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Use of CaH_2 as a reductive hydride source: reduction of ketones and imines with CaH_2/ZnX_2 in the presence of a Lewis acid

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Abstract—A new combination reagent of CaH_2/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 Ti(O-*i*-Pr)$_4$, Al(O-*i*-Pr)$_3$, B(O-*i*-Pr)$_3$ and ZnF_2.

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 and co-workers 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 and co-workers showed that reaction of alkynes or conjugated dienes with $ZnI_2/2LiH$ reagent underwent hydrometallation 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 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. The resulting mixture was stirred for 12 h at room temperature or 40 °C.

As revealed from Table 1, it was found that CaH_2 could act as a reductive hydride source: with a 1.3:1.4 mixture of CaH_2 and $ZnBr_2$, 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 CaH_2 and $ZnBr_2$ did not reduce **1a** and **2a** at all (entries 2 and 10). CaH_2 in the presence of a catalytic amount of $ZnBr_2$ 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 CaH_2 and ZnX_2 could reduce **1a** and **2a** quantitatively to afford **3a** and **4a**, respectively (entries 5–7 and 11), where $ZnCl_2$, $ZnBr_2$, ZnI_2 could be used equally. However, the reaction with ZnF_2 did not proceed at all (entry 8).

With these results, we studied the stoichiometry of CaH_2 and ZnX_2 in the reaction. As can be seen from Eq. 1, it was found that the reduction was stoichiometric on both CaH_2 and ZnX_2: thus, a 2:1 and 1:1 mixture of CaH_2 and $ZnBr_2$ reduced **1a** in a stoichiometric fashion to the amount of $ZnBr_2$. However, a 1:2 mixture of CaH_2 and $ZnBr_2$ was nearly inert.

Keywords: Calcium hydride; Reduction.

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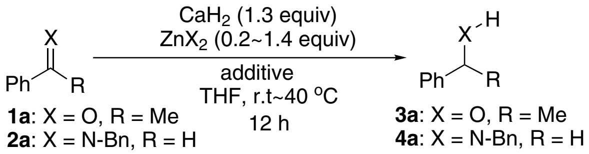
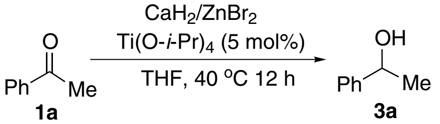
Table 1. [a]



Entry	Substrate	ZnX_2 (equiv)	Additive (mol%)	Product		Recovered **1** or **2**[b], %
					Yield[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)	Ti(O-*i*-Pr)$_4$ (5)	**3a**	Quant	0
6	**1a**	$ZnCl_2$ (1.2)	Ti(O-*i*-Pr)$_4$ (5)	**3a**	Quant	0
7	**1a**	ZnI_2 (1.2)	Ti(O-*i*-Pr)$_4$ (5)	**3a**	Quant	0
8	**1a**	ZnF_2 (1.2)	Ti(O-*i*-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)	Ti(O-*i*-Pr)$_4$ (5)	**4a**	Quant	0

[a] The reactions were performed at 40 °C except for entries 3 and 4 (room temperature).
[b] Yields were determined by ^{1}H NMR analysis of the crude residue using an internal standard.
[c] Elongation of the reaction time (48 h) did not improved the yield.
[d] The reaction was carried out in toluene.



equiv.		
CaH_2	$ZnBr_2$	yield , %
1.3	0.6	57
0.6	1.2	8
0.6	0.6	61

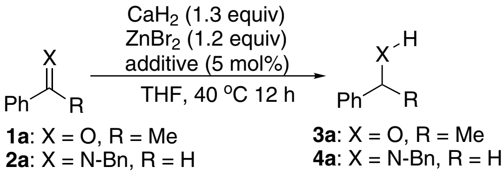
(1)

The results shown in Table 1 and Eq. 1 may be explained by the following assumptions: (i) CaH_2 and ZnX_2 except for ZnF_2 can make a complex(es) in a 1:1 ratio when one or more equivalent of CaH_2 was mixed with ZnX_2. A 1:2 mixture of CaH_2 and ZnX_2 may make a different species. (ii) A 1:1 complex(es) of CaH_2 and ZnX_2 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 CaH_2/ZnX_2 (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 CaH_2/$ZnBr_2$ (1.3:1.2). Similarly, ZnF_2 catalyzed the reduction of ketone and imine (entries 4 and 8).[6]

With these results in hand, we chose a reagent system CaH_2/$ZnBr_2$/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 Tables 3 and 4, respectively.

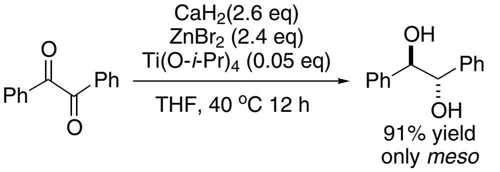
Table 2.



Entry	Substrate	Additive	Product	
				Yield, % [a]
1	Ketone **1a**	Ti(O-*i*-Pr)$_4$	**3a**	Quant (92)[b]
2	**1a**	Al(O-*i*-Pr)$_3$	**3a**	Quant
3	**1a**	B(O-*i*-Pr)$_3$	**3a**	Quant
4	**1a**	ZnF_2	**3a**	Quant
5	Imine **2a**	Ti(O-*i*-Pr)$_4$	**4a**	Quant (86)[b]
6	**2a**	Al(O-*i*-Pr)$_3$	**4a**	Quant
7	**2a**	B(O-*i*-Pr)$_3$	**4a**	78[c]
8	**2a**	ZnF_2	**4a**	Quant

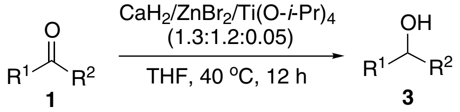
[a] Unless otherwise indicated, yields were determined by ^{1}H NMR analysis of the crude residue using an internal standard.
[b] Isolated yield.
[c] 22% of **2a** was recovered.

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, $ZnCl_2$ as well as $ZnBr_2$ could be equally used for the reduction.



(2)

Table 3.



Entry	R^1	R^2	Yield of **3**[a], %
1	Ph	*n*-Bu	86 (85)[b]
2	Ph	Ph	90
3	*p*-BrC_6H_4	CH_3	92
4	*p*-$MeOC_6H_4$	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]

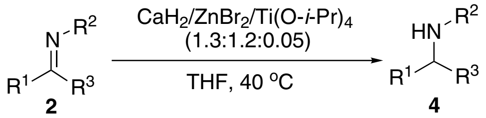
[a] Isolated yield unless otherwise indicated.

[b] $ZnCl_2$ was used instead of $ZnBr_2$.

[c] Determined by ^1H NMR analysis of the crude residue using an internal standard.

[d] 62% of **1** was recovered.

Table 4.



Entry	R^1	R^2	R^3	Yield of **4**[a], %
1	Ph	Bn	H	86 (85)[b]
2	Ph	*n*-Pr	H	83
3	Ph	Ph	H	92 (90)[b]
4	*p*-BrC_6H_4	Bn	H	91
5	2-Furyl	Bn	H	85
6	(*E*)-$PhCH{=}CH$	$CH_2CH{=}CH_2$	H	81
7	*n*-C_5H_{11}	Bn	H	84
8	Ph	Bn	CH_3	91

[a] Isolated yield.

[b] $ZnCl_2$ was used instead of $ZnBr_2$.

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 $CaH_2/ZnX_2/Ti(O\text{-}i\text{-}Pr)_4$ (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).

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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4. CaH_2 (powder), anhydrous $ZnCl_2$, $ZnBr_2$, ZnI_2 and ZnF_2 were purchased from Wako Pure Chemical Industries, Ltd.
5. Under similar conditions the reaction of CaH_2 with $MgBr_2$ in the presence or absence of $Ti(O\text{-}i\text{-}Pr)_4$ did not reduce **1a** at all.
6. Although formation of metal hydrides derived from $Ti(O\text{-}i\text{-}Pr)_4$, $B(O\text{-}i\text{-}Pr)_3$ or $Al(O\text{-}i\text{-}Pr)_3$ cannot be ruled out, the fact that ZnF_2, which was inert in the presence of $Ti(O\text{-}i\text{-}Pr)_4$, was an effective catalyst as well as $Ti(O\text{-}i\text{-}Pr)_4$ and activated the reaction with $CaH_2/ZnBr_2$ (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 equiv) with 1.3 equiv of $Ti(O\text{-}i\text{-}Pr)_4$, $B(O\text{-}i\text{-}Pr)_3$ or $Al(O\text{-}i\text{-}Pr)_3$ in the absence of ZnX_2 did not proceed at all.
7. *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.
8. It has been reported that CaH_2 and $B(OMe)_3$ gave a complex at 215 °C, which reduced carbonyl compounds: Hesse, Gerhard; Jager; Horst *Chem. Ber.* **1959**, *92*, 2022; Formation of B_2H_6 by the reaction of CaH_2 and BF_3 at 120 °C has been reported: Mikheeva, V. I.; Fedneva, E. M.; Alpatova, V. I. *Dok. Akad. Nauk SSSR* **1959**, *131*, 318; Formation of $Ca(BH_4)_2$ from CaH_2 and Et_3NBH_3 has been reported: Koester, R; Huber, H. *Inorg. Synth.* **1977**, *17*, 17.
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