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Reduction of ketones to alcohols using a decaborane/pyrrolidine/cerium(III) chloride system in methanol

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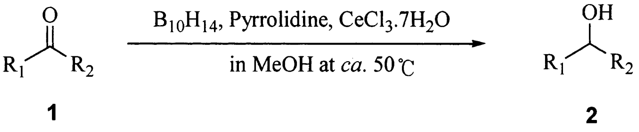
Abstract—Decaborane was found to be an effective agent for the chemoselective reduction of ketones to alcohols in the presence of pyrrolidine and cerium(III) chloride heptahydrate in methanol. © 2001 Elsevier Science Ltd. All rights reserved.

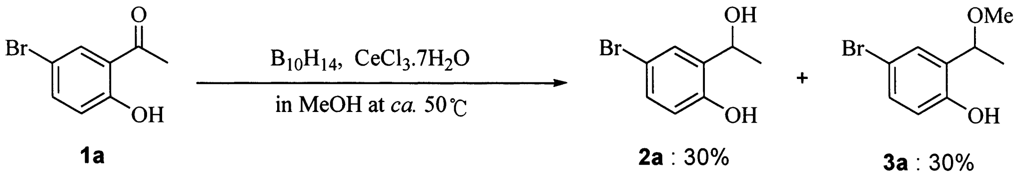
Reduction of ketones is a general synthetic method for the preparation of secondary alcohol in organic synthesis. Even if a wide variety of reagents are available for the reduction of ketone,[1] the development of mild methods without affecting other functional groups has been of interest in organic chemistry.[2]

Decaborane is quite a stable white boron cluster and is therefore easy to handle. During the continuous study on the reductive amination using decaborane as a mild reducing agent,[3] we found that ketones with a variety of other functional groups were reduced to the corresponding secondary alcohols with decaborane in methanol at ca. 50°C in the presence of pyrrolidine and cerium(III) chloride heptahydrate (Scheme 1). The optimum amounts of reagents were 30 mol% of decaborane, 30 mol% of pyrrolidine and 10 mol% of cerium(III) chloride heptahydrate (with respect to ketones).

The effects of the reaction temperature and additives were studied in detail. Without cerium chloride heptahydrate, the reaction did not proceed at all. Although the reduction of ketone proceeded in the presence of cerium chloride heptahydrate with 30 mol% of decaborane, it was slow and the yield of **2a** was low due to the formation of the reductive etherification side product **3a** and the incomplete reaction (Scheme 2).[4] When pyrrolidine as a base was added to the reaction, the yield of **2a** was found to be improved. The optimum amount of pyrrolidine needed in the reaction was studied and results are shown in Table 1. When 10 mol% of pyrrolidine was used in the reaction (entry 2), the formation of side product was reduced and the yield of **2a** was increased. The side product and starting ketone were not detected in TLC at all when 3:1 mole ratio of pyrrolidine and cerium chloride heptahydrate was used (entry 4).



Scheme 1.



Scheme 2.

Keywords: reduction; ketone; decaborane; pyrrolidine; cerium chloride heptahydrate; alcohol.

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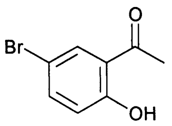
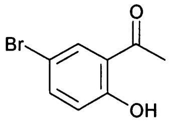
Table 1. Results depending on the ratio of base and cerium chloride heptahydrate

Entry	Ketone	Pyrrolidine (equiv.)	$CeCl_3 \cdot 7H_2O$ (equiv.)	Yield (%)[a]
1		None	0.1	30
2		0.1	0.1	81
3		0.2	0.1	84
4		0.3	0.1	95
5		0.1	0.2	83
6		0.1	0.3	81

[a] Isolated yields.

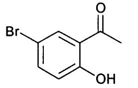
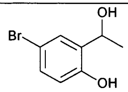
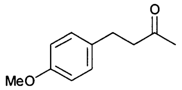
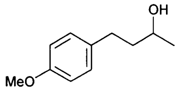
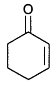
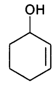
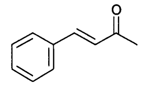
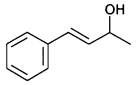
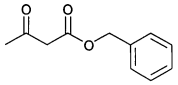
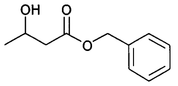
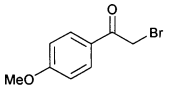
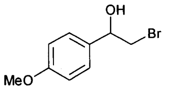
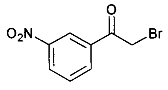
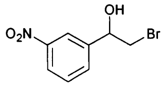
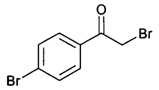
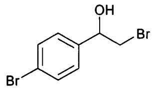
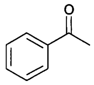
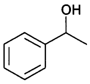
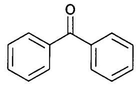
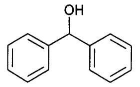
Table 2. Results depending on the amines used[a]

Entry	Ketone	Amine (equiv.)	$CeCl_3 \cdot 7H_2O$ (equiv.)	Time (h)	Yield (%)[b]
1	 **1a**	Piperidine (0.3)	0.1	4	97
2		Pyrrolidine (0.3)	0.1	4	95
3		Triethylamine (0.3)	0.1	4	85
4		Pyridine (0.3)	0.1	4	84

[a] To a solution of 5-bromo-2-hydroxy acetophenone (100 mg, 0.465 mmol) in methanol (5 ml) was added amine (30 mol%), cerium(III) chloride heptahydrate (10 mol%) and decaborane (30 mol%). The resulting solution was stirred at ca. 50°C under nitrogen for 4 h.

[b] Isolated yield of **2a**.

Table 3. Reduction of ketones[5]

Entry	Ketone (1)	Time (h)	Product (2)[a]	Yield[b] (%)
1		>4		96
2		6		95
3		4		92
4		5		98
5		1.5		98
6		2		96
7		2		92
8		2		95
9		4		97
10		8		97

a) All products were known compounds and gave spectra (GC-MS, ^1H NMR, IR) consistent with the assigned structures. b) Isolated yields.

Among amines examined, the secondary amines (pyrrolidine and piperidine) were more efficient than triethylamine and pyridine (Table 2). The roles of the amine in the present reduction are not clear[5] and are under investigation.

The reaction proceeded at room temperature but slowly. The reaction rate was increased when the reaction temperature was increased. The reaction was fast enough at ca. 50°C using the aforementioned optimum amount of additives (pyrrolidine, cerium chloride heptahydrate and decaborane). Under our reaction conditions, the reduction of ketones was completed within 8 h to give the corresponding alcohols in high yields. This system is also effective for the reduction of the relatively less reactive benzophenone (entry 10, Table 3).

Other functional groups such as nitro (entry 7), ester (entry 5) and bromide (entries 1, 6, 7, and 8) remained unaffected under the reaction conditions. The reduction of the double bond in conjugated ketones (entries 3 and 4) was not observed at all. Pyrrolidene rather than piperidine was chosen in the reaction because it is cheaper than piperidine.

In conclusion, ketones were reduced to the corresponding alcohols using decaborane in the presence of pyrrolidine and cerium(III) chloride heptahydrate in methanol. The reaction is efficient and compatible with other functional groups such as nitro, ester, bromide and the double bond of conjugated ketone.

Acknowledgements

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4. When excess amounts of cerium chloride (20, 50 and 100 mol%) were used, similar results (low yield) were obtained due to the same reason.
5. *Representative experimental procedure*: To a solution of benzophenone (100 mg, 0.548 mmol) in methanol (5 ml) was added pyrrolidine (14 mg, 0.164 mmol), cerium(III) chloride heptahydrate (20.4 mg, 0.0548 mmol) and decaborane (20.1 mg, 0.164 mmol). The resulting solution was stirred at ca. 50°C under nitrogen for 8 h. The reaction was followed by TLC using a solution of ethyl acetate and hexane (1:10). The reaction was concentrated under reduced pressure and chromatographed on a short pad of silica gel using a solution of ethyl acetate and *n*-hexane (1:15) to give the product alcohol as a white solid.