

Carbonyl addition reactions promoted by cerium reagents

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Abstract - Organocerium reagents are generated by the reaction of organolithiums with anhydrous cerium chloride or cerium iodide. The reagents are less basic than organolithiums or Grignard reagents, and they react with various carbonyl compounds to give the corresponding addition products in high yields, even though the substrates are susceptible to enolization or metal-halogen exchange with simple organolithiums. The same reagents react with α,β -unsaturated carbonyl compounds to yield 1,2-addition products with high regioselectivity. It has also been found that cerium chloride significantly promotes the addition reactions of Grignard reagents to carbonyl compounds with remarkable suppression of abnormal reactions. Various tertiary alcohols, which are difficult to prepare by the conventional Grignard reaction, can be synthesized by this method. Several applications of this methodology to practical organic syntheses are described.

INTRODUCTION

The elements of the rare earth series having f-orbitals exhibit unique electronic and stereochemical properties, and they have high potential for use as reagents and catalysts in organic synthesis (ref. 1). We have been deeply interested in the characteristic properties of these elements and explored new organolanthanide reagents which are useful in organic synthesis. Among 15 elements from lanthanum to lutetium, cerium is of the highest natural abundance, and its major inorganic salts are commercially available at moderate prices. We have utilized this relatively inexpensive element in carbon-carbon bond-forming reactions, studying generation and reactivities of organocerium reagents.

We have tried the generation of organocerium(III) reagents by transmetalation of cerium(III) halides with organolithiums and examined the reactivities toward carbonyl compounds. It has been found that organocerium reagents react with various carbonyl compounds to afford 1,2-addition products in high yields, even though substrates are susceptible to abnormal reactions. Furthermore, this methodology has been extended to the reactions of other carbanions with carbonyl compounds; various tertiary alcohols are prepared in higher yields than are obtainable by conventional methods.

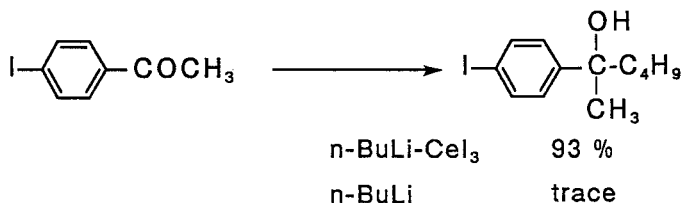
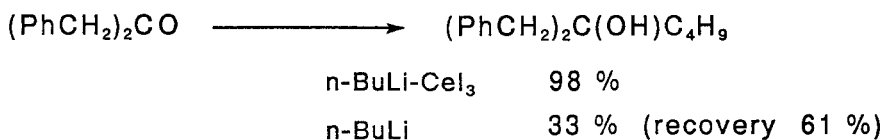
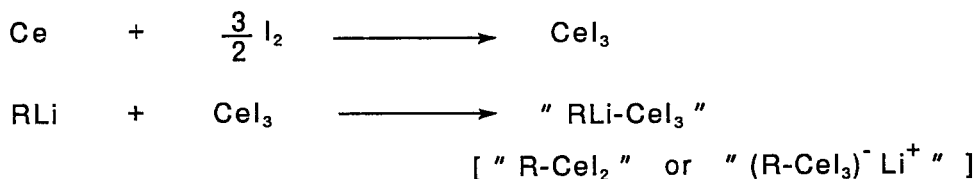
In this lecture, we present the scope and limitation of this methodology. In addition, several examples employed in practical organic synthesis are described with emphasis on the utility of this method.

GENERATION AND REACTIVITIES OF ORGANOCERIUM REAGENTS

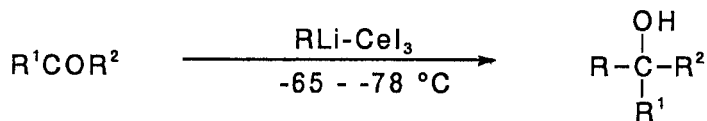
Our initial trial of the generation of organocerium(III) reagents was the reactions of organolithiums with 1 equivalent of cerium iodide (CeI_3). An organolithium reagent was added at -65°C to a suspension of cerium iodide prepared in situ by the reaction of cerium metal with iodine in THF (ref. 2,3).

In order to examine the reactivities of the generated reagents, various carbonyl compounds were allowed to react with the reagents at -65°C . In all the cases examined, the corresponding addition products were obtained in excellent yields, even though the substrates are readily subjected to

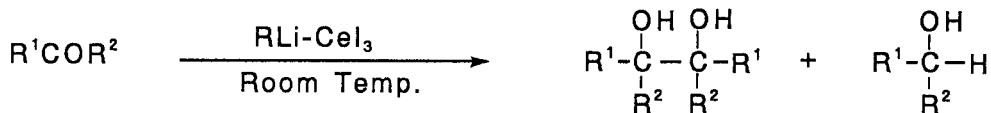
enolization or possess halogen atoms at vinylic positions. The results are in sharp contrast to those obtained by the use of organolithiums alone, in that the yields of the addition products are remarkably lowered due to competitive enolization or metal-halogen exchange. The most striking contrasts are shown in the reactions of 1,3-diphenyl-2-propanone and p-iodoacetophenone. The reaction of the former ketone with n-butylcerium reagent provided the addition product in 98% yield, while n-butyllithium alone afforded the product only in 33% yield, recovering 61% of the starting ketone due to enolization. In the case of p-iodoacetophenone, the cerium reagent provided the adduct in essentially quantitative yield, but the reaction of the parent lithium reagent resulted in the formation of a complex mixture, due to the lithium-iodine exchange reaction.



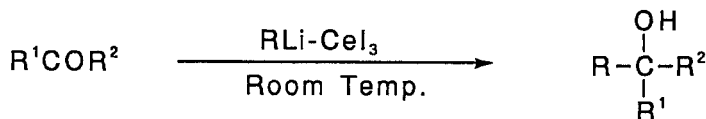
The effect of reaction temperature is also worth mentioning. When the reagents having β -hydrogens were warmed to room temperature and then treated with carbonyl compounds, reductive coupling and/or reduction proceeded to afford pinacols and/or secondary alcohols. In contrast, the reagent prepared from methyl lithium or phenyllithium underwent exclusive nucleophilic addition to carbonyl group even at room temperature. The reductive coupling and reduction of carbonyl compounds are probably induced by low-valent cerium and cerium hydride species which are generated through β -hydrogen elimination process.



R : C₂H₅, n-C₄H₉, sec-C₄H₉, CH₃, Ph

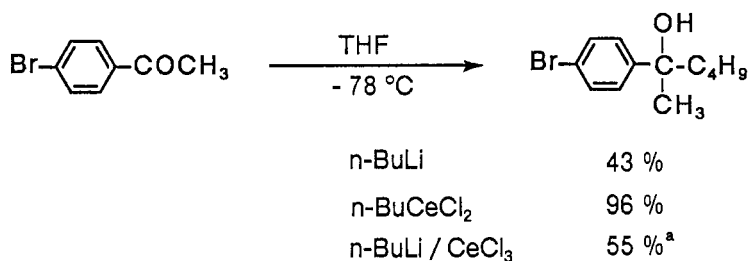
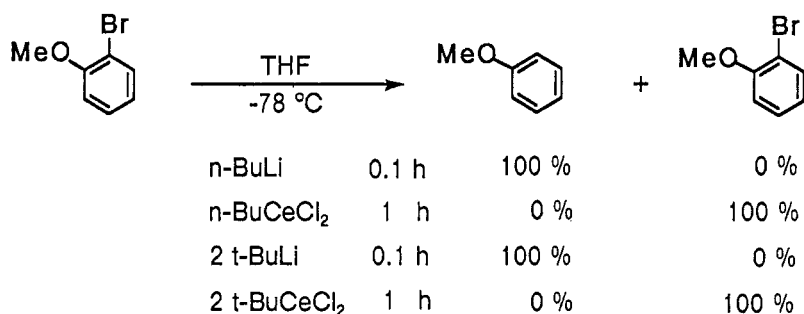
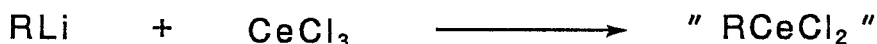


R : C₂H₅, n-C₄H₉, sec-C₄H₉



R : CH₃, Ph

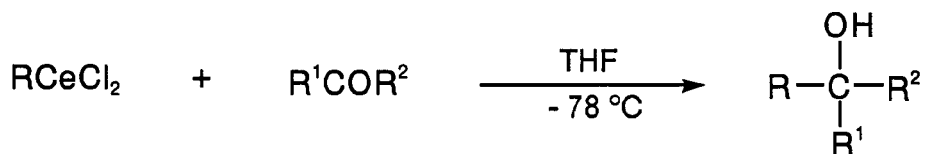
These results indicate that the reaction of cerium iodide with organolithiums generate organocerium compounds possessing cerium-carbon sigma-bonds. This method seems to be synthetically useful, but we have to be careful when handling cerium metal which is pyrophoric and often burns on contact with air. Therefore, we developed a much more convenient procedure for the generation of organocerium reagents using commercially available cerium chloride. Cerium chloride heptahydrate was dried in vacuo at 140 °C and was suspended in THF. Organolithium compounds were added to the suspension, and the resulting reagents were allowed to react with aromatic halides or carbonyl compounds. Typical examples are shown in the following scheme (ref. 3-5).

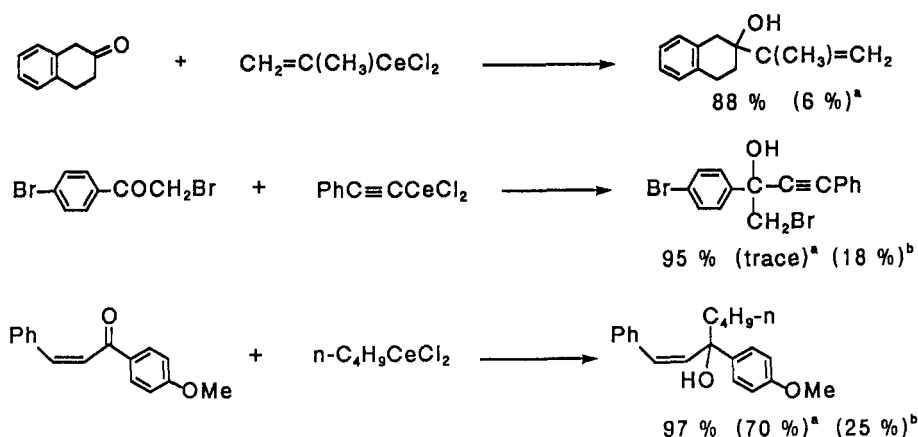


^an-Butyllithium was added to the mixture of p-bromoacetophenone and CeCl₃ in THF at -78 °C.

No metal-halogen exchange occurred with the cerium reagents at -78 °C. The reaction of p-bromoacetophenone with n-butylcerium reagent provided the corresponding addition product in 96 % yield. Addition reaction of n-butylcerium reagent to 1,3-diphenylacetone proceeded smoothly to give the adduct in 96% yield. When the reagent was warmed to room temperature, and then was allowed to react with the ketone, a reduced product, 1,3-diphenyl-2-propanol was obtained in 28% yield with the recovery of the starting ketone (50%). These results suggest that the reaction of anhydrous cerium chloride with alkylolithiums also generates organocerium reagents.

On the basis of these observations, we prepared various cerium reagents from the corresponding organolithium compounds and examined their reactivities toward carbonyl compounds. A few representative results are shown below.





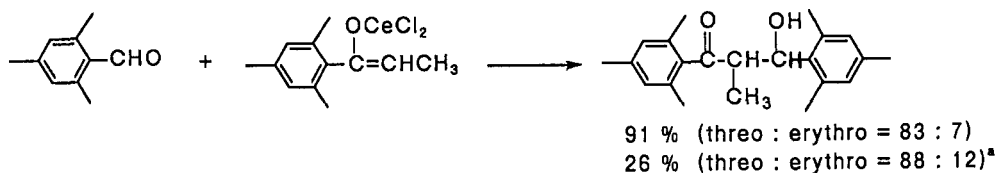
^aLithium reagent. ^bGrignard reagent

The method exploited here has the following characteristic features. (1) Not only alkyl- but also alkenyl and alkynylcerium reagents can be generated. (2) The method is applicable to extremely enolizable ketones including α -bromo-ketones. (3) The reaction with α,β -unsaturated carbonyl compounds provides 1,2-addition products in high regioselectivity (ref. 6,7).

The reaction of α -cyanbenzyl lithium with α -enones in the presence of cerium chloride is worth mentioning. The reaction with 2-cyclohexenone afforded the 1,2-addition product in 60-62% yield, regardless of reaction time. Similarly, the reaction with benzalacetone at -78°C for 5 h provided the 1,2-adduct in 89% yield (ref. 7). These results are reasonably explained in terms of kinetic control rather than thermodynamic control. Thus, trivalent cerium possesses strong oxophilicity and intercepts the intermediates 1,2-adducts by virtue of the strong bonding with the alkoxide oxygen so that the reverse reaction is suppressed.

CERIUM ENOLATES

Cerium enolates were generated by the addition of cerium chloride to lithium enolates. The cerium enolates reacted readily with a variety of carbonyl compounds to produce aldols, even though the acceptor carbonyl compounds are prone to enolization or are sterically hindered. The reason why cerium enolates achieved higher yields of aldols than lithium enolates is that the trivalent cerium intercepts the intermediate six-membered chelates more effectively than the lithium ion (ref. 8,9).



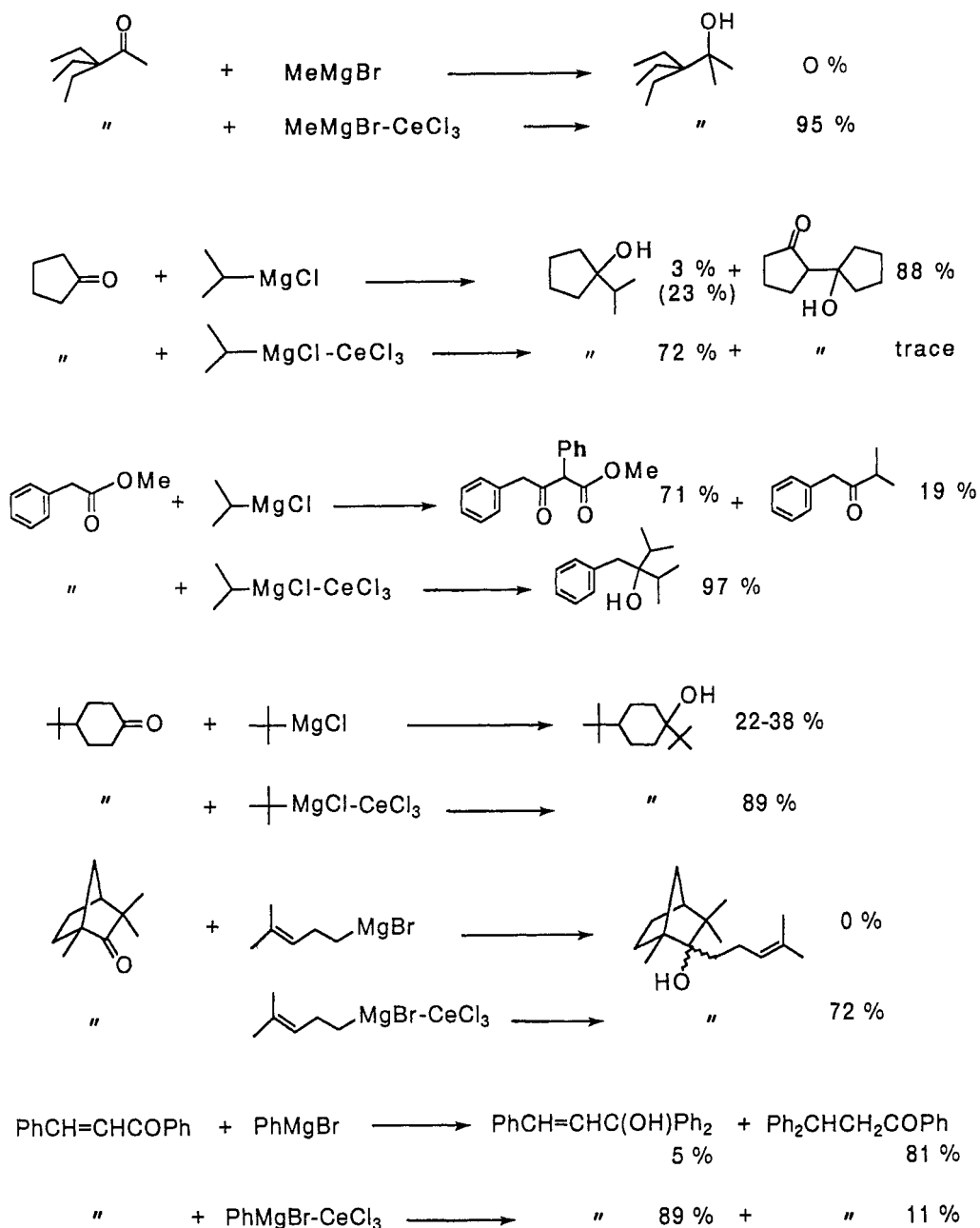
^aThe corresponding lithium enolate was used.

GRIGNARD REAGENTS-CERIUM CHLORIDE SYSTEM

The Grignard reaction of carbonyl compounds to yield alcohols is undoubtedly one of the most fundamental and versatile reactions in all of organic chemistry and has widespread synthetic applications. Nevertheless, it is also well recognized that the Grignard reaction is often accompanied by so-called abnormal reactions such as enolization, reduction, condensation, conjugate addition, and pinacol coupling. In some cases such abnormal reactions prevail over the normal reaction resulting in poor yields of the desired products.

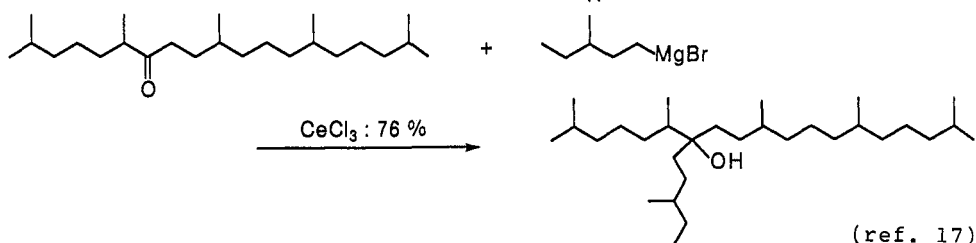
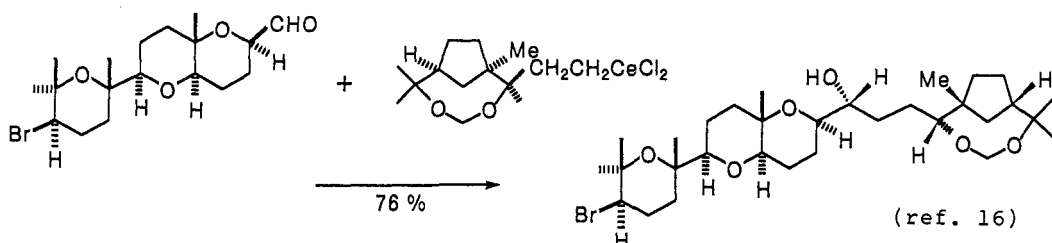
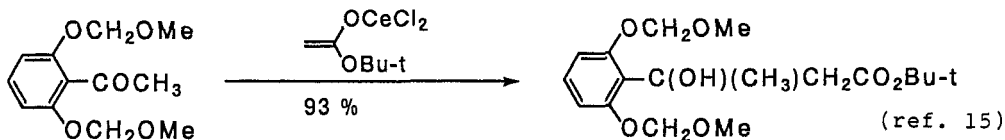
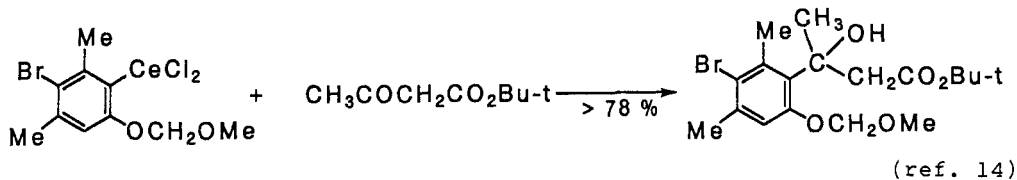
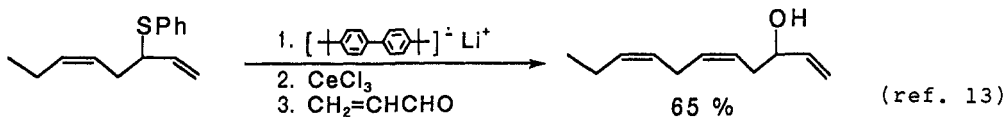
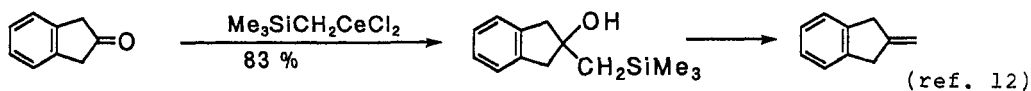
It has been found that use of cerium chloride as an additive effectively suppresses abnormal reactions, resulting in the formation of normal addition products in significantly improved yields (ref. 10, 11). Representative

examples of the reactions of various carbonyl compounds are shown below. It is emphasized that enolization, aldol reaction, ester condensation, reduction and 1,4-addition are remarkably suppressed by the use of cerium chloride. Various tertiary alcohols, which are difficult to prepare by the conventional Grignard reaction, can be synthesized by this method.



SYNTHETIC APPLICATIONS

Carbonyl addition reactions promoted by cerium chlorides have been employed to synthesize key intermediates of natural products used by other researchers. Following examples, which are difficult to achieve by conventional methods, indicate that this methodology is highly useful in its application to a variety of organic syntheses.



REFERENCES

1. For a representative review, see: H. B. Kagan and J. L. Namy, *Tetrahedron*, **42**, 6573 (1986).
2. T. Imamoto, T. Kusumoto and M. Yokoyama, *J. Chem. Soc., Chem. Commun.*, **1982**, 1042.
3. T. Imamoto, T. Kusumoto, Y. Tawarayama, Y. Sugiura, T. Mita, Y. Hatanaka and M. Yokoyama, *J. Org. Chem.* **49**, 3904 (1984).
4. T. Imamoto, Y. Sugiura and N. Takiyama, *Tetrahedron Lett.*, **25**, 4233 (1984).
5. T. Imamoto and T. Oshiki, unpublished results.
6. T. Imamoto and Y. Sugiura, *J. Organometal. Chem.*, **285**, C21 (1985).
7. T. Imamoto and Y. Sugiura, *J. Phys. Org. Chem.*, **2**, 93 (1989).
8. T. Imamoto, T. Kusumoto and M. Yokoyama, *Tetrahedron Lett.*, **24**, 5233 (1983).
9. T. Imamoto, T. Kusumoto, Y. Sugiura, N. Suzuki and N. Takiyama, *J. Chem. Soc. Jpn.*, **1985**, 445.
10. T. Imamoto, N. Takiyama and K. Nakamura, *Tetrahedron Lett.*, **26**, 4763, (1985).
11. T. Imamoto, N. Takiyama, K. Nakamura, T. Hatajima and Y. Kamiya, *J. Am. Chem. Soc.*, **111**, 4392 (1989).
12. C. R. Johnson and B. D. Tait, *J. Org. Chem.*, **52**, 281 (1987).
13. B. S. Guo, W. Doubleday and T. Cohen, *J. Am. Chem. Soc.*, **109**, 4710 (1987).
14. K. Nagasawa and K. Ito, *Heterocycles*, **28**, 703 (1989).
15. K. Nagasawa, H. Kanbara, K. Matsushita and K. Ito, *Tetrahedron Lett.*, **26**, 6477 (1985).
16. E. J. Corey and D.-C. Ha, *Tetrahedron Lett.*, **29**, 3171 (1988).
17. J. N. Robson and S. J. Rowland, *Tetrahedron Lett.*, **29**, 3837 (1988).