

Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

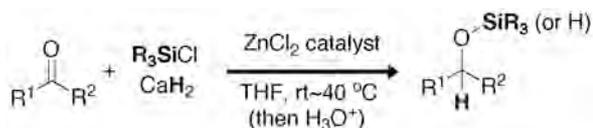
Carbonyl reduction with CaH_2 and R_3SiCl catalyzed by ZnCl_2

Akiko Tshako, Jing-Qian He, Mariko Mihara,
Naoko Saino and Sentaro Okamoto*

*Department of Material & Life Chemistry,
Kanagawa University 3-27-1 Rokkakubashi,
Kanagawa-ku, Yokohama 221-8686, Japan*

Ketones and aldehydes were effectively reduced by the reaction with CaH_2 and R_3SiCl in the presence of a catalytic amount of ZnCl_2 . In the absence of the carbonyl substrate, the reagent reduced R_3SiCl to the corresponding hydrosilane under mild reaction conditions.

Leave this area blank for abstract info.





Pergamon

TETRAHEDRON
LETTERS

Carbonyl reduction with CaH₂ and R₃SiCl catalyzed by ZnCl₂

Akiko Tshako, Jing-Qian He, Mariko Mihara, Naoko Saino and Sentaro Okamoto*

Department of Material & Life Chemistry, Kanagawa University, 3-27-1 Rokkakubashi, Kanagawa-ku, Yokohama 221-8686, Japan

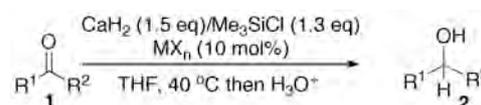
Abstract—Ketones and aldehydes were effectively reduced to the corresponding alcohols (or their silyl ethers) by the reaction with CaH₂ and R₃SiCl in the presence of a catalytic amount of ZnCl₂. In the absence of the carbonyl substrate, the reagent reduced R₃SiCl to the corresponding hydrosilane under mild reaction conditions. © 2011 Elsevier Science. All rights reserved

Reduction of carbonyl compounds with metal hydride reagents is one of the most basic transformations in organic synthesis.¹ Recently, efforts have been devoted to utilize basically inert metal hydrides LiH and CaH₂ as a reductive hydride source because they are inexpensive, stable, easy to handle and environmentally benign: With use of LiH, reduction (formal hydrosilylation) of ketones by cat. ZnX₂/LiH/Me₃SiCl² and hydrozincation of dienes and alkynes by cat. (cyclopentadienyl)₂TiCl₂/2LiH/ZnI₂³ have been reported by Noyori et al. and by Sato et al., respectively, where a zinc hydride species derived from LiH and ZnX₂ was proposed as an active hydride. Generation of dialkylzinc hydride ate complexes from LiH and ZnR₂ has also been documented.⁴ Meanwhile, although there had been no report for the use of CaH₂ as a reductive hydride, except for reactions through synthesis of boron⁵ and aluminium⁶ hydrides and reductions of sulfates to sulfides,⁷ we have recently reported the first example of a direct use of CaH₂ for the reduction of carbonyl compounds, where a mixture of CaH₂ and ZnX₂ reduced ketones and imines in the presence of a catalytic amount of a Lewis acid such as Ti(O-*i*-Pr)₄, B(O-*i*-Pr)₃, Al(O-*i*-Pr)₃ and ZnF₂.⁸ Carbonyl reduction with these stable metal hydrides is promising as a practical process applicable to a large-scale synthesis. However, the reaction of aldehydes having α-hydrogen with the LiH-based reagent gave a complex mixture including aldol condensation products^{2,9} and the CaH₂-based reagent also resulted in formation of a complex mixture from aldehydes and no reaction with acyclic aliphatic ketones.⁸ Herein we report development of a new CaH₂-based reagent, cat. ZnX₂/CaH₂/R₃SiCl, which effectively reduced (hydrosilylated) a variety of carbonyl compounds including aromatic, aliphatic ketones with a cyclic and acyclic form and aldehydes.

To overcome the aforementioned drawbacks to the reported LiH- and CaH₂-based reduction, we concentrated our effort to develop more general reagent system based on CaH₂. Inspired by the LiH-based reducing agent developed by

Noyori et al., initial investigations were begun by reacting acetophenone (**1a**), 2-octanone (**1b**) and 3-phenylpropanal (**1c**) with a combination reagent cat. ZnX₂/CaH₂/Me₃SiCl. Thus, the reactions with CaH₂ (1.5 equiv) in the presence of Me₃SiCl (1.3 equiv) and a catalytic amount of ZnX₂ were carried out and the results are summarized in Table 1, where the yields were given for the corresponding alcohol obtained after acidic work-up. Possibility of the use of other metal salts instead of ZnX₂ was also examined.

Table 1. Reaction of carbonyl compounds with CaH₂/Me₃SiCl/MX_n



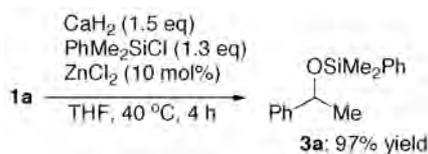
entry	R ¹	R ²	MX _n ^a	h	yield, % ^b
1	1a : Ph	Me	-	24	~0
2 ^c	1a : Ph	Me	ZnCl ₂	1	40~98
3	1a : Ph	Me	ZnCl ₂	0.5	96
4	1a : Ph	Me	ZnBr ₂	1.5	93
5	1a : Ph	Me	MgBr ₂	24	~0
6	1a : Ph	Me	CuCl ₂	24	~0
7	1a : Ph	Me	Co(acac) ₃	24	~0
8	1a : Ph	Me	FeCl ₃	24	~0
9	1b : <i>n</i> -C ₆ H ₁₃	Me	ZnCl ₂	0.3	87
10	1c : Ph(CH ₂) ₂	H	ZnCl ₂ ^d	24	74 ^e

^aCommercial anhydrous was used. ^bIsolated yield. ^cPerformed at room temperature. ^d0.2 equiv of ZnCl₂ was used. ^e26% of **1c** was recovered.

As revealed from the results of the reaction of acetophenone (**1a**) (entries 1-8), in the absence of metal salt the reaction did not take place at all (entry 1), whereas, in the presence of ZnX₂ the reaction proceeded to afford the

expected alcohol (entries 2-4). Though the reaction at room temperature sometimes faced the problem of reproducibility (entry 2), performing the reaction at 40 °C helped to overcome this matter (entries 3 and 4). Other metal salts such as MgBr₂, CuCl₂, Co(acac)₃ and FeCl₃ did not catalyze the reaction (entries 5-8). To our delight, acyclic aliphatic ketone **1b** and aldehyde **1c** having α -hydrogens was reduced to the corresponding alcohols in good yields (entries 9 and 10), although the reduction of aldehyde needed longer reaction time even with use of 0.2 equiv of ZnCl₂. Thus, the present method overcame the aforementioned limitation of the reported LiH- and CaH₂-based carbonyl reduction.^{2,8}

Since the reaction with cat. ZnX₂/CaH₂/Me₃SiCl system provided a mixture of the reduced alcohol and its silyl ether after neutral aqueous work-up or on TLC analysis of the reaction mixture, the reaction might initially formed the corresponding Me₃Si ethers but they often were unstable to isolate. Therefore, an acidic aqueous work-up (or treatment with ammonium fluoride) was performed to isolate the products as the corresponding alcohol in the above-mentioned reactions. While the reaction using more bulky silyl chloride such as PhMe₂SiCl than Me₃SiCl, the work-up under neutral conditions gave the corresponding silyl ether **3a** as an isolated product in good yield (Scheme 1).



Scheme 1. Reaction with PhMe₂SiCl.

Figure 1 shows the reduction (or hydrosilylation) of other representative carbonyl compounds **1** with a CaH₂/R₃SiCl/ZnX₂ (1.5/1.3/0.1 or 0.2equiv) reagent, where the structure of the product alcohol **2** (with use of Me₃SiCl) and silyl ether **3** or **4**, the reaction time and the yield are given. The reagent effectively reduced a variety of carbonyl compounds including aromatic, aliphatic, alkenyl ketones and aldehydes to the alcohols **2** by using a CaH₂/Me₃SiCl/ZnX₂ reagent after an acidic work-up. 1,2-Dione **1k** was converted to 1,2-diol **2k** in a *meso*-selective fashion. The reactions with PhMe₂SiCl or Et₃SiCl instead of Me₃SiCl, the corresponding silyl ethers **3d**, **4f**, **3h** and **3j** were obtained after a neutral work-up. In addition, imine **5** was also reduced effectively to give the corresponding amine **6**.

The results in Table 2 indicate a functional group compatibility of the present reaction. Thus, 4-substituted acetophenones **1m-p** were reduced to the corresponding aryl alcohols in good yields where cyano, iodo and nitro groups present in the substrates survived (entries 1-3). As shown in entries 4 and 5, acetophenone (**1a**) was reduced with the reagent in the presence of 1 equiv of substituted benzene (Ar-FG, **7**). The reduction of **1a** to **2a** proceeded with complete recovering of the ester **7a** and **7b** having a

propargyl ether with a terminal alkyne. It was noteworthy that the reaction in the presence of Ph-CO₂Et was somewhat slow and gave **2a** in 63% along with 35% of recovered **1a** (entry 2). Lewis basicity of an ester moiety may affect on the reaction, probably due to the coordination to the metal center of an active species.

Scheme 2 demonstrates the steric nature of the present reagent system and the reported systems for LiH- and CaH₂-based reduction. Thus, 4-*t*-butylcyclohexanone was subjected to the reduction with these reagents, providing a mixture of two diastereoisomers, i.e., *ax*-**2q** and *eq*-**2q**. CaH₂-based reagents, cat. Ti(O-*i*-Pr)₄/ZnCl₂/CaH₂ and cat. ZnCl₂/CaH₂/Me₃SiCl systems, exhibited the similar stereoselectivity and gave equatorial alcohol predominantly. The results suggest that the reaction may involve a small hydride source allowing an attack from the axial position and/or the reactions may proceed through the product-developing control process.⁹ Meanwhile, interestingly, it has been reported that reduction of **1q** with cat. Zn(OSO₂Me)₂/LiH/Me₃SiCl system gave the axial alcohol predominantly.²

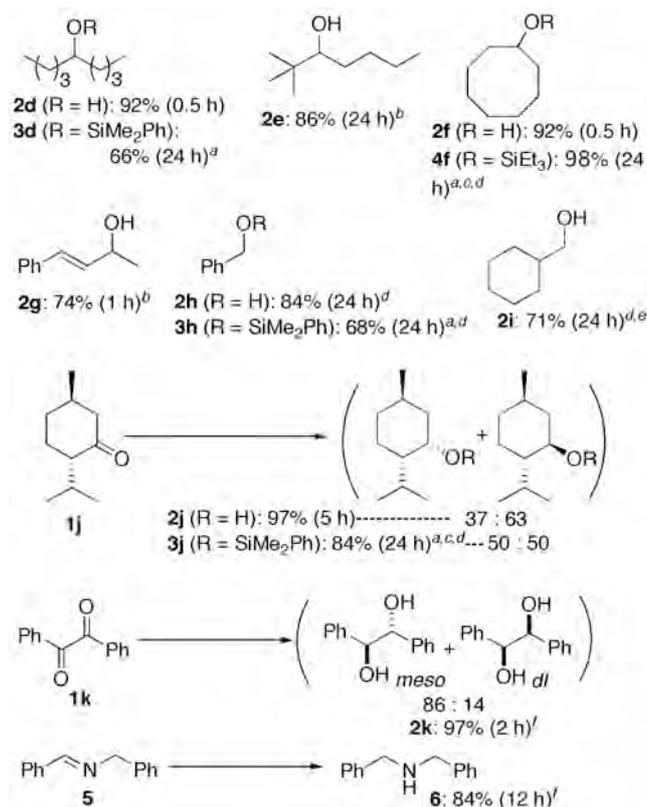


Figure 1. Reduction of carbonyl compounds with a CaH₂/R₃SiCl/ZnCl₂ catalyst system.[†] ^aFor work-up, H₂O was used instead of 1M HCl. ^bFor work-up, *n*-Bu₄NF in THF was used instead of 1M HCl. ^c1.8 eq of R₃SiCl was used. ^d0.2 equiv of ZnCl₂ was used. ^e26 % of the substrate was recovered. ^f0.2, 6 and 2.6 eq of ZnCl₂, CaH₂ and Me₃SiCl, respectively, were used.

Table 2. Functional group compatibility.

entry	substrate(s)	isolated yield, %
1		2m : 94%
2		2n : 98%
3		2p : 75%
4	1a + Ph-CO ₂ Et (7a , 1.0 eq)	2a : 62% (1a : 35% recovered) 7a : quantitatively recovered
5	1a +	2a : 80% 7b : quantitatively recovered

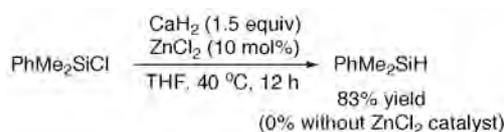
reagents and conditions	ax-2q : eq-2q
CaH ₂ /ZnCl ₂ /cat. Ti(O- <i>t</i> Pr) ₄ (1.4/1.3/0.05) THF, 40 °C, 24 h	16 : 84
CaH ₂ /Me ₃ SiCl/cat. ZnCl ₂ (1.5/1.3/0.1) THF, 40 °C, 24 h	17 : 83
LiH/Me ₃ SiCl/cat. Zn(OSO ₂ Me) ₂ (2.0/2.0/0.012) CH ₂ Cl ₂ , 40 °C, 50 h	[see ref. 2] 72 : 28 ^{ref. 2}

Scheme 2. Reduction of 4-*t*-butylcyclohexanone with LiH- and CaH₂-based reagents.

The reduction with cat. ZnX₂/CaH₂/Me₃SiCl was heterogeneous throughout the reaction. After mixing the reagents, solid and liquid phases of the resulting heterogeneous mixture were separated by filtration and the reactivity of these phases was investigated. It was found that the filtrate from a mixture of CaH₂ (1.5 eq), ZnCl₂ (0.1 eq) and Me₃SiCl (1.3 eq) reduced **1a** in 15% yield after 2 h at 40 °C but the precipitate was essentially inert even after addition of Me₃SiCl (1.3 eq) and ZnCl₂ (0.1 eq). These suggest that a certain species soluble in THF was generated and it could reduce **1a**.

On the basis of the results, we thought the possibility of generation of a hydrosilane(s) from CaH₂ and silyl chloride.

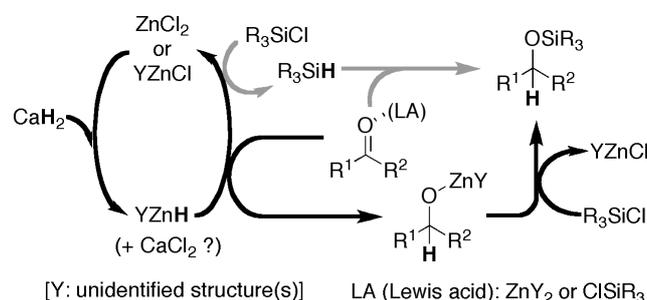
Thus, we carried out the reaction of PhMe₂SiCl (1.0 equiv) and CaH₂ (1.5 equiv) in the presence or absence of ZnCl₂ (0.10 equiv) in THF (for 2 h at 40 °C) (Scheme 3).

**Scheme 3.** Reduction of PhMe₂SiCl with cat. ZnCl₂/CaH₂.

Though the reaction without the zinc salt did not provide the corresponding hydrosilane at all, 83% yield of PhMe₂SiH was obtained by the reaction in the presence of ZnCl₂, after aqueous work-up. It has been reported that the reaction of CaH₂ and Me₃SiCl provided Me₃SiH in the presence of a catalytic amount of AlCl₃¹⁰ but it needed a high reaction temperature (270 °C). Accordingly, it should be noted that the present hydrosilane formation proceeded under much milder conditions.

The results may suggest that the present carbonyl reduction would proceed *via* hydrosilylation by *in situ* generated R₃SiH.¹¹ However, **1a** did not react with Et₃SiH or PhMe₂SiH (1.3 equiv) in the presence of a catalytic amount of ZnCl₂ (10 mol%) in THF at 40 °C (12 h).

Possible mechanism of the present reduction (or hydrosilylation) is illustrated in Scheme 4, which involves hydrozincation of carbonyl compounds with a zinc hydride species generated from CaH₂ and ZnX₂, where R₃SiCl may act as a Lewis acid to activate carbonyl compounds and as a silylation agent of the resulting zinc-alkoxides to give the corresponding silyl ether and zinc-chloride species. However, a hydrosilylation pathway (shown with gray arrows in Scheme 4) by *in situ* generated R₃SiH can not be neglected even when the results in Scheme 3 could be considered, because in the reaction mixture zinc salts may be no longer ZnCl₂. Further study to clarify the mechanism is underway.

**Scheme 4.** Possible reaction mechanism.

In summary, we have demonstrated that CaH₂/silyl chloride reduced carbonyl compounds in the presence of a catalytic amount of zinc salt.¹² The cat. ZnX₂/CaH₂/R₃SiCl system developed here is more general for carbonyl reduction than

the previously developed CaH_2 - or LiH -based reagents. Although reaction mechanism is unclear at this time, the method may be useful because of its inexpensiveness and high functional group compatibility. In addition, it was found that hydrosilanes from chlorosilanes could be obtained under the mild reaction conditions by treatment with CaH_2 in the presence of a ZnX_2 catalyst.

Acknowledgment

This study was partially supported by the Scientific Frontier Research Project from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References and notes

1. N. Greeves, In *Comprehensive Organic Synthesis*; B. M. Trost and I. Fleming, Eds.; Pergamon Press: Oxford, 1991, vol. 9, p. 1. J. Seyden-Penne, *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; VHC: 1991.
2. Ohkuma, T.; Hashiguchi, S.; Noyori, R. *J. Org. Chem.* **1994**, *59*, 217.
3. Gao, Y.; Urabe, H.; Sato, F. *J. Org. Chem.* **1994**, *59*, 5521. Gao, Y.; Harada, K.; Hata, T.; Urabe, H.; Sato, F. *J. Org. Chem.* **1995**, *60*, 290.
4. Uchiyama, M.; Furumoto, S.; Saito, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1997**, *119*, 11425.
5. Gerhard, H.; Horst, J. *Chem. Ber.* **1959**, *92*, 2022. Mikheeva, V. I.; Fedneva, E. M.; Alpatova, V. I. *Doklady Akademii Nauk SSSR* **1959**, *131*, 318. Koester, R.; Huber, H. *Inorg. Synth.* **1977**, *17*, 17.
6. Schwarz, M.; Haidue, A.; Stil, H.; Paulus, P.; Greerlings, H. *J. Alloys and Compounds* **2005**, *404-406*, 762.
7. Caldwell, W. E.; Krauskopf, F. C. *J. Am. Chem. Soc.* **1929**, *51*, 2936.
8. Aida, T.; Kuboki, N.; Kato, K.; Uchikawa, W.; Matsuno, C.; Okamoto, S. *Tetrahedron Lett.* **2005**, *46*, 1667.
9. It has been reported that Me_2ZnHLi reagent reduces effectively aldehydes having a α -hydrogen. See ref 4.
10. R. Calas, P. Bourgeois, *Bull. Soc. Chim. Fr.* **1971**, 3263.
11. ZnCl_2 -Catalyzed hydrosilylation has been reported: Lapkin, I. I.; Dvinskikh, V. V. *Zh. Obshchei Khim.* **1978**, *48*, 2509.
12. General procedure for reduction (or hydrosilylation) of carbonyl compounds: A mixture of CaH_2 (3.0 mmol) and ZnX_2 (10~20 mol%) in THF (10 mL) was stirred for 1 h at 40 °C. To this were added the substrate **1** (2.0 mmol) and R_3SiCl (2.6 mmol) and the mixture was stirred at 40 °C. After checking the completion of the reaction by TLC analysis, the mixture was filtered through a pad of Celite with ether[†] and the filtrate was washed with aqueous 1M HCl (for isolation of the alcohol) or saturated aqueous NH_4Cl (for isolation of the silyl ether) and extracted with ether. The combined organic layers were washed with saturated aqueous NaHCO_3 . The following usual work-up gave the corresponding alcohol **2** or its silyl ether. [†]For work-up, other appropriate solvents such as hexane and pentane than ether can be used for filtration and extraction. After filtration, the resulting cake containing the remaining CaH_2 should be quenched by treatment with 2-propanol for safe. CaH_2 (powder), anhydrous ZnCl_2 and ZnBr_2 were purchased from Wako Pure Chemical Industries, Ltd.