



Anhydrous Cerium(III) Chloride - Effect of the Drying Process on Activity and Efficiency

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Abstract: The activity and efficiency of anhydrous CeCl_3 depend strongly on the drying procedure. Deactivation of CeCl_3 occurs during the drying process as a result of hydrolysis by the hydrate water, when heating above 90°C . The highly active CeCl_3 , prepared by an improved drying procedure, is demonstrated to activate rapidly (in catalytic and stoichiometric amounts) ketones at room temperature, providing excellent addition of organometallic reagents. Copyright © 1996 Elsevier Science Ltd

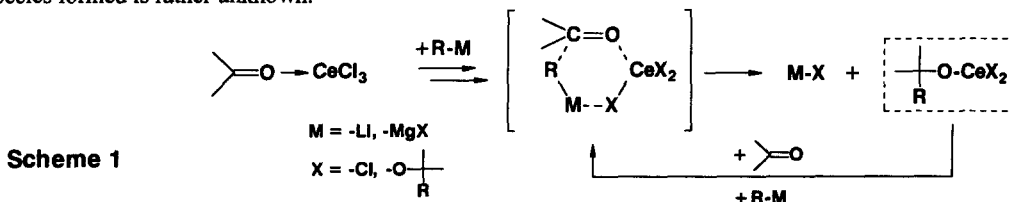
The application of anhydrous CeCl_3 for the preparation of organocerium(III) reagents for addition reactions to carbonyl compounds has been undoubtedly one of the most important synthetic methods developed in the recent years.¹ The use of these reagents allowed to avoid the so-called abnormal reactions, appearing in some cases when *Grignard* reagents have been applied, such as enolisation, reduction, condensation and conjugate addition. The advantages of different organocerium reagents have been widely demonstrated^{1e, 2} and have been recently applied for various organic transformations.³ The key step in the method developed by *Imamoto*^{1c,e} represents first a drying procedure for $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ *in vacuo* by heating it up to $135\text{-}140^\circ\text{C}$. In a second step the anhydrous CeCl_3 is stirred in THF at room temperature for the formation of a suspension of $\text{CeCl}_3 \cdot n\text{THF}$ -complex, which can be improved by sonication.⁴ The preparation of " RCeCl_2 "-reagents occurs *in situ* in a temperature range between 0° and -78°C , depending on the thermal stability of the reagents, which is followed by the addition of the substrate. In the reverse addition, described by *Imamoto*,^{1c} the *Grignard* reagent has been added to the mixture of carbonyl compound/ CeCl_3 /THF at 0°C and has been also shown to provide satisfactory results. In the reported experimental procedures CeCl_3 has been usually used in a large excess^{1c,e, 3c,e, 4} and the reaction mixtures are usually highly heterogeneous.^{3a, 5a}

We have reported recently a modified procedure for activation of ketones with catalytic or stoichiometric amounts of CeCl_3 , providing excellent addition of organometallic reagents.⁵ Investigating the addition reactions of different organometallics to camphor and fenchone, we found that these ketones were very sensitive to the quality of the anhydrous CeCl_3 used and the addition procedure, and the results are presented below. The addition reactions to camphor⁶ and fenchone,^{1c,e} as well as to related ketones⁷ have been previously reported in isolated cases⁸ because of their low reactivity.

The success of the addition of organometallics to camphor and fenchone (Table 1, entries 1-11) was found to depend strongly on the activity of CeCl_3 irrespectively of the addition procedure used. When applying the *Imamoto*-procedure^{1c,e, 6} (see above) it was difficult to achieve complete conversion of the ketones.^{5a, 9} The room temperature activation of the ketone with CeCl_3 was found to be decisive and the organometallic reagents could be added rapidly at room temperature in excellent yields. In fact camphor and fenchone served as very sensitive "indicators" for the quality of CeCl_3 and for the addition procedure.¹⁰ In the course of further investigations some examples published earlier^{1c} were checked up with CeCl_3 , prepared by the improved drying procedure presented here, and the results obtained were either similar (entries 13-15) or better (entries 16 and 17), however for shorter reaction times and using stoichiometric amounts of CeCl_3 .











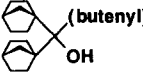




The obtained results can be summarized in the following important features:

- **The drying procedure of CeCl_3** - When heating cerium(III) chloride heptahydrate *in vacuo* the hydrate water begins to hydrolyse¹¹ the metal chloride above 90°C and the liquid collected in the liquid nitrogen trap during the drying was found to be hydrochloric acid. Therefore when drying the precursor $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, at least ca. 80% of the water have to be removed by increasing the temperature no more than 90°C. The residual hydrate water could be then removed raising the temperature up to 140°C without significant deactivation of CeCl_3 .¹²
- **The activation of the ketones** - The ketone, THF and CeCl_3 (stoichiometric or catalytic amounts) have to be mixed and stirred at room temperature until a gel-like mixture (usually yellow coloured) is formed, which is decisive as an indication for a successful activation. The time for the formation of this mixture depends on the activity of CeCl_3 and varies from 15 min. to 0.5 h, using "slow dried CeCl_3 " (see Experimental Procedure). The stirring of CeCl_3 and THF alone results in the formation of a colourless gel-like mixture,¹¹ however after a longer time in comparison with the case when the ketone is present. This observation can be explained by the additional interaction of the ketone and CeCl_3 , proceeding with complex formation.⁵
- **The addition of the organometallic reagent** - The organometallic reagents were added to the CeCl_3 -activated ketones in most of the cases at room temperature resulting in very fast reactions, usually within 0.5-1h, with the formation of almost homogeneous reaction mixtures (or even turbid solutions). The additions of the reagents occur *via* CeCl_3 /ketone-associates rather than with the uncomplexed CeCl_3 , present in the mixture, because some organometallics, e.g. $\text{CH}_2=\text{CHMgBr}$, decompose rapidly even at low temperature on contact with CeCl_3 .^{1c,5a} The formation of species of the type " RCeCl_2 " and/or " $[\text{RCeCl}_3]$ " is possible to be assumed in these cases, the latter are formed in close proximity to the carbonyl function (complex interaction) and are able to react immediately⁹. In the case of substrates, in which competing reactions with the *Grignard* reagents are possible (entry 14, reaction at 0°C) or the reagent is unstable at room temperature,¹³ the ketone/ CeCl_3 /THF-mixtures were cooled (in some cases up to -78°C) and the reactions were carried out at low temperature, resulting also in high yielded additions.
- **The catalytic activity** - Catalytic additions were observed only in the case of camphor and fenchone. However, it should be noted that by using the same organometallic reagent, when a catalytic amounts of CeCl_3 were efficient for camphor, no catalytic addition was observed with fenchone (entry 1 vs entry 6). On the contrary, when catalytic activity was observed for fenchone, stoichiometric additions were necessary for camphor (entries 3, 4 and 5 vs entries 8, 9 and 11). The addition of $\text{CH}_2=\text{CHMgI}$ appears a medial case of moderate catalytic activity (entries 2 and 7). The assumption^{5a} that the product alkoxide species $(\text{RO})_3\text{Ce}$, formed during the reactions appear as the acting catalysts (Scheme 1) was supported by the experiments. The cerium(III) alkoxide, prepared from 0.33 equivalents CeCl_3 , camphor and $\text{CH}_2=\text{CHMgBr}$ was isolated and was found to be able to catalyze the addition of the vinyl reagent to camphor. However, it is difficult to discuss cases as e.g. the catalytic addition of 1,1'-dilithium ferrocene¹⁴ (entries 9 and 11), since the nature of the cerium alkoxide species formed is rather unknown.



In conclusion we have shown that properly dried CeCl_3 enhances the efficiency of the addition reactions of organometallics to ketones and nitriles, allowing catalytic applications as well. The deactivation of CeCl_3 *via* hydrolysis during the drying process is obviously an inorganic problem, however it has to be taken into account by the organic synthetic community.

Table 1. Reactions of CeCl₃ activated ketones and nitriles with organometallic reagents^a.

No.	Substrate	CeCl ₃ equiv	Reagent (equiv)	Product	Yield ^b [%]
1		0.05	CH ₂ =CHMgBr (1.1)		R = -CH=CH ₂ 93
2		0.33	CH ₃ MgI (1.1)		-CH ₃ 91
3		1.00	NMe ₂ (CH ₂) ₃ Li (1.1)		- 77
4		1.00	 (0.5)		(CH ₂) ₃ NMe ₂ 84
5		1.00	 (1.0)		1,1'-ferrocenyl 71
					ferrocenyl
6		1.00	CH ₂ =CHMgBr (1.1)		R = -CH=CH ₂ 95
7		0.10	CH ₃ MgI (1.1)		-CH ₃ 85
8		0.05	NMe ₂ (CH ₂) ₃ Li (1.1)		- 97
9		0.05	 (0.5)		(CH ₂) ₃ NMe ₂ 70
10		1.00	 (1.0)		1,1'-ferrocenyl 84
11		0.05	 (1.0)		1,1'-ferrocenyl 76
					ferrocenyl
12		1.00	CH ₃ CH=CHCH ₂ MgBr (1.1)		(butenyl) 90 ^c
13		1.00	i-PrMgCl (1.1)		i-Pr 80 (72) ^e
14		1.00	i-PrMgCl (1.1) ^d		i-Pr 93 (80) ^e
15	PhCH=CHCOPh	1.00	PhMgBr (1.1)	PhCH=CH(OH)Ph ₂	66 (15-89) ^f
16	PhCH ₂ CN	1.00	n-BuMgBr (1.4)	PhCH ₂ CO(n-Bu)	50
17	PhCH ₂ CN	1.00	n-BuMgBr (5.0)	PhCH ₂ CO(n-Bu)	77 (28) ^g

^aTHF and the substrate were added to the anhydrous CeCl₃ and the mixture was vigorously stirred for 0.5 h at room temperature; the organometallic reagent was added rapidly at room temperature, if not noted otherwise. ^bYields of isolated analytically pure compounds, fully characterised by spectroscopic methods. ^cThe butenyl product was isomer mixture of *Z*-, *E*-crotyl and α -methylallyl alcohols, for discussion see Lit.^{5b} ^dThe *Grignard* reagent was added at 0°C and the mixture allowed to warm to room temperature. ^eLit., ^{1c} reactions at 0°C with a molar ratio of ketone/CeCl₃/*Grignard* reagent = 1:1.5:1.5. ^fLit., ^{1c} the yields are reported to be temperature dependant between -78° and +40°C; the reactions have been carried out with a molar ratio of ketone/CeCl₃/*Grignard* reagent = 1:2.5:1.5. ^gLit., ^{1c} molar ratio of nitrile/CeCl₃/*Grignard* reagent = 1:1.5:1.5.

Procedure for drying of CeCl₃. Cerium(III) chloride (45 g, CeCl₃·7H₂O, Fluka) was placed in a *Schlenk* flask equipped with PTFE stirring bar and connected through G-3 frit to a liquid nitrogen trap. The apparatus is evacuated (0.001 Torr, high vacuum pumping unit *Vakuubrand*; mechanical oil pump reaching 0.05-0.01

Torr was also used, however extended drying time was necessary) and heated at 50°C (4h), 60°C (4h), 70°C (5h) and 80°C (7h), during which ca. 80% of the hydrate water is removed. Then the temperature is increased slowly to 140°C and maintained until no more water condenses in the cold trap (ca. 20h). The anhydrous CeCl_3 is stored in a *Schlenk* flask under argon atmosphere, without loss of any activity during 10 months.

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- For data concerning additions of organometallic reagents to camphor and fenchone see Lit.⁵; for detailed analysis of earlier literature see Momtchev, M.; Vassilev, V.; Blagoev, B. *Bull. Soc. Chim. Fr.* **1985**, 844-848.
- The structure and reactivity of the *in situ* formed so-called " RCeCl_2 "-reagents seem to depend significantly on the carbanionic moiety used. (a) For the tendency of the formation of ate-complexes e.g. in the reaction of CeCl_3 with $\text{Me}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{Li}$, see Shakoor, A.; Jacob, K.; Thiele, K.-H. *Z. anorg. allg. Chem.* **1985**, *521*, 57-60. (b) For excellent discussion of the reagent stoichiometries reviewing recent studies, see Lit.^{3a}
- The CeCl_3 obtained according to Lit.^{3f} (drying of 52.92 g $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ at 150°C for 2 h) was inactive in the case of camphor and fenchone.
- On heating of the lanthanide chlorides hydrates the formation of species of the type $\text{M}(\text{OH})\text{Cl}_2$ and $\text{MOCl} \cdot \text{H}_2\text{O}$ has been described as a result of hydrolysis of the chlorides by the hydrate water, *Gmelin Handbook of Inorganic Chemistry*, Eds.: Bergman, H.; Hein, H.; Koch, E.; Merlet, P.; Vetter, U.; Springer Verlag; Berlin, 1982, Vol. Syst.-No. 39/C4a, p 171 and pp 212-214, and references cited therein.
- It has been recently reported, Evans, W.J.; Feldman, J. D.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 4581-4584, that the material obtained after drying of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (at 150°C and 0.03 Torr for 12 h) was $[\text{CeCl}_3 \cdot (\text{H}_2\text{O})]_n$. We have not analysed the CeCl_3 prepared by the presented procedure, however the material was highly efficient without excess of the organometallic reagents.
- The addition reactions of e.g. 2-pyridyllithium to camphor and fenchone had to be carried out at -78°C, since the lithium reagent is rather unstable, Genov, M.; Dimitrov, V. unpublished results.
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