

Graphical Abstract

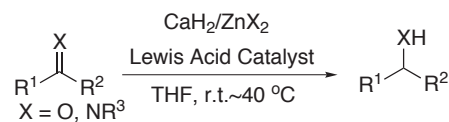
**Use of CaH_2 as a reductive hydride source:
Reduction of ketones and imines with
 $\text{CaH}_2/\text{ZnX}_2$ in the presence of a Lewis acid**

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Use of CaH_2 as a reductive hydride source: Reduction of ketones and imines with $\text{CaH}_2/\text{ZnX}_2$ in the presence of a Lewis acid

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Abstract—A new combination reagent of $\text{CaH}_2/\text{ZnX}_2$ effectively reduced a variety of ketones and imines to the corresponding alcohols and amines, respectively, in the presence of a catalytic amount of a Lewis acid such as $\text{Ti}(\text{O}-i\text{-Pr})_4$, $\text{Al}(\text{O}-i\text{-Pr})_3$, $\text{B}(\text{O}-i\text{-Pr})_3$ and ZnF_2 . © 2011 Elsevier Science. All rights reserved

Reduction with metal hydride reagents has been widely utilized as a routine protocol in organic synthesis, and numerous hydride compounds and reagent systems have been developed and are used. Recently, efforts have been made to utilize LiH as a hydride source, which is a basically inert metal hydride, inexpensive, stable to handle and environmentally benign. Thus, in 1994 Noyori *et al.* demonstrated that LiH could be used as an agent for carbonyl reduction in the presence of TMSCl and a catalytic amount of ZnX_2 .¹ At the same time, Sato *et al.* showed that reaction of alkynes or conjugated dienes with $\text{ZnI}_2/2\text{LiH}$ reagent underwent hydrometalation in the presence of Cp_2TiCl_2 .² Generation of dialkylzinc hydride ate complexes from LiH and ZnR_2 has been also reported.³ These results prompted us to investigate use of CaH_2 as a reductive hydride source, which is also a basically inert, inexpensive, and stable metal hydride and is usually used as a drying agent. Herein we report that a reagent combination of CaH_2 and ZnX_2 reduces effectively ketones and imines to the corresponding alcohols and amines in the presence of a catalytic amount of a Lewis acid.

To investigate the possibility of the use of CaH_2 as a reductive hydride source, we carried out the reactions of acetophenone (**1a**) and an imine **2a** derived from benzaldehyde and benzyl amine with CaH_2 and ZnX_2 under various reaction conditions (Table 1).^{4,5} Thus, a mixture of CaH_2 (powder, 1.3 mmol) and anhydrous ZnX_2 (0.2~1.4

Table 1^a

entry	sub- strate	ZnX_2 (equiv)	additive (mol%)	product yield, % ^b	recovered 1 or 2 , % ^b
1	1a	ZnBr_2 (1.4)	—	3a <5	~90%
2	1a	ZnBr_2 (1.2)	—	3a 0	quant.
3	1a	ZnBr_2 (0.2)	TMSCl (150)	3a 40 ^c	60 ^c
4 ^d	1a	ZnBr_2 (0.2)	TMSCl (150)	3a 0 ^c	quant ^c
5	1a	ZnBr_2 (1.2)	$\text{Ti}(\text{O}-i\text{-Pr})_4$ (5)	3a quant	0
6	1a	ZnCl_2 (1.2)	$\text{Ti}(\text{O}-i\text{-Pr})_4$ (5)	3a quant	0
7	1a	ZnI_2 (1.2)	$\text{Ti}(\text{O}-i\text{-Pr})_4$ (5)	3a quant	0
8	1a	ZnF_2 (1.2)	$\text{Ti}(\text{O}-i\text{-Pr})_4$ (5)	3a 0	quant
9	2a	ZnBr_2 (1.4)	—	4a quant	0
10	2a	ZnBr_2 (1.2)	—	4a 0	quant
11	2a	ZnBr_2 (1.2)	$\text{Ti}(\text{O}-i\text{-Pr})_4$ (5)	4a quant	0

^aThe reactions were performed at 40 °C except for entries 3 and 4 (room temperature). ^bYields were determined by ¹H NMR analysis of the crude residue using an internal standard.

^cElongation of the reaction time (48 h) did not improved the yield.

^dThe reaction was carried out in toluene.

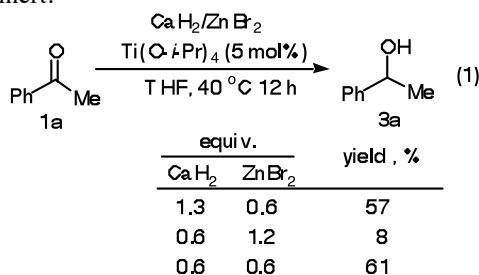
mmol) in THF (3 mL) was stirred at room temperature or 40 °C for 1.5 h. To this were added a solution of ketone **1a** or the imine **2a** (1.0 mmol) in THF (1 mL) and the additive.

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The resulting mixture was stirred for 12 h at room temperature or 40 °C.

As revealed from Table 1, it was found that CaH₂ could act as a reductive hydride source: With a 1.3:1.4 mixture of CaH₂ and ZnBr₂, a trace amount of **3a** was obtained by the reaction of **1a** (entry 1) and imine **2a** was effectively reduced to amine **4a** (entry 9). However, a 1.3:1.2 mixture of CaH₂ and ZnBr₂ did not reduce **1a** and **2a** at all (entries 2 and 10). CaH₂ in the presence of a catalytic amount of ZnBr₂ and a stoichiometric amount of TMSCl reduced **1a** in THF; however, the reaction did not complete (entry 3). We found that in the presence of a catalytic amount of Ti(O-*i*-Pr)₄ an essentially inert 1.3:1.2 mixture of CaH₂ and ZnX₂ could reduce **1a** and **2a** quantitatively to afford **3a** and **4a**, respectively (entries 5-7 and 11), where ZnCl₂, ZnBr₂, ZnI₂ could be used equally. However, the reaction with ZnF₂ did not proceed at all (entry 8).

With these results, we studied the stoichiometry of CaH₂ and ZnX₂ in the reaction. As can be seen from eq 1, it was found that the reduction was stoichiometric on both CaH₂ and ZnX₂: thus, a 2:1 and 1:1 mixture of CaH₂ and ZnBr₂ reduced **1a** in a stoichiometric fashion to the amount of ZnBr₂. However, a 1:2 mixture of CaH₂ and ZnBr₂ was nearly inert.



The results shown in Table 1 and eq 1 may be explained by the following assumptions: (i) CaH₂ and ZnX₂ except for ZnF₂ can make a complex(es) in a 1:1 ratio when one or more equivalent of CaH₂ was mixed with ZnX₂. A 1:2 mixture of CaH₂ and ZnX₂ may make a different species. (ii) A 1:1 complex(es) of CaH₂ and ZnX₂ thus generated is essentially inert for reduction of ketones and imines. Ti(O-*i*-Pr)₄ may act as a Lewis acid activating the substrates in a catalytic manner to undergo the reduction with a CaH₂/ZnX₂ (1:1) reagent.⁶

Based on these hypotheses we carried out the reaction with other Lewis acid catalysts (Table 2). As expected, in addition to Ti(O-*i*-Pr)₄ other metal alkoxides (5 mol%) such as Al(O-*i*-Pr)₃ and B(O-*i*-Pr)₃ could effectively catalyze the reduction of **1a** and **2a** with CaH₂/ZnBr₂ (1.3:1.2). Similarly, ZnF₂ catalyzed the reduction of ketone and imine (entries 4 and 8).⁶

With these results in hand, we chose a reagent system CaH₂/ZnBr₂/Ti(O-*i*-Pr)₄ (1.3:1.2:0.05) and carried out the reduction of other ketones and imines.⁷ The results of the reactions with the representative carbonyl compounds and imines are summarized in Table 3 and Table 4, respectively.

Table 2

entry	substrate	additive	product	yield, % ^a
1	ketone 1a	Ti(O- <i>i</i> -Pr) ₄	3a	quant (92) ^b
2	1a	Al(O- <i>i</i> -Pr) ₃	3a	quant
3	1a	B(O- <i>i</i> -Pr) ₃	3a	quant
4	1a	ZnF ₂	3a	quant
5	imine 2a	Ti(O- <i>i</i> -Pr) ₄	4a	quant (86) ^b
6	2a	Al(O- <i>i</i> -Pr) ₃	4a	quant
7	2a	B(O- <i>i</i> -Pr) ₃	4a	78 ^c
8	2a	ZnF ₂	4a	quant

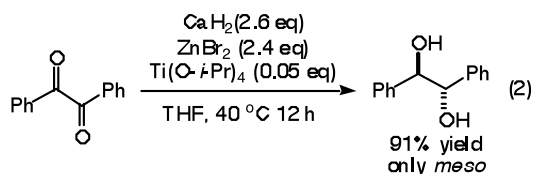
^aUnless otherwise indicated, yields were determined by ¹H NMR analysis of the crude residue using an internal standard. ^bIsolated yield. ^c22% of **2a** was recovered.

Table 3

entry	R ¹	R ²	yield of 3 , % ^a
1	Ph	<i>n</i> -Bu	86 (85) ^b
2	Ph	Ph	90
3	<i>p</i> -BrC ₆ H ₄	CH ₃	92
4	<i>p</i> -MeOC ₆ H ₄	CH ₃	90
5	—(CH ₂) ₇ —		91 (91) ^b
6	—(CH ₂) ₅ —		38 ^{c,d}
7	CH ₃ (CH ₂) ₆	CH ₃	trace ^c
8	Ph	H	complex mixture ^c

^aIsolated yield unless otherwise indicated. ^bZnCl₂ was used instead of ZnBr₂. ^cDetermined by ¹H NMR analysis of the crude residue using an internal standard. ^d62% of **1** was recovered.

As revealed from Table 3, diaryl and aryl alkyl ketones and cyclic ketones could be effectively reduced. Aldehydes and acyclic aliphatic ketones, however, were not good substrates. As shown in entries 1 and 5, ZnCl₂ as well as ZnBr₂ could be equally used for the reduction.



The reduction of benzil by the present method provided *meso*-hydrobenzoin exclusively (eq 2). The stereoselectivity can be explained by considering the

chelation control mechanism similar to that proposed for the reduction with other metal hydrides.

As listed in Table 4, a $\text{CaH}_2/\text{ZnX}_2/\text{Ti}(\text{O}-i\text{-Pr})_4$ (1.3:1.2:0.05) reagent could reduce a variety of imines in excellent yields. Thus, imines derived from aromatic and aliphatic aldehydes were cleanly converted to the corresponding amines. Imines having a benzyl, alkyl, or aromatic group as an *N*-substituent were good substrates. Functional groups such as bromo and alkenyl moieties present in the substrate were tolerant as shown in entries 4 and 6. Ketimine was also reduced in excellent yield (entry 8). ZnCl_2 was again found to be equally effective as ZnBr_2 (entries 1 and 3).

Table 4

entry	R ¹	R ²	R ³	yield of 4, % ^a
1	Ph	Bn	H	86 (85) ^b
2	Ph	<i>n</i> -Pr	H	83
3	Ph	Ph	H	92 (90) ^b
4	<i>p</i> -Br C ₆ H ₄	Bn	H	91
5	2-Furyl	Bn	H	85
6	(<i>E</i>)-PhCH=CH	CH ₂ CH=CH ₂	H	81
7	<i>n</i> -C ₅ H ₁₁	Bn	H	84
8	Ph	Bn	CH ₃	91

^a Isolated yield. ^b ZnCl_2 was used instead of ZnBr_2 .

In summary, herein we have reported that CaH_2 could be used as a reductive hydride source together with ZnX_2 and a catalytic amount of a Lewis acid, the reagent system of which could perform the reduction of ketones and imines to the corresponding alcohols and amines in good yield. To our knowledge, this is the first example of a CaH_2 -based reduction of organic molecules except for those through boron hydride formation and reduction of sulfate to sulfide.^{8,9}

Acknowledgments

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Gao, Y.; Harada, K.; Hata, T.; Urabe, H.; Sato, F. *J. Org. Chem.* **1995**, *60*, 290.
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- CaH_2 (powder), anhydrous ZnCl_2 , ZnBr_2 , ZnI_2 and ZnF_2 were purchased from Wako Pure Chemical Industries, Ltd.
- Under similar conditions the reaction of CaH_2 with MgBr_2 in the presence or absence of $\text{Ti}(\text{O}-i\text{-Pr})_4$ did not reduce **1a** at all.
- Although formation of metal hydrides derived from $\text{Ti}(\text{O}-i\text{-Pr})_4$, $\text{B}(\text{O}-i\text{-Pr})_3$ or $\text{Al}(\text{O}-i\text{-Pr})_3$ can not be ruled out, the fact that ZnF_2 , which was inert in the presence of $\text{Ti}(\text{O}-i\text{-Pr})_4$, was an effective catalyst as well as $\text{Ti}(\text{O}-i\text{-Pr})_4$ and activated the reaction with $\text{CaH}_2/\text{ZnBr}_2$ (1.3:1.2) may suggest a role of these metal alkoxide as a Lewis acid. In addition, the reaction of **1a** and CaH_2 (1.3 eq.) with 1.3 equiv of $\text{Ti}(\text{O}-i\text{-Pr})_4$, $\text{B}(\text{O}-i\text{-Pr})_3$ or $\text{Al}(\text{O}-i\text{-Pr})_3$ in the absence of ZnX_2 did not proceed at all.
- General procedure:** A suspension of CaH_2 (1.3 mmol) and ZnX_2 (1.2 mmol) in THF (3 mL) was stirred for 1.5 h at 40 °C. To this were added a solution of ketone or imine (1.0 mmol) in THF (1 mL) and Lewis acid (0.05 mmol). The resulting mixture was stirred for 12 h at 40 °C. After being cooled to room temperature, the mixture was slowly poured into aqueous saturated NH_4Cl . The mixture was extracted with ether or AcOEt , dried over MgSO_4 and concentrated.
- It has been reported that CaH_2 and $\text{B}(\text{OMe})_3$ gave a complex at 215 °C, which reduced carbonyl compounds: Hesse, Gerhard; Jager, Horst, *Chem. Ber.* **1959**, *92*, 2022.
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