

CERIUM CHLORIDE-PROMOTED NUCLEOPHILIC ADDITION OF GRIGNARD REAGENTS TO KETONES
AN EFFICIENT METHOD FOR THE SYNTHESIS OF TERTIARY ALCOHOLS

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Abstract: In the presence of anhydrous cerium(III) chloride, Grignard reagents react with ketones to afford addition products in high yields, even though the substrates are susceptible to abnormal reactions with Grignard reagents alone.

The reaction of Grignard reagents with carbonyl compounds is well-known as one of the most versatile methods for the synthesis of alcohols.¹⁾ Nevertheless, the reaction is often accompanied by so-called abnormal Grignard reactions (enolization, reduction, condensation, conjugate addition etc.), and in some cases they prevail over "normal" addition to result in very poor yield of desired alcohols.

Previously, we reported that organocerium(III) reagents, generated by the reaction of organolithiums with cerium(III) halide, undergo exclusive nucleophilic addition to carbonyl group at -78 °C, even though the substrates are susceptible to enolization or conjugate addition with simple organolithiums or Grignard reagents.^{2,3)} Despite the superior results obtained, we have sought to extend the investigation to Grignard reagent-CeCl₃ system in order to establish a convenient and generally applicable method. In this letter we wish to describe an efficient method for the preparation of tertiary alcohols by the use of RMgX-CeCl₃ reagent system.

Our method is outlined in the following scheme. The Grignard reagent prepared in THF or ether is added to an equimolar amount of anhydrous cerium chloride suspended in THF⁴⁾, and the mixture is stirred at 0 °C for 1.5 h. The resulting reagent exhibits enhanced carbonylophilicity and reacts readily with ketone at 0 °C to provide the corresponding tertiary alcohol.

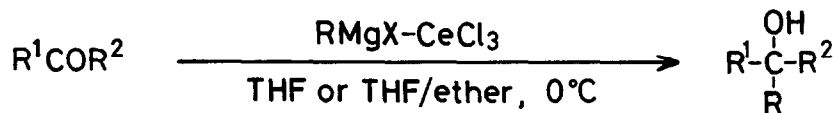


Table 1 shows typical examples together with the results obtained by the use of Grignard reagents alone.

Table 1. The Reaction of Ketones with RMgX-CeCl_3 or RMgX^{a}


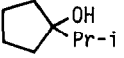
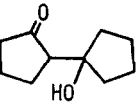


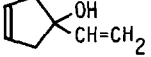
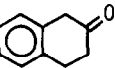
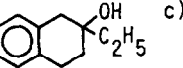
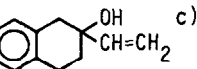


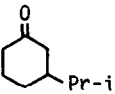
Entry	Ketone	Reagent	Product(s)	Yield (%) ^{b)}
1	$(\text{PhCH}_2)_2\text{CO}$	$n\text{-BuMgBr-CeCl}_3$	$(\text{PhCH}_2)_2\text{C}(\text{OH})\text{Bu-n}^{\text{c)}$	93
2 ^{d)}	"	"	"	84
3 ^{e)}	"	"	"	91
4 ^{f)}	"	"	"	45
5	"	$n\text{-BuMgBr}$	"	36
6 ^{g)}	"	$\text{CH}_2=\text{CHMgBr-CeCl}_3$	$(\text{PhCH}_2)_2\text{C}(\text{OH})\text{CH}=\text{CH}_2^{\text{c)}$	95
7 ^{h)}	"	$\text{CH}_2=\text{CHMgBr}$	"	66
8 ⁱ⁾		$i\text{-PrMgCl-CeCl}_3$	 80%, 	trace
9 ^{j)}	"	$i\text{-PrMgCl}$	" 3%, "	88%
10		PhMgBr-CeCl_3		93
11	"	PhMgBr	"	47
12 ^{g)}	"	$\text{CH}_2=\text{CHMgBr-CeCl}_3$		80 ^{k)}
13 ^{h)}	"	$\text{CH}_2=\text{CHMgBr}$	"	60 ^{k)}
14		$\text{C}_2\text{H}_5\text{MgCl-CeCl}_3$	 ^{c)}	76
15	"	$\text{C}_2\text{H}_5\text{MgCl}$	"	8
16 ^{g)}	"	$\text{CH}_2=\text{CHMgBr-CeCl}_3$	 ^{c)}	66
17 ⁱ⁾	$(i\text{-Pr})_2\text{CO}$	$i\text{-PrMgCl-CeCl}_3$	$(i\text{-Pr})_3\text{COH}$ 52% ^{l)} ,	$(i\text{-Pr})_2\text{CHOH}$ 31% ^{l,m)}
18 ^{j,n)}	"	$i\text{-PrMgCl}$	" 3% ^{l)} ,	" 58% ^{l,o)}
19 ⁱ⁾		$i\text{-PrMgCl-CeCl}_3$	$i\text{-Pr}$  91% ^{l)} ,	 5% ^{l)}
20 ^{j)}	"	$i\text{-PrMgCl}$	" 12% ^{l)} ,	" 53% ^{l)}

Table 1. Continued

21	PhCH=CHCOCH ₃	n-BuMgBr-CeCl ₃	PhCH=CHC(OH)(CH ₃)Bu-n	78%,	PhCH(Bu-n)CH ₂ COCH ₃	6%
22	"	n-BuMgBr	"	21%,	"	69%
23	PhCH=CHCOPh	PhMgBr-CeCl ₃	PhCH=CHC(OH)Ph ₂	58%,	Ph ₂ CHCH ₂ COPh	33%
24 ^{d)}	"	"	"	86%,	"	8%
25	"	PhMgBr	"	5%,	"	81%

a) All reactions in the presence of CeCl₃ were carried out with ketone (1 mmol), Grignard reagent (1.5 mmol), and CeCl₃ (1.5 mmol) in THF at 0 °C for 1 h unless otherwise stated. The reactions of Grignard reagents alone were carried out with ketone (1 mmol) and Grignard reagent (1.5 mmol) in THF at 0 °C for 1 h. b) Isolated yield unless otherwise noted. c) For easier separation of the product from starting ketone, the extract was treated with NaBH₄ in ethanol, and the product was isolated by preparative TLC. d) A molar ratio of 1:1.5:0.75 ketone/Grignard reagent/CeCl₃ was used. e) The Grignard reagent prepared in ether was used. The reaction was conducted in THF/ether (4/1). f) Cerium chloride was suspended in ether and subsequent reaction was carried out in ether. g) Treatment of vinylmagnesium bromide with CeCl₃ and subsequent reaction with ketone were carried out at -78 °C. h) At -78 °C. i) Ten mmol scale with a molar ratio of 1:1.3:1.3 ketone/Grignard reagent/CeCl₃. j) Ten mmol scale with a molar ratio of 1:1.3 ketone/Grignard reagent. k) Yield was determined by ¹H-NMR using 1,4-dichlorobenzene as an internal standard. l) Yield was determined by GLC. m) Unchanged starting ketone: 10%. n) At 25 °C for 3 h. o) Starting ketone: 35%. p) A molar ratio of 1:1.5:2.5 ketone/Grignard reagent/CeCl₃ was used.

It should be emphasized that easily enolizable ketones were subjected to nucleophilic addition with RMgX-CeCl₃ with remarkable suppression of enolization and ketol formation.⁵⁾ Of particular note are the observations that the reaction of cyclopentanone with *i*-C₃H₇MgCl-CeCl₃ provided 1-isopropyl-1-cyclopentanol in 80% yield (Entry 8),⁶⁾ and that extremely enolizable β -tetralone reacted smoothly with C₂H₅MgCl-CeCl₃ to give 2-ethyl-1,2,3,4-tetrahydro-2-naphthol in 76% yield (Entry 14).

The reaction of 2,4-dimethyl-3-pentanone with *i*-C₃H₇MgCl-CeCl₃ (Entry 17) is also worthy to mention. In contrast to the conventional method (Entry 18), it produced 2,4-dimethyl-3-isopropyl-3-pentanol as the major product.

Another prominent feature of this method is exemplified by the reaction of α,β -unsaturated ketones. The reaction with RMgX-CeCl₃ yielded 1,2-addition products (allyl alcohols) in good selectivity (Entries 19, 21, 23, 24).^{7,8)} This cerium chloride-promoted reaction is in sharp contrast to that of Grignard reagents alone which afforded 1,4-addition products predominantly.

In summary, we have developed an efficient method for the synthesis of tertiary alcohols. The mild reaction conditions (usually at 0 °C) and use of non-toxic cerium chloride render this method synthetically useful. This development provides a valuable method for new carbon-carbon bond formations which are difficultly achieved by the conventional Grignard reaction.

A typical experimental procedure is described for the preparation of 1-isopropyl-1-cyclopentanol. Cerium chloride (CeCl₃·7H₂O) (4.8 g, 13 mmol) was quickly and finely powdered in a mortar and was placed in a 100-mL two-necked flask. Most of water of crystallization was removed in vacuo by immersing the flask in an oil bath heated at 135-140 °C for 1 h. A magnetic stirrer

bar was then placed and cerium chloride was completely dried in vacuo with stirring at the same temperature for 1 h. While the flask was still hot, argon gas was introduced and the flask was cooled in an ice bath. Tetrahydrofuran (30 mL) freshly distilled from sodium/benzophenone was added with stirring and the suspension was well stirred for 2 h⁹⁾ at room temperature. The flask was again immersed in an ice bath and isopropylmagnesium chloride (13 mmol, 8.5 mL of 1.53 M THF solution) was added. After stirring for 1.5 h at 0 °C, cyclopentanone (0.84 g, 10 mmol) was added and stirring was continued for 1 h. The reaction mixture was treated with water (50 mL) containing 2 mL of acetic acid. The mixture was extracted with ether, and the combined extracts were washed with brine, NaHCO₃ solution, and brine, and dried (MgSO₄). The solvent was removed under reduced pressure at 0-5 °C and the residual oil was distilled in a Kugekrohr oven (75 °C/18 Torr) to give 1-isopropyl-1-cyclopentanol (1.03 g, 80%).

References and Notes

- 1) For excellent reviews, see the following: a) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, New York (1954). b) J. C. Stowell, "Carbanion in Organic Synthesis", Wiley, New York (1979). c) R. L. Augustine, "Carbon-Carbon Bond Formation", Vol. 1, Marcel Dekker, New York (1979). d) E. Negishi, "Organometallics in Organic Synthesis", Vol. 1, Wiley, New York (1980).
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- 3) Our methodology has been successfully employed for the preparation of key intermediates to biologically active compounds. a) M. Suzuki, Y. Kimura, and S. Terashima, *Chem. Lett.*, **1984**, 1543. b) K. Suzuki, T. Ohkuma, and G. Tsuchihashi, *Tetrahedron Lett.*, **1985**, 861. c) Y. Tamura, M. Sasho, H. Ohe, S. Akai, and Y. Kita, *Tetrahedron Lett.*, **1985**, 1549.
- 4) The use of ether in place of THF resulted in lower yield of the addition products.
- 5) The reaction of organotransition metal reagents with enolizable ketones has been reported. a) D. Seebach, B. Weidmann, and L. Widler, "Modern Synthetic Method" Vol. 3, Verlag, Frankfurt, (1983). b) Ref. 2a-c. c) T. Hiyama, M. Sawahata, and Y. Kusano, *Chem. Lett.*, **1985**, 611.
- 6) This compound was previously prepared in 23% yield by slow addition of cyclopentanone to four molar excess of isopropylmagnesium bromide. G. S. Skinner and F. P. Florentine, Jr. *J. Am. Chem. Soc.*, **76**, 3200 (1954).
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- 8) Recently selective 1,2-addition of organolanthanoid complexes to α,β -enones has been reported. a) Ref. 2c,d. b) K. Yokoo, Y. Yamanaka, T. Fukagawa, H. Taniguchi, and Y. Fujiwara, *Chem. Lett.*, **1983**, 1301. c) A. B. Sigalov, E. S. Petrov, L. F. Rybakova, and I. P. Beletskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1983**, 2615. d) H. Schumann, J. Müller, N. Bruncks, H. Lauke, and J. Pickardt, *Organometallics*, **3**, 69 (1984).
- 9) Stirring overnight afforded nearly the same result.

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