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TMDS–Pd/C: a convenient system for the reduction of acetals to ethers

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ABSTRACT

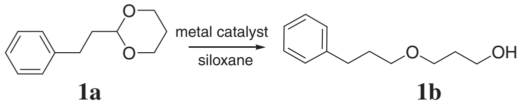
A simple and practical procedure for the reduction of acetals to ethers is described. It is based on the use of a 1,1,3,3-tetramethyldisiloxane (TMDS)–Pd/C system in the presence of a Brønsted acid as the co-catalyst. The reaction occurs under mild conditions and ethers are obtained in high yields.

Reduction of C–O bond of acetals is a valuable method for the straightforward synthesis of ethers. It is widely used not only as a deprotecting strategy but also as a strategy for constructing building blocks in carbohydrate chemistry.[1] Since Doukas and Fontaine reduced acetals using $LiAlH_4$ in the presence of HCl,[2] numerous other catalytic systems have been developed with different hydride sources including, $LiAlH_4$, NaH,[3] DIBAL-H,[4] $NaBH_3CN$,[5] BH_3,[6] Et_3SiH,[7] and $PhSiH_3$.[8] Among these hydride sources, silane derivatives have emerged as attractive potent reducing reagents since some of them are stable to air and moisture, easy to handle, and readily available. However, most of the other methods suffer from serious drawbacks such as incompatibility with sensitive functionalities, and the need for a careful control of the reaction conditions as well as the use of rigorously dry reagents and solvents.[7a] Thus, in the literature, different silane systems have been developed; Et_3SiH–TFA, Et_3SiH–TfOH, Et_3SiH–$PhBCl_2$, Et_3SiH–$EtAlCl_2$, Et_3SiH–$BF_3·Et_2O$. All of these systems combine the alkyl-silane with stoichiometric amount or excess of acid and the reduction reaction of acetals is performed at low temperatures.[7] To the best of our knowledge, only one publication reported the reduction of acetals using a silane in the presence of catalytic amount of metal complex.[8a]

Although silane derivatives have many advantages as hydride sources they are also known to generate, under certain conditions, highly pyrophoric and toxic gas.[9] Therefore, more convenient alternatives, that is, the use of new hydride sources must be explored. Hydrosiloxane derivatives would constitute attractive promising reducing agents that are, as the silanes, stable to air and moisture.[10] Moreover, when used, hydrosiloxanes give rise to polysiloxanes as byproducts which is innocuous.[11] In addition, when TMDS is used a linear polymer easy to separate from the reaction medium is generated. For several years now, our laboratory has been exploring the potentialities of hydrosiloxane derivatives and their use as substitutes to silanes in various reduction reactions. In fact, we have already successfully developed and reported the reduction of phosphine oxides to phosphines,[12] nitriles to amines,[13] and amides to aldehydes,[14] using the shortest chain polymer, the 1,1,3,3-tetramethyldisiloxane (TMDS) activated by titanium (IV) isopropoxide. We also reported the reduction of nitro compounds to amines activated by iron (III).[15] Herein, we describe the use of a new reducing system composed of TMDS as the solvent and source of hydride, Pd/C as the catalyst, and camphorsulfonic acid as the co-catalyst, for the reduction of acetals to ethers.

We began our investigation with the reduction of 2-phenethyl-1,3-dioxane **1a** that we chose as a model molecule following Scheme 1. This molecule was synthesized in one step starting from the commercially available 3-phenylpropanal and 1,3-dihydroxypropane.

The first experiment was conducted using a ruthenium metal complex $[RuCl_2(PPh_3)_3]$ as the catalyst and TMDS as the hydride



Scheme 1. Acetal reduction.

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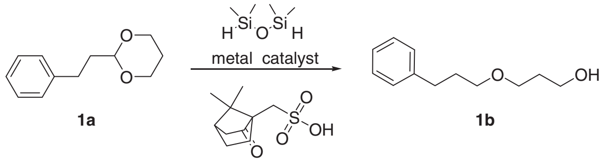
Table 1
Reduction of acetals with different TMDS-catalyst systems



Entry[a]	Siloxane (equiv)	Metal catalyst (mol %)	Conversion[b] of **1a** (%)	Yield[b] **1b** (%)
1	TMDS, 5	Ti(O*i*Pr)$_4$, 100	0	0
2	TMDS, 5	PdCl$_2$, 15	41	29
3[c]	TMDS, 2	Pd/C, 2.5	75	72

[a] General conditions: 60 °C, 24 h.
[b] Determined by ^{1}H NMR based on starting material **1a**.
[c] Reaction time = 48 h. In this case, 53% of conversion was estimated by ^{1}H NMR after 24 h of reaction.

Table 2
Reduction of acetals in the presence of camphorsulfonic acid

Entry[a]	Siloxane (equiv)	Metal catalyst (mol %)	CSA (wt %)	Conversion[b] of **1a** (%)	Yield[b] **1b** (%)
1	TMDS, 5	Pd/C, 1	5	47	46
2	TMDS, 5	Ru/C, 1	5	12	9
3	PMHS, 12	Pd/C, 1	5	0	0

[a] General conditions: 60 °C, 24 h.
[b] Determined by ^{1}H NMR based on starting material **1a**.

Table 3
Effect of different factors[a]

Entry	TMDS (equiv)	Pd/C (mol %)	CSA (wt %)	Time (h)	Conversion[b] of **1a** (%)	Yield[b]**1b** (%)
1	5	5	5	15	100	>99
2	2	1	5	24	39	27
3	3	1	30	24	91	90

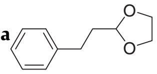
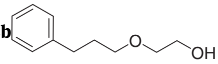
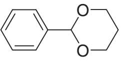
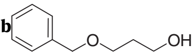
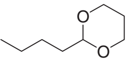
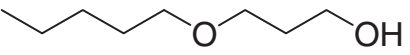
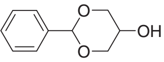
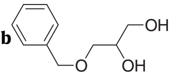
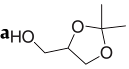
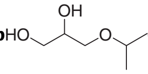
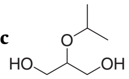
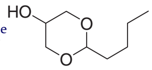
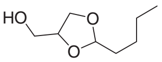
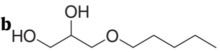
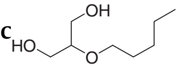
[a] General condition: 60 °C.
[b] Determined by ^{1}H NMR based on starting material **1a**.

donor. Unfortunately, in this case, no reaction was observed after 24 h at 60 °C. This is probably due to the TMDS lack of reactivity. Indeed, hydrosiloxane compounds are not sufficiently potent hydride sources themselves and require activation. Therefore, TMDS activated by titanium (IV) isopropoxide (Ti(O*i*Pr)$_4$) was then tried for the reduction of 2-phenethyl-1,3-dioxane (**1a**). It should be noted that this TMDS–Ti(O*i*Pr)$_4$ system has already been used in our laboratory to reduce various nitriles and amides. In this case too, no reaction had occurred (Table 1, entry 1). However, when 15 mol % of PdCl$_2$ and 5 equiv of TMDS were employed, 29% of the starting material was converted into the corresponding ether **1b** (Table 1, entry 2). With 2.5 mol % of Pd/C and 2 equiv of TMDS, 75% of acetal **1a** was converted into the corresponding ether **1b** after 48 h at 60 °C (Table 1, entry 4). After acidic work-up, and solvent extraction, ether **1b** could be obtained in 72% yield (Table 1, entry 3).

Although the best results were obtained using reasonable quantities of Pd/C and TMDS (2.5 mol % Pd/C and 2 equiv TMDS), further efforts were engaged to decrease these quantities while optimizing the reaction conditions and testing new catalysts as well as new hydride sources. The idea was to activate acetal **1a** by the use of a Brønsted acid, that is, camphorsulfonic acid (CSA) which would enable us to decrease the amount of catalyst and/or the hydride source. In fact, very recently, our group reported the synthesis of glycerol mono-ethers (GME) by reductive alkylation of alcohols and using Pd/C as the catalyst and camphorsulfonic acid as the co-catalyst under hydrogen pressure.[16] In this process the use of CSA as the co-catalyst gave the best yields. In addition Bethmont et al. reported the synthesis of ethers from aldehydes and linear alcohols under hydrogen pressure. They showed that the acid function promotes ether formation from the ketal.[17]

With 1 mol % of Pd/C, 5 equiv of TMDS, and 5 wt % of CSA, 47% acetal **1a** were converted after 24 h at 60 °C (Table 2, entry 1). After acidic work-up, ether **1b** could be obtained in 46% yield (Table 2, entry 1). Under the same reaction conditions, but replacing Pd/C by Ru/C catalyst, 9% of ether **1b** was detected (Table 2, entry 2). Surprisingly, when polymethylhydrosiloxane (PMHS) was used as

Table 4
Reduction of acetals to ethers under the optimized conditions[a]

Entry	Acetal	Product	Conversion[b] (%)	Yield[b] (%)
1	**2a** 	**2b** 	100	>99
2[c]	**3a** 	**3b** 	100	95
3	**4a** 	**4b** 	100	87
4[c]	**5a** 	**5b** 	90	63
5	**6a** 	**6b**  **6c** 	100	94[d]
6	**7a**[e]  	**7b**  **7C** 	87	87[f]

[a] General conditions: 3 equiv TMDS, 1 mol % Pd/C, 30 wt % CSA, 60 °C, 24 h.
[b] Detemined by ^{1}H NMR based on starting materials.
[c] 10 wt % CSA.
[d] Ratio between two products: **6b**/**6c** = 6:5.
[e] As detected by gas chromatography the ratio between six-membered ring acetals and five-membered ring acetals is 1:1.
[f] Ratio between the two products: **7b**/**7c** = 7:3.

a hydride source under the same conditions as described above, no reaction had occurred (Table 2, entry 3). That might be due to the lack of accessibility of the PMHS active sites because of the absence of solvent and therefore of a good stirring. From these preliminary results, we concluded that Pd/C is the best for the reduction reaction and that the use of CSA as the co-catalyst is important for decreasing the catalyst quantity.

In order to optimize the reaction conditions, we repeated the reduction of acetal **1a** with various amounts of TMDS, Pd/C and CSA. As shown in Table 3, the best result for the reduction of acetal **1a** was obtained with 5 equiv of TMDS, 5 mol % of Pd/C and 5 wt % of CSA at 60 °C for 15 h. Under these conditions, ether **1b** could be obtained in quantitative yield (Table 3, entry 1). When decreasing the quantities of TMDS (2 equiv) and Pd/C (1 mol %), lower yields were detected when performing the reaction under the same conditions as described for entry 1 in terms of temperature and CSA amount. In this case, ether **1b** was detected in 27% yield (Table 3, entry 2). A better result could be obtained when 30 wt % of CSA were used even with only 1 mol % of Pd/C. In this case ether **1b** was detected in 90% yield as estimated by ^{1}H NMR (Table 3, entry 3).

From these results, we adopted the following conditions as the optimized ones, for the rest of our investigations: 3 equiv TMDS, 1 mol % Pd/C, 30 wt %, 60 °C, 24 h.[17] In order to test the versatility of our approach we finally applied these conditions for the reduction of different acetals (Table 4). All linear and aromatic acetals were reduced with good conversion rates. Thus the corresponding ethers were obtained in high yields (Table 4, entries 1–6). It should be noted that benzaldehyde acetals (**3a**, **5a**) are more active than other acetals, since only 10 wt % CSA were sufficient to reach good conversion rates. Although all ethers were synthesized in good yields, the selectivity of the reaction for glycerol derivatives remained low between primary and secondary ethers (Table 4, entries 5 and 6). This drawback renders this method less competitive than the one that uses H_2.[16,18] However, this method would constitute a good alternative to the reductive alkylation method since it avoids the reduction of the aromatic rings that can occur when using H_2.[19]

In summary, we reported in this Letter a convenient and straightforward method to reduce acetals to ethers in high yields and under mild conditions. This method uses TMDS as the hydride source with catalytic quantity of Pd/C as the catalyst in the presence of camphorsulfonic acid as a promoter. Nevertheless, this method has also its limitations in terms of chemoselectivity.

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18. *General procedure for reduction of acetals*: In a screw-caped vial, 1 mmol acetal, 1 mol % Pd/C and 30 wt % CSA were introduced at room temperature under Argon atmosphere. Then 0.54 ml (3 equiv) of TMDS was added and mixture was stirred at 60 °C. After 24 h at this temperature, the reaction medium was diluted with 5 ml of dichloromethane and filtered over Celite. The filtrate was then mixed with 3 equiv HCl and the resulting solution stirred for 1 h at room temperature. The organic layer was separated and the organic solvents evaporated in vacuo. The resulting crude was finally analyzed by ^{1}H NMR with no further purification.
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