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CERIUM(III) CHLORIDE AS CATALYTIC AND STOICHIOMETRIC PROMOTER OF THE QUANTITATIVE ADDITION OF ORGANOMETALLIC REAGENTS TO (+)-CAMPHOR AND (-)-FENCHONE

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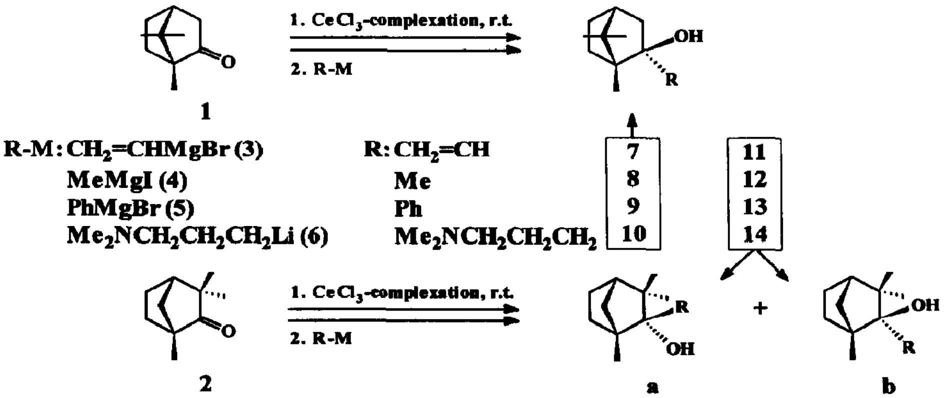
Abstract: Quantitative addition of organolithium and *Grignard* reagents to camphor (1) and fenchone (2) proceeds *via* precomplexation of the ketone with $CeCl_3$ at room temperature. Excellent addition using catalytic or substoichiometric amounts of $CeCl_3$ is demonstrated for the first time.

The use of organocerium reagents has been pioneered by *Imamoto*[1a-d] as a route providing a novel reactivity within the nucleophilic additions to carbonyl compounds. The advantages of these reagents have been widely demonstrated[2]. The used procedures include the initial preparation of anhydrous $CeCl_3$ and the corresponding tetrahydrofuran complex as a suspension by stirring at room temperature[1c] or by sonication[3]. The addition of the organometallic reagent, typically at low temperature, leads ordinarily to a heterogeneous mixture in which the *in situ* formed reagent is formulated as "$RCeCl_2$" (Scheme 2, method A). In the addition reactions to carbonyl compounds the organocerium reagent is applied in moderate or often in large excess.

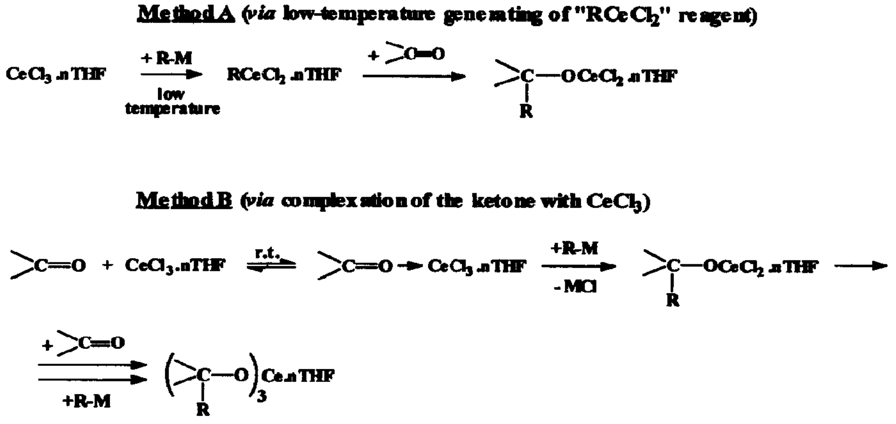
We report herein a modified approach for activation of carbonyl compounds by initial complexation with stoichiometric amounts of $CeCl_3$ at room temperature providing excellent addition of organolithium and *Grignard* reagents. With the ketones 1 and 2, following this approach, we demonstrate the first example of the use of $CeCl_3$ in catalytic amounts.



Scheme 1

We selected the sterically hindered unreactive ketones (+)-camphor (**1**) and (-)-fenchone (**2**) as relatively inexpensive starting materials leading to optically active tertiary alcohols. It has been shown that successful addition of vinyl[4] and 4-methylpentenyl[1c] *Grignard* reagents to **1** and **2**, respectively, could be achieved by the mediation of $CeCl_3$. Usually, the reactivity of **1** and especially of **2** towards some lithium and magnesium organometallics is low even with extended reaction times and excess of reagent[5a-e].

On the basis of systematic investigations we suggest a simpler, faster and more effective procedure for the quantitative conversion of the ketones **1** and **2** into the corresponding alcohols **7-10** and **11-14** (Scheme 1 and 2, method B) than the low temperature generation of "$RCeCl_2$" reagents (method A). The addition of $CeCl_3$/vinylmagnesium bromide to **1** and **2** *via* method A, according to Lit.[4] ($RCeCl_2$ generation at -78°C), led to the alcohols **7** and **11** with 92% and 87% conversion, respectively, even with an excess of organocerium reagent and extended reaction times. In contrast, applying method B in the same addition reactions, we observed a quantitative conversion within very short reaction times (Table 1, entries 1 and 2). Our method B includes as a decisive step the complexation of the ketone with $CeCl_3$ in THF at room temperature, recognizable by the formation of an yellow gel-like mixture. We found that $CeCl_3$ possessed different ability to form this gel-like mixture (formation times between 15 min. and 2 h) depending on the drying rate of $CeCl_3.7H_2O$ in vacuo[6]. The organometallic reagent is added, in most cases, rapidly at room temperature in the course of which, the initial heterogeneous mixture of $CeCl_3$ and the complexed ketone turned to an almost homogeneous one, in some cases even to a turbid solution. On the contrary, the low temperature mixing of $CeCl_3$ and the organometallic reagent results in the formation of a highly heterogeneous mixture with unknown concentration of "$RCeCl_2$" species. The exact stoichiometry in the case of method A is difficult to assess, as it has been shown that after mixing of MeLi and $CeCl_3$ in 1:1 ratio in THF the remaining undissolved solid is pure $CeCl_3$[7]. It should be further noted, that the "reversed addition" (like our method B) described by *Imamoto* - addition of a Grignard reagent to the mixture of ketone and $CeCl_3$ at 0°C (there is no data on complex formation)[1c] - even though providing satisfactory results with some ketones can not compete with method A.



Scheme 2

The complexation of **1** and **2** with stoichiometric amounts of $CeCl_3$, using method B, led in all cases to quantitative addition of the organometallic reagents **3-6**. For the first time we observed that diminished or catalytic amounts of $CeCl_3$ could provide an excellent addition of the organometallic reagent, e.g. 5 mol % of $CeCl_3$ allows a quantitative addition of vinylmagnesium bromide to camphor within 1h (Table 1).

We reasoned that when method B was used the reaction of the organometallic reagent at room temperature would occur with the $CeCl_3$ complexed ketone rather than with the uncomplexed $CeCl_3$, present in the mixture, because it is known that for example the vinyl *Grignard* reagent decomposes even at 0°C on contact with uncomplexed $CeCl_3$[1c]. The addition of equimolar quantities of $CeCl_3$/organometallic reagent would lead to alkoxide of the type $ROCeCl_2$. The application of $CeCl_3$ in 0.33 equivalents would result in the formation of the alkoxide $(RO)_3Ce$. When 0.10 or 0.05 equivalents are used, the initially formed $(RO)_3Ce$ would appear as the acting catalyst, being able to activate further amounts of the ketone *via* complexation.

Table 1. Addition of organometallic reagents to **1** and **2** using method B[a] (0.33, 0.10 and 0.05 equivalents of $CeCl_3$ were tested in all additions; representative examples are shown only).

Entry	Ketone (equiv)	Reagent composition $CeCl_3$ equiv	Reagent composition R-M (equiv)	Time[b] [h]	Product composition[c] (%)	(%)	Yield[d] [%]	bp/Torr (mp) [°C]
1	**1** (1)	0.05	**3** (1.10)	1	**7** (100)	**1** (-)	93	61/3
2	**2** (1)	1.20	**3** (1.20)	1	**11** (100)	**2** (-)	95	58/2
					(**11a**/**11b** = 91/9)[e]			
3	**2** (1)	0.33	**3** (1.20)	1	**11** (77)	**2** (23)		
4	**2** (1)	0.05	**3** (1.20)	15	**11** (58)	**2** (42)		
5	**1** (1)	0.33	**4** (1.10)	3	**8** (100)	**1** (-)	91	(158-160)[f]
6	**2** (1)	0.10	**4** (1.10)	2	**12** (100)	**2** (-)	85	(53-54)
					(**12a**/**12b** = 100/0)[e]			
7	**1** (1)	1.20	**5** (1.20)	1	**9** (100)	**1** (-)	75	105/0.5[g]
8	**1** (1)	0.05	**5** (1.10)	4	**9** (66)	**1** (44)		
9	**2** (1)	1.20	**5** (1.20)	1	**13** (100)	**2** (-)	87	92/0.5
					(**13a**/**13b** = 17/83)[e]			
10	**2** (1)	0.05	**5** (1.10)	24	**13** (12)	**6** (88)		
11	**1** (1)	1.20	**6** (1.20)[h]	2	**10**[i]		77	(38-40)
12	**1** (1)	0.05	**6** (1.10)[h]	2	**10**[i]		53	
13	**2** (1)	0.05	**6** (1.10)[h]	1	**14**[i]		97	70°C/0.001[j]
					(**14a**/**14b** = 100/0)[e]			

[a] **Method B**: THF and the ketone are added to the anhydrous $CeCl_3$. The initial white suspension is vigorously stirred at room temperature until an yellow gel-like mixture is formed (formation times up to 2h). The organometallic reagent is added at room temperature (within 5-10 min), if not noted otherwise.
[b] Stirring at room temperature after the introduction of the organometallic reagent.
[c] Ratio by NMR.
[d] Yields of isolated analytically pure compounds, fully characterised by spectroscopic methods (MS, ^1H and ^{13}C NMR, $[\alpha]_D{}^{20}$).
[e] Ratio of isomers by NMR.
[f] Compound **8** is pure by GC; Lit.[5a] mp 168°C.
[g] Lit.[5d] bp 120-140°C/3.5 Torr.
[h] The organolithium compound **6** is added at -20°C and the mixture is allowed to warm to room temperature within 45 min.
[i] Product composition is not determined.
[j] Distillation by Kugelrohr.

In most cases we observed the expected stereochemistry[4,5,8] of the reaction products - only *exo*-alcohols with **1** and *endo*-alcohols with **2**. Similar *endo*- and *exo*-addition selectivities in addition of organometallic reagents to the related ketones 1-vinyl-7,7-dimethyl norbornanone and 1-vinyl-3,3-dimethyl norbornanone have been recently observed[9]. Interestingly, phenylmagnesium bromide adds to fenchone predominantly from the *endo*-side resulting in preferred *exo*-alcohol formation (**13a**/**13b**=17/83). It may be explained with increased steric hindrance between the phenyl protons of the reagent and the fenchone protons in C-7 position and those of the C-3 bonded methyl groups. The anomalous behaviour of phenyl reagents has been first described in additions to substituted cyclohexanones[3b,8].

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6. Cerium(III) chloride ($CeCl_3.7H_2O$, Fluka) was dried, according to Lit.[1c], in 30 g quantities in a *Schlenk* flask equipped with PTFE stirring bar and connected to a liquid nitrogen trap. The flask is evacuated (0.001 Torr, high vacuum pumping unit *Vakuumbrand*) and heated at 80°C for 2-3h, and for additional 3-4h at 100°C. Then the temperature is raised to 140-145°C and maintained until no more water condenses in the cold trap (ca. 30h). The anhydrous $CeCl_3$ is stored in a *Schlenk* flask under argon atmosphere, without loss of any activity during several months.
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