal is an intermediate in the reaction.

TMDS REDUCTION OF ACIDS TO ALDEHYDES

Due to the general ease of reduction of aldehydes, there are few conditions that will selectively reduce a carboxylic acid to an aldehyde without further reduction to the alcohol. The general preference for this conversion is to over-reduce the acid to the alcohol and selectively oxidize the alcohol back to the aldehyde. TMDS does, however, provide some useful exceptions.

Darcel and co-workers reported the TMDS reduction of carboxylic acids. The yields were in the range of 48 to 95%, as determined by ³H NMR spectroscopy, when the catalyst trans-4-phenyl-but-3-en-2-one/Fe(CO)₅ (t-PBO/Fe(CO)₅) was used. PMHS gave results inferior to those of TMDS. When a combination of PhSiH₃/(CO)₃Fe(COD) and UV was used, the alcohol was formed in 67−97% yield with only traces of the aldehyde. Conversely, the use of different conditions, t-PBO in place of 1,5-cyclooctadiene as part of the iron complex and TMDS as the reductant, led to modest to high yields of the dialdehyde (eq 88). The mechanism proposed involved the formation of an intermediate tetra-silylated acetal, which was hydrolyzed to the aldehyde final product and supported the observation that 2 equiv of TMDS were needed for quantitative reaction.

TMDS REDUCTION OF ALDEHYDES

The TMDS reduction of aldehydes catalyzed by TMSI or TMSBr resulted in the reductive halogenation of the aldehyde. A more convenient and practical approach made use of NaI/TMSCl (eq 89) and LiBr/TMSCl (eq 90) rather than the more costly TMSI (30−95%) and TMSBr (20−97%), respectively. The use of TMSCl alone did not result in the formation of the corresponding alkyl chloride, but the use of SOCl₂/ZnI₂ furnished the chlorides in 40−91% yields. Symmetrical ethers were found to be byproducts of these reactions in certain cases. In fact, the reductive etherification of aldehydes was found to be the exclusive product with the TMDS/TMSOTf or TMDS/TMSI reagents (eq 91). Alternatively, the use of trifluoroacetic acid as solvent instead of TMSOTf catalysis competitively led to the ether along with some of the trifluoroacetate ester of the alcohol produced. In this same paper the authors demonstrated the reduction of quinones to hydroquinones in 75−98% yield (eq 92).
silyl ether to react with another aldehyde to form the silylated hemiacetal. This was further reduced to yield the ether.

The Lemaire group had shown the reductive etherification of carboxylic acids and extended this to aldehydes and ketones as well (eqs 95 and 96). Application to the dialdehyde 16 gave the cyclic trimer in good yield (eq 97).

**TMDS REDUCTIVE CLEAVAGE REACTIONS**

The reductive demethoxylation of anisoles has been shown to occur under conditions with TMDS and Ni(0) catalysis. This potentially highly useful transformation occurred in yields of 55–99% and with considerable functional group tolerance including esters, amides, ethers, oxazolines, acetals, trimethylsilyl, and various nitrogen heterocycles. Considering that the methoxy group is not only a strong o,p-director in electrophilic aromatic substitutions, but has also been shown to direct lithiation to the ortho position, brings about the potential for using these directing effects followed by subsequent removal of the methoxy directing group (eqs 98 and 99).

In a related application of traceless directing groups, the carbamate metalation-directing group was cleanly removed reductively from a series of substrates with TMDS and a nickel catalyst with yields between 77 and 93%. This allowed for the cine substitution of the carbamate wherein the carbamate directed substitution to the adjacent position on an aromatic ring and was then reductively replaced by a hydrogen (eqs 100 and 101). The illustrative example starting with N,N-diethyl(4-methoxyphenyl)carbamate shows the strong directing effect of the carbamate versus that of the methoxy group for locating the boronate. Furthermore, the chemical selectivity of the reductive removal of the carbamate moiety leaves the methoxy and the boronate intact, resulting in the overall electrophilic m-substitution of anisole. This was further applied to the 4-substitution of N-methylindole from the more readily available 5-carbamoyl-substituted derivative (eqs 102 and 103).

Considering the ease for forming carbamates from phenols, this presents a significant method for the use of a traceless directing group in the substitution of aryl systems.

A nickel-catalyzed decyanation of aryl and aliphatic nitriles has been reported. The procedure appears to be one that lends itself well to scale up, although catalytic amounts of the pyrophoric Me₃Al were used to expedite the oxidative addition step. Various substrate types, including aryl, heteroaromatic and aliphatic nitriles were reduced in 49–98% yields (eqs 104–107).

Two examples were given wherein the synthetic utility of the nitrile group was utilized and then, having done its job, was reductively removed. The first of these utilized the α-alkylation of an aliphatic nitrile (eq 108) and the second the cross-coupling directing effect of an aryl nitrile (eq 109). Competition
experiments indicated aromatic cyano cleavage is faster than that of $-\text{OAr}$ or $-\text{OMe}$, but slower than $-\text{SMe}$.

### TMDS Reductive Amination of Esters

Tosylated amines may be prepared via the reductive amination of esters in the presence of the ruthenium catalyst 2. By introducing variations in the structure of the ester and the silyl reducing agent, it proved possible to perform a reductive $N$-alkylation on primary and secondary alkyl groups with TMDS as the reductant, or perform a $N$-tertiary alklylation with tertiary alkyl groups with EtMe$_2$SiH as the reductant (eqs 110 and 111). The structure of the ester plays a significant role in determining the amine formed. When the ester was that of a tertiary alcohol, cleavage of the alcohol C$-$O bond occurred, leading to amination of the tertiary alcohol carbon. When the structure was that of an acid with a primary or secondary group attached to the carboxyl group, cleavage of the carboxyl C$-$O bond took place to provide amination of the carboxyl carbon. The reductive $N$-alkylation proceeded for a number of esters. If the ester and tosylated amine were bound together on a single molecule, cyclic amines result, although a 5-membered ring is the minimum that strain allowed to be formed (eqs 112 and 113).

### Reduction of Conjugated Arrays

In an early application of a silane reduction of an enone, the TMDS reduction of phenalenone to phenalanone was accomplished, albeit in low yield, using the simple Pd/C catalyst (eq 114). A large variety of silicon-based reductions of $\alpha,\beta$-unsaturated carbonyl derivatives have since been reported. The TMDS/I$_2$ combination was demonstrated to convert carbonyl compounds and oxiranes to iodides, and also to reduce quinones to hydroquinones (eqs 115 and 116). A report on a much faster alternative to Stryker’s reagent for hydrosilylation has been published. The precatalyst 17 was prepared by a simple one-step reaction of the diarylimidazole derivative with Cu(OAc)$_2$ in toluene. This system proved to perform better than Stryker’s reagent in the 1,2-reduction of aldehydes and ketones and the conjugate reduction of enones (eq 117). Both PMHS and TMDS were found to be effective in these hydrosilylations with PMHS giving shorter reaction times due to its ability to activate the catalyst more rapidly.

Phenylsilane and diphenylsilane were also shown to carry out the reductions, but phenyldimethylsilane did not. PMHS was used to reduce $\alpha,\beta$-unsaturated nitriles to the alkyl nitrile in 82 to 94% yields (eq 118). The (C$_6$F$_5$)$_3$B-catalyzed organosilane reduction of a variety of pyridines was reported. Diethylsilane was the reagent of choice in this study. These reductions gave differing products depending on the nature of the substitution pattern on the pyridine being reduced (eq 119). As a part of these investigations, they also reported the use of TMDS, which gave interesting results as the result of the addition of both silyl groups to the ring in a stereospecific cis manner (eq 120). The enantioselective formation of 1,2-disubstituted indanes was reported by Lam and co-workers who effected a reductive Michael cyclization of benzodienones. (S)-SEGPHOS was found to give the best diastereo- and enantioselectivities (eqs 121–122). They found that they needed to go to an iron-containing ligand, Taniaphos, along with a copper catalyst and PMHS to satisfactorily reduce analogues with aromatic groups on the carbonyls in good ee and dr (eq 123).

Lipshutz and co-workers report Stryker’s reagent catalyzed a 1,4-reduction/alkylation reaction (eq 124). The copper complex could lead to silyl derivatives of 1,4-reduction but if immediately reacted with an electrophile (aldehyde), the product of an aldol reaction could be recovered. The reaction with the silyl hydride took only minutes instead of hours as with other hydrides,
emphasizing the dual-silyl accelerating effect. For unhindered enones converting to silyl enol ethers, PMHS was even faster (<2 min vs 0.5−0.75 h).

■ MISCELLANEOUS TMDS REDUCTIONS

An intramolecular reductive nitro-Mannich reaction of nitroalkyl lactams to bicyclic amines was accomplished with the TMDS/IrCl(CO)(PPh3)2 combination, which serves well to reduce the lactam to the iminium intermediate. The reaction proceeded by carbonyl reduction and elimination to form a stable enamine. The iminium ion formed upon acid addition. Under the influence of subsequent base, the nitro group became a putative nitroate anion, which could then cyclize (eqs 125−127).

The Lemaire group continued their work with TMDS reductions with an environmentally attractive and scalable reduction of acetals to ethers.112 The reaction made use of cheap metal triflates Cu(OTf)2 or Bi(OTf)3 as catalysts and only a slight excess of silyl hydride from TMDS (eqs 129 and 130).

This represented an improvement over their earlier report of the TMDS/Pd−C/camphorsulfonic acid reduction of acetals.113 In the case of the acetals of benzaldehyde some diether formation occurred. The reduction protocol was found to tolerate hydroxyl, ester, nitro, and nitrile groups. The considerable efficiency of this reaction was presumably due to the triflate group’s transfer to a silicon atom in the presence of a nucleophile: the oxygen atom of the acetal.

The TMDS conversion of oxiranes to alkoxysilanes in the absence of solvent was reported by the Lemaire group. Whereas styrene oxide was opened in a regioselective manner (eq 131), hexane oxide gave a mixture of isomeric silylated alcohols.114 Tetrahydrofurans also gave alkoxysilanes via a reductive ring opening (eq 132). Here again the reaction was not regioselective with 3-methyltetrahydrofuran giving a mixture of all three possible regioisomeric products. The reaction of tetrahydrofururyl alcohol took place via a dehydrogenative silylation at the hydroxyl without ring opening (eq 133). It also proved possible to prepare alkoxysilanes from aldehydes and ketones under these conditions (eqs 134 and 135). Terephthalaldehyde provided a polymer (eq 136).

The reaction was scaled up to a 2 g level with no loss in yield or diastereoselectivity; however, forming a [5.0.3] and a [6.0.3] bicyclic ring resulted in some reduction in diastereoselectivity in some cases. The steps of the amide reduction and cyclization were conveniently followed by 'H NMR spectroscopy, indicating the subsequent formation of the enamine, the iminium ion, and finally the cyclized product. The yields for 15 examples ranged from 37 to 81%. This reductive cyclic nitro-Mannich approach was used in a short synthesis of (±)-epi-epiquinamide (eq 128).
Palomo reported the reductive halogenation of oxiranes using combinations of TMDS/NaI (eq 137) or TMDS/LiBr (eq 138). Remarkably, the regiochemistry is completely opposite between the two. With the TMDS/LiBr reagent mix, bromohydrins were also formed from cyclohexene oxide (eq 139).115,116

Woerpel and co-workers showed that TMDS/Ti(O-i-Pr)4 would reduce triphenylphosphine oxide in the presence of a silyl peroxide thereby allowing for triphenylphosphine to be catalytically.117 Silyl peroxides were reduced with yields of 46−79%, and the product was the silyl-protected alcohol. The reaction tolerated a ketal. An insertion of the triphenylphosphine into the O−O bond with intramolecular migration of the silyl group and loss of triphenylphosphine oxide was proposed. Crossover experiments showed no exchange of the silyl groups supporting the postulated mechanism (eq 140).

The organosilane reduction of lignin model systems was investigated as a potentially useful route to biomass sourced organic compounds.118 The initial and mechanistic work was carried out with Et3SiH/(C6F5)3B, but the more economical TMDS and PMHS were found to be equally good with the same catalyst (eq 141). It was pointed out that the byproducts of cyclic and linear silicone materials from these latter two are capable of being converted to polysiloxane polymers offering a potential additional economic advantage.

Lalic and co-workers reported on the TMDS reduction of alkyl triflates resulting in the effective deoxygenation of alcohols. The reaction was catalyzed by the carbene Cu(I) catalyst 18 (eq 142).119 This is related to the precatalyst used by Yun for 1,2/1,4 reductions.107 Tosylates and nosylates were less noticeably reactive than the triflates. The reaction was possible in the presence of several functional groups including ester, cyano, nitro, tosylate, and remarkably, considering the presence of CsF, a TBS ether (eqs 143 and 144). The reaction shown in eq 144 was scaled up to a 20 mmol level (3.6 g of product).

In this same work, the authors reported the TMDS reduction of primary iodides (eq 145). Again good functional group tolerance was demonstrated and excellent yields obtained. It was found that, although TMDS led to some elimination, substituting diphenylsilane as the reductant solved this problem. A primary bromide was reduced in 98% yield. Based on trapping and cyclization experiments, it is argued that the reaction is essentially a two-electron process.

Stratakis and co-workers report on a hydrosilylation of both ketones and aldehydes catalyzed by Au/TiO2.120 Reduction of aldehydes by TMDS was reported above, but this variation reacts both classes of carbonyls (eqs 146 and 147). The products were isolated as their silyl ethers. Aliphatic ketones resulted in the formation of the silylated alcohol and the silyl enol ether (eq 148). The authors note the remarkably enhanced activity of TMDS as compared to monohydrosilanes, such as Et3SiH, PhMe2SiH, and Ph3SiH. For the comparison of TMDS to PMDS (1,1,1,3,3-pentamethyldisiloxane) on 4-methylbenzaldehyde, the reaction proceeded ~20 times faster. They attribute the reactivity to a gold dihydride intermediate unlike the other previously reported examples of dual Si−H increased reactivity.

Finally, there is a recently reported example of an iridium-catalyzed reductive synthesis of nitrones from N-hydroxyamides.121 An N-hydroxy or N-siloxylactam is reacted with Vaska’s complex (1 mol %) and TMDS (2.5 equiv) followed by acid or F−. They either isolate the nitrene in good to excellent yield (eq 149) or
if followed by a dienophile (nitrones are unstable), the results of [3 + 2] cycloadition (eq 150). The method showed high chemoselectivity and endurance to sensitive functional groups.

**ORGANOSILANE REDUCTIONS IN SCALE-UP APPLICATIONS**

The potential for TMDS as a selective reducing agent has been demonstrated only in the past decade or so. Its consideration for practical and safe large-scale reductions should be clear from the several examples reviewed herein. Its properties lend themselves to large-scale use: stable to water, air, and heat as long as the pH is near neutral limits. Its chief drawback is a low flash point (12 °C). Organosilane reducing agents in general possess a remarkable gamut of uses, lending themselves well for large-scale use. Although there are few examples of large-scale applications of TMDS reductions, the variety of applications and its safety profile make this versatile reagent a strong candidate for scale up purposes. Some examples of truly larger scale applications of TMDS are given in this section.

Excellent conditions for potential scale-up reduction were presented by the Boehringer Ingelheim group wherein they described the reduction of several classes of amides in good yields employing the combination of TMDS and triruthenium dodecacarbonyl, Ru3(CO)12. In particular this protocol was highly successful in the reduction of primary and secondary amides, which have proven more difficult to reduce using other organosilane reductants (eq 151). Notably, they were able to carry out the key reduction in a synthesis of the calcimetric drug Cinacalcet-HCl 19 (eq 152) as well as an efficient and scalable reduction of tartrate diamide 20 (eq 153).

The generation of the aromatic fragment 22 of empaglitiflozin 23 was accomplished by the TMDS reduction of benzophenone derivative 21. It was found that AlCl3 was a better catalyst than the more commonly employed BF3·OEt2 in this instance (eq 154). A treatise on the use of silane reductions in the preparation of various gliflozins has appeared.

A second example is the scaled-up TMDS reduction of α-chloroacetophenone derivative 24 to the substrate 25, in an improved synthesis of ziprasidone 26. The reduction with TMDS was shown to be much cleaner than with triethylsilane. Triethyilsilane led to under reduction to the alcohol and over reduction to the ethyl derivative (eq 155).224

**CONCLUSIONS**

It was in the mid-1970s when the vast potential of organosilanes as synthetic organic reagents, beyond that of being excellent functional group protecting agents, first began to be seriously investigated. From this work, which continues unabated today, came transformations that include the Mukaiyama cross-aldol and related chemistry, silicon-based cross-coupling protocols, various cyation reactions, mild ester saponification methods, and an extensive number of examples of selective silicon-based reductions. In all of this chemistry the silicon atom is not found to the final product, for example, as a final active pharmaceutical ingredient. With few exceptions, such as the strong bases formed from hexamethyldisilazane for selective deprotonation, and the chemistry of cyanotrimethylsilane, the organosilane reagents have not been highly utilized in large-scale commercial synthetic applications. This has changed recently where triethyilsilane was used in a synthetic sequence leading to Tamiflu. As presented in this review tetratetramethylsiloxane, TMDS, bears serious consideration as a scalable, safe, regio-, stereo-, chemo-selective, and economically viable reducing agent.

**AUTHOR INFORMATION**

**Corresponding Author**

E-mail: jlarson@gelest.com.

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