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ORGANOCERIUM COMPOUNDS IN SYNTHESIS

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I. Introduction

The nucleophilic addition of a Grignard reagent or organolithium compound to the carbonyl group constitutes one of the most important processes in organic synthesis.[1] In spite of its versatility and broad synthetic utility, the addition reaction is often accompanied by competing reactions such as enolization, conjugate addition in the case of α,β-unsaturated carbonyl compounds, reduction and condensation.[2] These side reactions, which are mainly due to the high basicity and oxidation potential of the Grignard and organolithium reagents, can sometimes take over the normal addition process, resulting in low yields of the desired products. The improvement of the properties of organometallic reagents to facilitate the normal addition has drawn extensive interest from synthetic organic chemists. Since the late 1970s, extensive efforts have been directed to the formation and synthetic utility of organolanthanides. For carbon-carbon bond formation, several types of organolanthanides,[3-5] including those based on lanthanum, praseodymium, neodymium, ytterbium and especially cerium and samarium, are synthetically useful. The research on organocerium compounds was pioneered by Imamoto and co-workers who, in the early 1980s,[6] prepared the first series of organocerium compounds and successfully examined their chemistry. This area of research has since grown at a remarkably rapid pace, and organocerium reagents are now widely applied as the reagent of choice to facilitate nucleophilic addition reactions which could not be achieved effectively by the use of the corresponding Grignard and organolithium reagents. The chemistry of organocerium compounds has been extensively reviewed previously, covering the literature up to 1993.[3-5] The intent of this article is to provide an overview of organocerium chemistry with emphasis on the more recent developments in this area.

II. Preparation

Organocerium compounds are generally prepared *in situ* from the corresponding organomagnesium or organolithium compounds via transmetallation and are used directly without isolation. Several other procedures are also known. These methods are illustrated below with selected examples.

A. Preparation of alkyl-, alkenyl-, alkynyl- and arylcerium compounds

(a) From organolithium reagents

In 1982 Imamoto *et al.*[6] reported the first generation of organocerium reagents by treatment of organolithium compounds with cerium iodide which was prepared *in situ* by the reaction of cerium metal with iodine in tetrahydrofuran over a temperature range of 0-25 °C. In a typical procedure, *n*-butyllithium was added at -65 °C to a slurry of cerium iodide (1 equiv.) in tetrahydrofuran under an argon atmosphere and the resulting suspension was vigorously stirred at -65 °C for 30 min (Eq. 1). Although organocerium reagents are conveniently presented by the formula $RCeX_2$, based on the stoichiometry of the reactants, the actual structure of these compounds remains unknown.

$$n\text{-BuLi} + CeI_3 \xrightarrow[30\text{ min}]{\text{THF, -65 °C}} \text{"}n\text{-BuCeI}_2\text{"} + LiI \qquad \text{[Eq. 1]}$$

A more convenient procedure was developed later. In this procedure, anhydrous cerium chloride, which can be easily obtained by heating the commercially available cerium chloride heptahydrate (finely ground powder) at ~140 °C under reduced pressure (~0.5 mmHg)[7-14] conveniently carried out using a Kugelrohr distillation apparatus,[8] is involved as the source of cerium. For the preparation of organocerium reagents, the highly hygroscopic anhydrous cerium chloride (beige in color) thus obtained is treated with organolithium compounds at low temperature. As a specific example, a suspension of anhydrous cerium chloride in tetrahydrofuran was vigorously stirred at 25 °C for 2 h under an atmosphere of argon. *n*-Butyllithium (1 equiv.) was then added at -78 °C and stirring was continued for 30 min to generate *n*-butylcerium chloride (Eq. 2).[7]

$$n\text{-BuLi} + \text{CeCl}_3 \xrightarrow[\text{30 min}]{\text{THF, -78 °C}} \text{"}n\text{-BuCeCl}_2\text{"} + \text{LiCl} \qquad \text{[Eq. 2]}$$

This procedure has been used extensively for the preparation of various alkyl, alkenyl, alkynyl and arylcerium compounds. Several examples are summarized in Eq. 3.[7,15-17]

$$\text{RLi} + \text{CeCl}_3 \xrightarrow[\text{30 min}]{\text{THF, -78 °C}} \text{"RCeCl}_2\text{"} + \text{LiCl} \qquad \text{[Eq. 3]}$$

$$\text{R} = t\text{-Bu, Ph, PhC}{\equiv}\text{C, CH}_2{=}\text{C(CH}_3\text{)}$$

There is some evidence that organocerium compounds prepared from the lithio compounds are thermally rather unstable. Those possessing a β-hydrogen tend to decompose at temperatures above 0 °C and those without a β-hydrogen can sustain temperatures up to ~60 °C. The reactions involving organocerium reagents derived from organolithium compounds are normally carried out at low temperature, typically below -60 °C.

(b) From Grignard reagents

Grignard reagents can also be converted to the respective organocerium compounds by transmetallation. Anhydrous cerium chloride is again the common source of cerium. The preparative procedure is virtually the same as that used for the transformation of organolithium compounds to organocerium compounds. Thus, the formation of *n*-butylcerium chloride was effected by addition of *n*-butylmagnesium bromide to a suspension of anhydrous cerium chloride (1 equiv.) in tetrahydrofuran, which was stirred vigorously in advance at room temperature for 2 h at 0 °C under an argon atmosphere, and allowing the reaction mixture to stir for 1.5 h (Eq. 4).[18] This procedure is generally applicable to the transmetallation of a variety of Grignard reagents with cerium chloride as shown by examples compiled in Eq. 5,[18,19] with the exception of alkenyl Grignard reagents. The transmetallation of the latter reagents with cerium chloride is normally carried out at -78 °C, because the resulting alkenylcerium compounds are unstable at 0 °C.[20] Again the structure of the organocerium compounds generated from the Grignard reagents remains unknown and is expressed by the general formula shown in Eq. 5 for convenience. However, it is clear that the organocerium compounds derived from Grignard reagents are quite different from those derived from organolithium reagents. The former compounds, in general, are thermally more stable than the latter ones. In fact, the reactions involving the former reagents are often carried out at 0 °C which appears to be an ideal temperature. For alkenylcerium reagents, however, the reactions are normally performed at -78 °C due to the instability of the reagents at higher temperatures.[20]

$$n\text{-BuMgBr} + \text{CeCl}_3 \xrightarrow[\text{1.5 h}]{\text{THF, 0 °C}} n\text{-BuMgBr-CeCl}_3 \qquad \text{[Eq. 4]}$$

$$\text{RMgX} + \text{CeCl}_3 \xrightarrow[\text{1.5 h}]{\text{THF, 0 °C}} \text{RMgX-CeCl}_3 \qquad \text{[Eq. 5]}$$

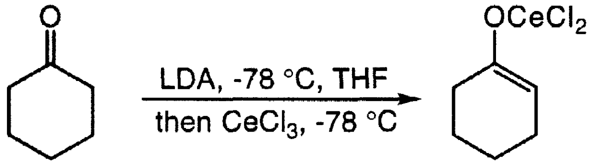
$R = t\text{-Bu}, i\text{-Pr}, \text{Ph}$

B. Cerium enolates

(a) From lithium enolates

Cerium enolates of ketones, esters, amides and nitriles have been reported. As shown in Eq. 6 with ethyl acetate, these enolates are generally produced by deprotonation of the starting substrate with a suitable base, such as the commonly used lithium diisopropylamide, followed by transmetallation. Thus, ethyl acetate was first treated with lithium diisopropylamide (1.1 equiv.) in tetrahydrofuran at -78 °C for 25 min under an argon atmosphere. The resulting lithium ester enolate was transferred via a cannula to a suspension of anhydrous cerium chloride (1 equiv.) in tetrahydrofuran which was vigorously stirred previously at room temperature for 2 h and then chilled to -78 °C. The resulting mixture was stirred at -78 °C for 2 h to generate the cerium enolate of ethyl acetate (Eq. 6).[8] This procedure proved to be general for the preparation of cerium enolates from a variety of active methylene compounds. Selected examples are listed in Eqs. 7-9.[21-24]

$$\text{CH}_3\text{CO}_2\text{Et} \xrightarrow[\text{then CeCl}_3\text{, -78 °C}]{\text{LDA, -78 °C, THF}} \text{Cl}_2\text{CeCH}_2\text{CO}_2\text{Et} \qquad \text{[Eq. 6]}$$



[Eq. 7]

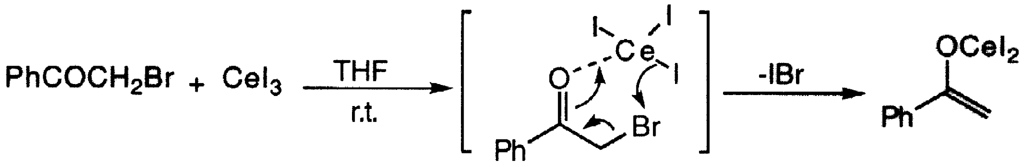
$$\text{CH}_3\text{CN} \xrightarrow[\text{then CeCl}_3\text{, -78 °C}]{\text{LHMDS, -78 °C, THF}} \text{Cl}_2\text{CeCH}_2\text{CN} \qquad \text{[Eq. 8]}$$

$$\text{CH}_3\text{CONMe}_2 \xrightarrow[\text{then CeCl}_3\text{, -78 °C} \rightarrow \text{r.t.}]{\text{LDA, -78 °C, THF}} \text{Cl}_2\text{CeCH}_2\text{CONMe}_2 \qquad \text{[Eq. 9]}$$

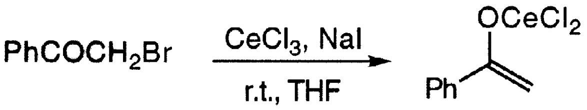
The structure of cerium enolates is also unconfirmed and the general representations as shown in the above equations are for practical purposes only. Cerium enolates appear to be reasonably stable. Many reactions can be carried out at room temperature over a long period of time without apparent decomposition of the reagent.

(b) Miscellaneous methods

A less used but quite convenient procedure for the generation of cerium enolates from ketones makes use of α-halo (bromo in particular) ketones as starting substrates. These ketones are readily converted to the cerium enolates upon treatment with cerium iodide. For example, treatment of α-bromoacetophenone with cerium iodide in tetrahydrofuran at room temperature resulted in the formation of the corresponding enolate (Eq. 10).[25] For the formation of the chloro analogue, the use of cerium chloride alone proved to be ineffective. As shown in Eq. 11,[25] this transformation requires a catalytic amount of sodium iodide. An advantage of the method is that the cerium enolates can be prepared in the presence of the electrophile required for the subsequent transformation.

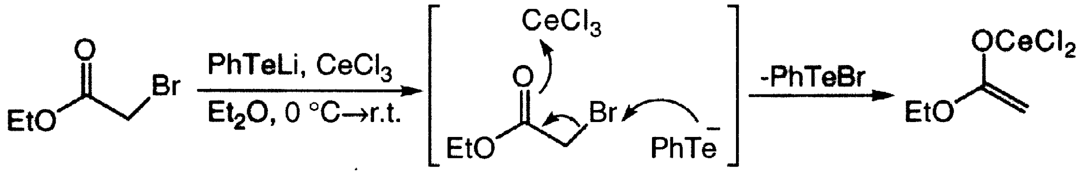


[Eq. 10]



[Eq. 11]

The above procedure appears to be limited to the formation of ketone enolates and is not applicable to α-halo esters such as ethyl bromoacetate. However, upon treatment with lithium benzenetellurolate (PhTeLi) in the presence of cerium trichloride, α-halo esters, including ethyl bromoacetate (Eq. 12), can be efficiently converted to cerium enolates[26] for Reformatsky-type reactions in high yields.



[Eq. 12]

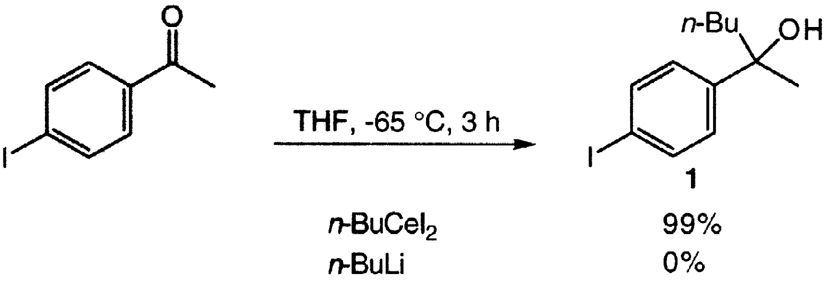
III. Reactions

In general, organocerium compounds possess substantially lower basicity and greater nucleophilicity towards carbon-oxygen double bond and carbon-nitrogen multiple bond than the corresponding organolithium and Grignard reagents and show greater selectivity towards conjugated carbonyl compounds in favor of 1,2-addition and lower oxidation potential towards the carbonyl group. These highly desirable characteristics for nucleophilic addition reactions were recognized experimentally early in the research into organocerium chemistry and have since served as guidelines for synthetic practice.

A. Alkyl-, alkenyl-, alkynyl- and arylcerium reagents

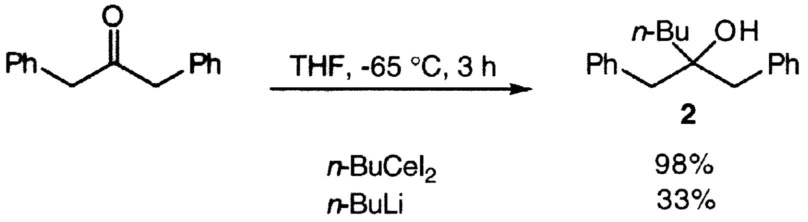
(a) Addition to carbonyl compounds

In 1982 Imamoto *et al.*[6] first observed that nucleophilic addition of organocerium reagents to ketones proceeded readily giving the corresponding tertiary alcohols in excellent yields. The most interesting example was the addition of *n*-butylcerium(III) iodide (prepared from *n*-butyllithium and cerium iodide) to *p*-iodoacetophenone, from which a near-quantitative yield of alcohol **1** was obtained (Eq. 13).[6] This result is in sharp contrast to that employing *n*-butyllithium, in which case neither the desired product nor the starting material was isolated, probably due to metal-halogen exchange. Another interesting example was the addition of *n*-butylcerium iodide to 1,3-diphenyl-2-propanone (Eq. 14),[6] which gave alcohol **2** in 98% yield. When *n*-butyllithium was used, alcohol **2** was produced only in 33% yield along with a 61% recovery of the starting material probably due to competitive enolization. The addition of *s*-butylcerium iodide to acetophenone, giving virtually quantitative yield of alcohol **3**, was also far superior to that using *s*-butyllithium which gave **3** in 53% yield (Eq. 15).[6] These results obtained from the preliminary studies on organocerium compounds quickly established their excellent nucleophilic reactivity towards ketones.



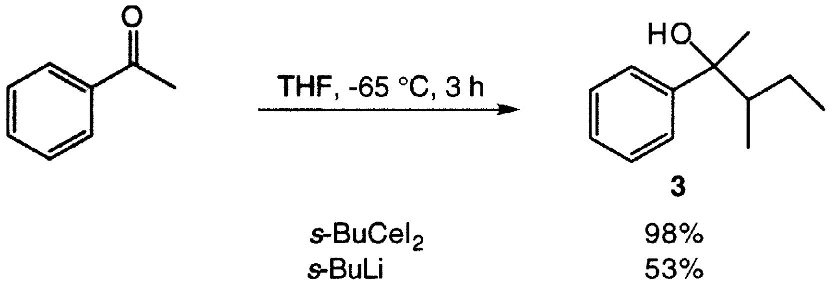
1

[Eq. 13]



2

[Eq. 14]

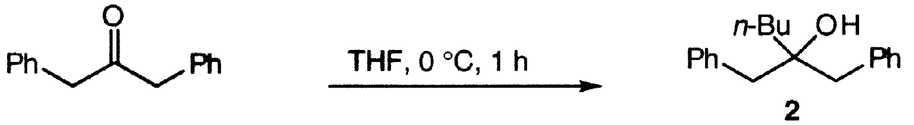


3

[Eq. 15]

Organocerium chlorides, which can be more conveniently prepared by transmetallation of the corresponding organolithium and Grignard reagents with cerium chloride (*vide supra*), were found to be equally reactive towards the ketone carbonyl. The addition of *n*-butylcerium chloride (prepared from *n*-butylmagnesium bromide) to 1,3-diphenyl-2-propanone at 0 °C, for example, gave alcohol **2** in 98% yield which was several magnitudes better than that obtained using *n*-butylmagnesium bromide (Eq. 16).[18] Under similar conditions, the addition of *n*-butylcerium chloride prepared from *n*-butyllithium gave a 96% yield of **2**, when the reaction was carried out at -78 °C (Eq. 17).[14] Interestingly, when the reaction was performed at 0 °C, the yield of **2** was substantially lower (28%). These results clearly indicated that the cerium reagents prepared from two different sources may possess different structures and thermal stabilities. Experimentally, it is clear that the addition reactions involving unstabilized organocerium reagents prepared from lithio compounds should be carried out at low temperature (below -60 °C in general), whereas those reactions using cerium reagents derived from Grignard reagents may be performed at much higher temperature (0 °C in general).

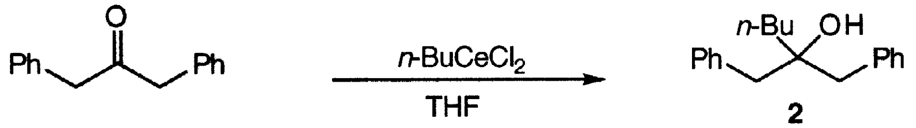
The use of organocerium reagents is also known to suppress the undesirable self-aldol condensation and reduction of ketones. For example, the reaction of *i*-PrMgCl with cyclopentanone provided an 88% yield of the aldol condensation product **4** along with a 3% yield of the addition product **5**. In sharp contrast, in the presence of cerium(III) chloride the reaction provided the addition product **5** in 80% yield along with a trace amount of **4** (Eq. 18).[20] As an example of reduction, treatment of diisopropyl ketone with isopropylmagnesium bromide gave mainly the reduction product **6** (Eq. 19).[20] In the presence of cerium chloride, however, the reaction gave the desirable addition product **7** in 52% yield.



2

[Eq. 16]

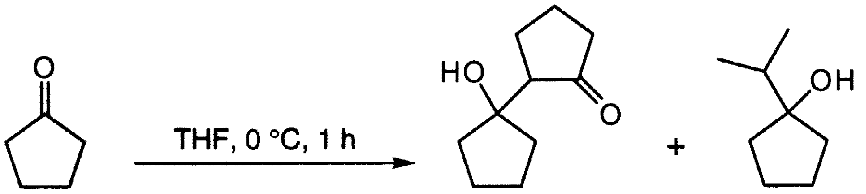
	2
n-BuMgBr-CeCl$_3$ (1:1)	98%
n-BuMgBr	18-36%



2

[Eq. 17]

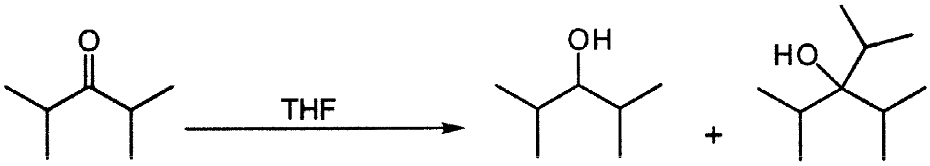
	2
-78 °C, 30 min	96%
0 °C, 30 min	28%



4 **5**

[Eq. 18]

	4	**5**
i-PrMgCl	88%	3%
i-PrMgCl-CeCl$_3$	trace	80%

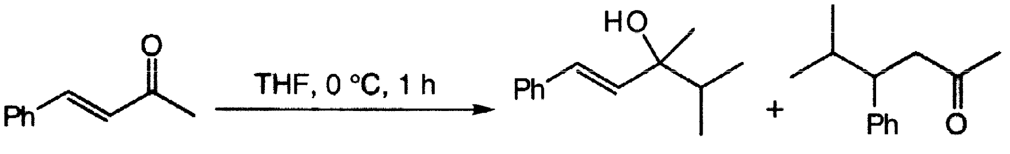


6 **7**

[Eq. 19]

	6	**7**
i-PrMgCl, 25 °C, 3 h	58%	3%
i-PrMgCl-CeCl$_3$, 0 °C, 1 h	31%	52%

Another area of major synthetic utility of organocerium reagents is based on their high regioselectivity towards conjugated α,β-unsaturated ketones. While the Grignard reagents often afforded a mixture of 1,2- and 1,4-addition products, the corresponding cerium reagents gave predominantly 1,2-adducts. The addition of isopropylmagnesium chloride to benzalacetone, for example, afforded 1,2-adduct **8** and 1,4-adduct **9** in 12% and 53% yields, respectively (Eq. 20).[17] When the reaction was cerried out in the presence of cerium chloride, a 91% yield of 1,2-adduct **8** was formed.

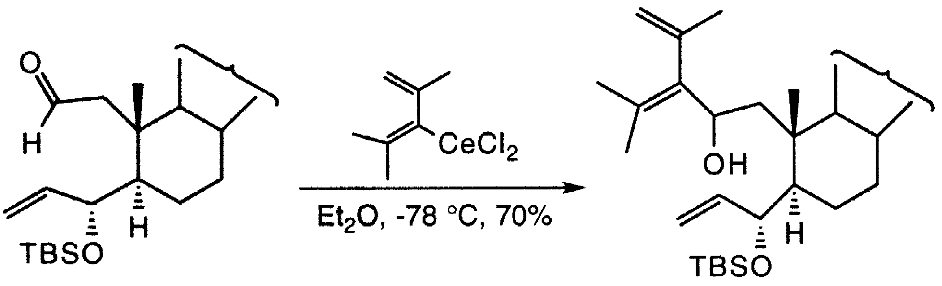


8 **9**

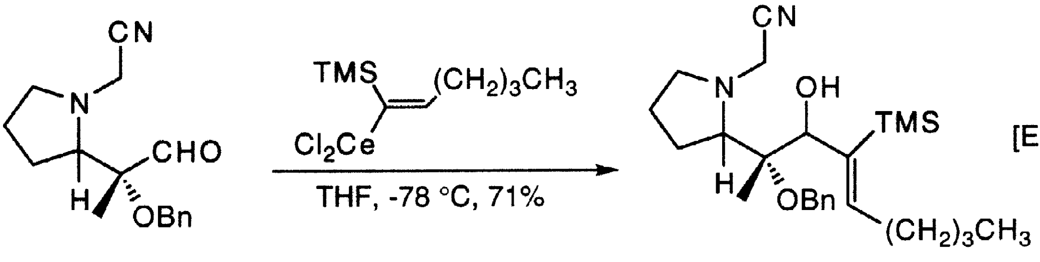
[Eq. 20]

	8	9
i-PrMgCl	12%	53%
i-PrMgCl-CeCl$_3$	91%	5%

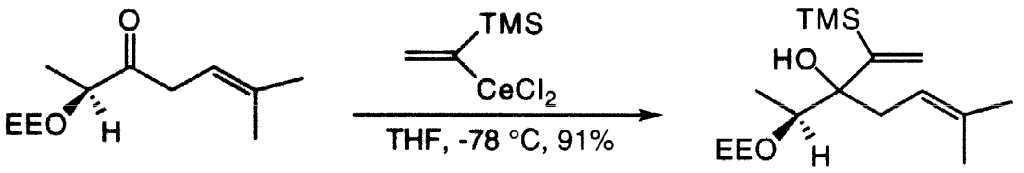
The chemical properties of alkenyl-, alkynyl- and arylcerium reagents are very similar to those of alkylcerium reagents described above. As illustrated below with selected examples (Eqs. 21-26),[27-36] these reagents can undergo nucleophilic addition with ketones and aldehydes readily to give high yields of adducts, even in more difficult cases, and with a high degree of 1,2-selectivity when conjugated enones are involved. The transformation can be performed normally under conditions similar to those using alkylcerium reagents. However, there are some indications that alkenylcerium reagents are thermally rather unstable[20] and low temperature is required (~ -78 °C) in order to carry out the reactions effectively. An interesting example involving addition of an alkynylcerium chloride to a disilyl ketone is also given below (Eq. 27).[37] In this case, the normal addition was accompanied by migration of a silyl group, giving rise to enone **10**.



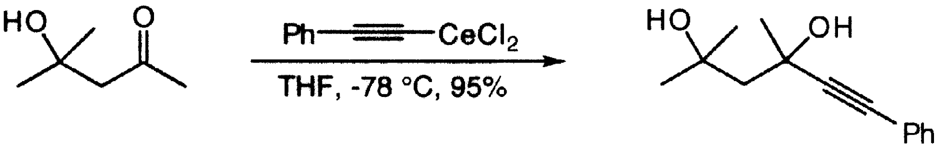
[Eq. 21]



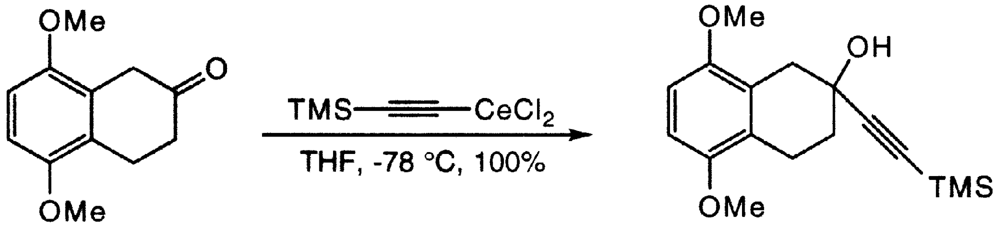
[Eq. 22]



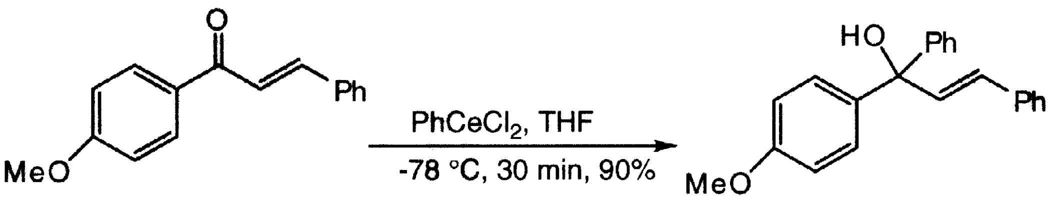
[Eq. 23]



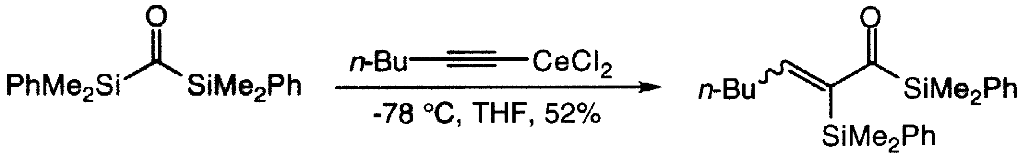
[Eq. 24]



[Eq. 25]



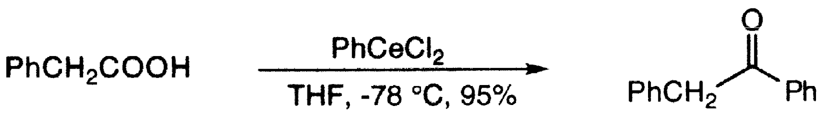
[Eq. 26]



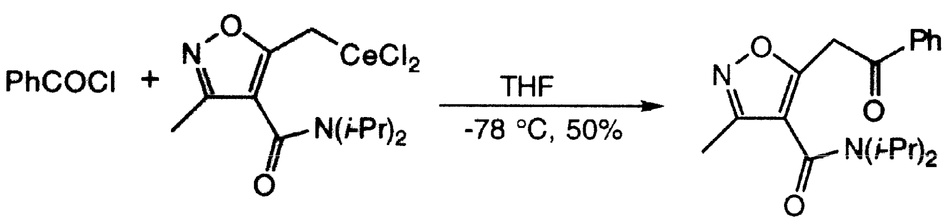
10

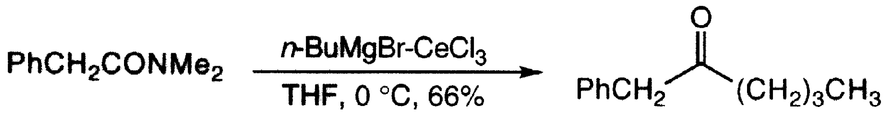
[Eq. 27]

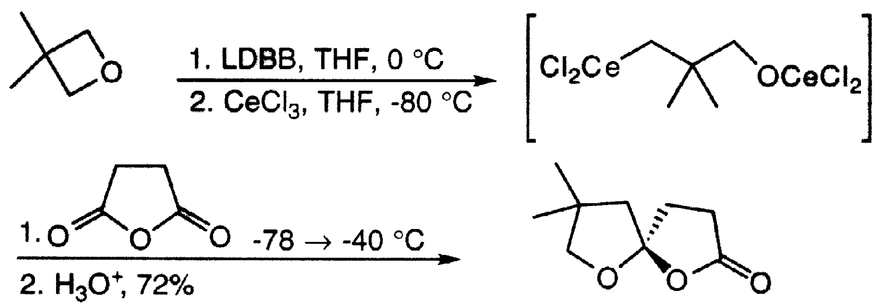
Organocerium reagents are also known to react with carboxylic acids and their derivatives. Under controlled conditions, ketones can be prepared effectively from acids (Eq.28),[38] acid chlorides (Eq. 29),[39] amides (Eq. 30),[40] anhydrides (Eq. 31),[41,42] lactones (Eq. 32),[41,42] esters (Eq. 33)[43] and ketenes (Eq. 34).[44] With suitable cerium reagents and reaction conditions, tertiary alcohols and derivatives thereafter (such as allylsilanes) can be synthesized from esters (Eqs. 35 and 36),[20,45] lactones (Eq. 37)[46,47] and acid chlorides (Eq. 38).[48]

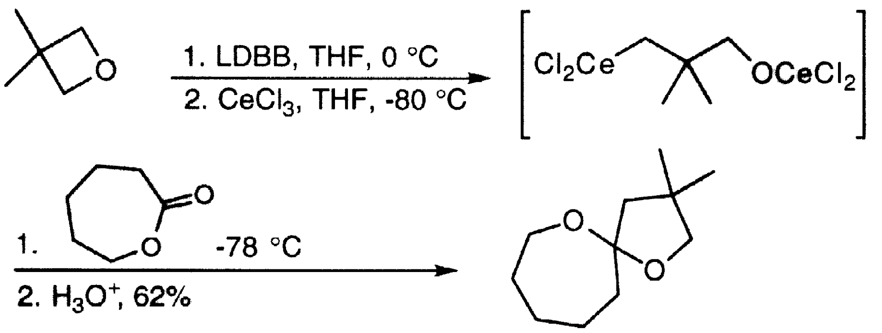


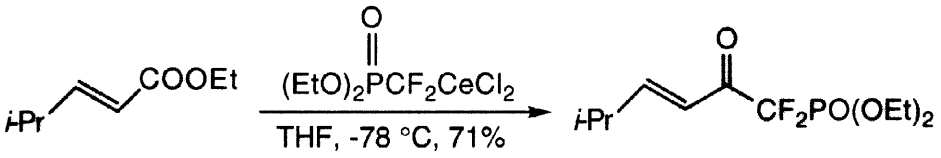
[Eq. 28]

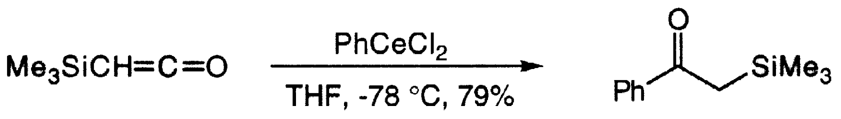

[Eq. 29]

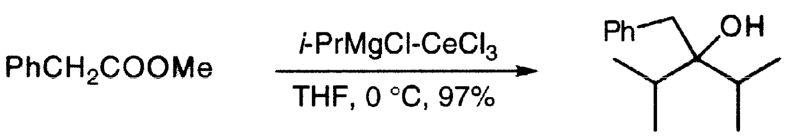

[Eq. 30]

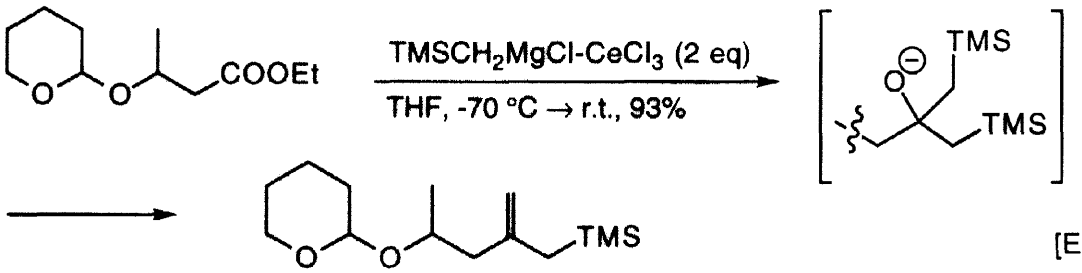

[Eq. 31]


[Eq. 32]

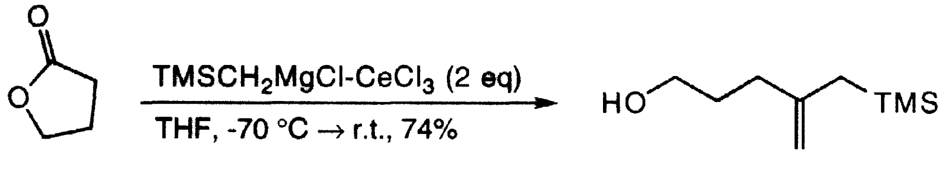

[Eq. 33]


[Eq. 34]

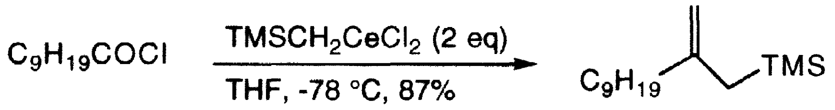

[Eq. 35]



[Eq. 36]



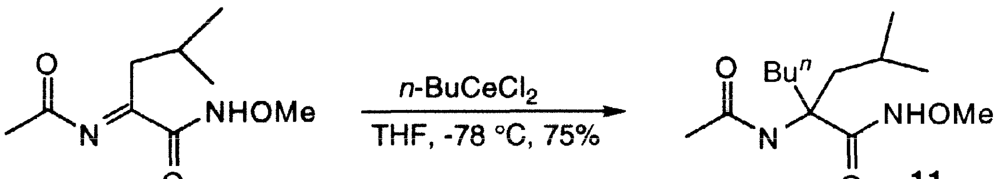
[Eq. 37]



[Eq. 38]

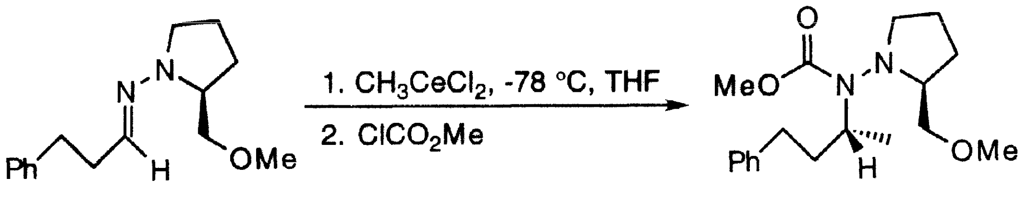
(b) Addition to nitriles, imines and related compounds

One of the most direct methods for synthesizing amines is the nucleophilic addition of organometallic reagents to imines and their derivatives (oximes, hydrazones *etc.*). However, due to the poor electrophilicity of the C=N double bond compared with the C=O double bond, organolithium, Grignard and other organometallic reagents failed to add to the C=N double bond effectively and its synthetic applications were greatly limited. In 1986, Lipshutz and co-workers reported the preparation of bisamides such as **11** in good yields via the addition of organocerium reagents to the corresponding acyl imines (Eq. 39).[49] A year later, Denmark *et al.* described a new method for the synthesis of chiral amines by the use of organocerium reagents to induce addition with SAMP-hydrazone type compounds (e.g., **12**) to give addition products in high yields with excellent diastereoselectivity (Eq. 40).[50] The method is apparently general. Various SAMP-hydrazones including highly enolizable, aromatic and α,β-unsaturated ones were successfully examined and nearly all types of simple organocerium reagents could be employed. Exclusive 1,2-addition was observed for α,β-unsaturated hydrazones (Eq. 41).[51-53] This is consistent with the general characteristics of organocerium reagents.



11

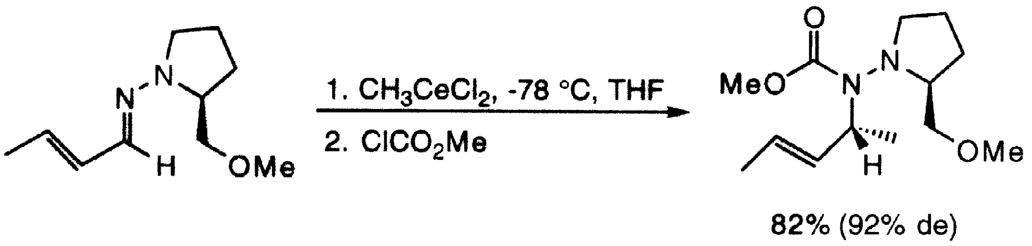
[Eq. 39]



12

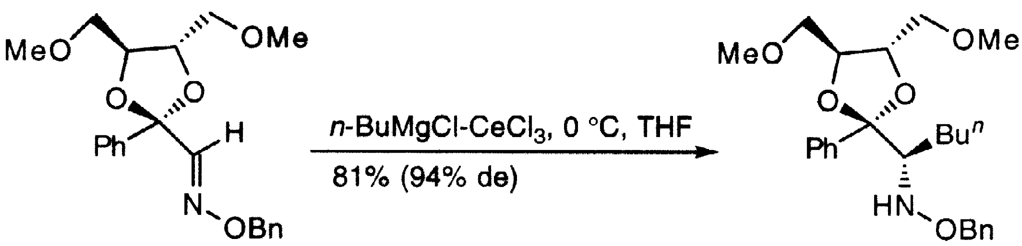
81% (96% de)

[Eq. 40]

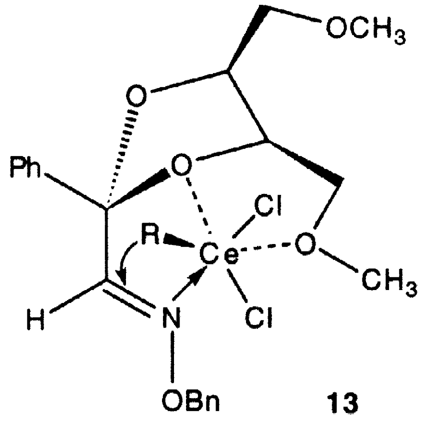


[Eq. 41]

Shortly after, a new asymmetric synthesis of chiral amines was developed. As shown by the representative example in Eq. 42,[54] this method made use of the stereoselective addition of organocerium reagents to chiral α-aldoxime-ether acetals as a key operation. Cerium reagents prepared either from organolithium or Grignard reagents could be effectively applied. However, the reagents derived from Grignard reagents gave superior diastereoselectivity. The *si*-face selectivity was rationalized by assuming a chelating model for the transition state as depicted in formula **13**.

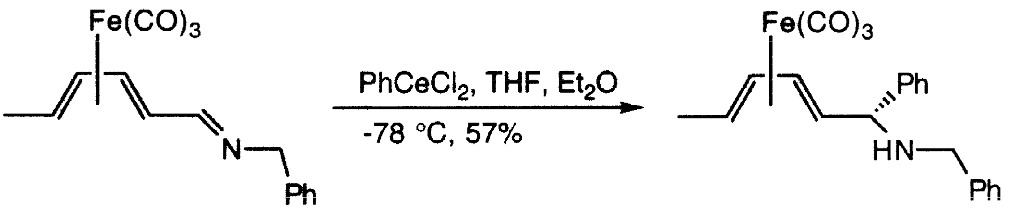


[Eq. 42]



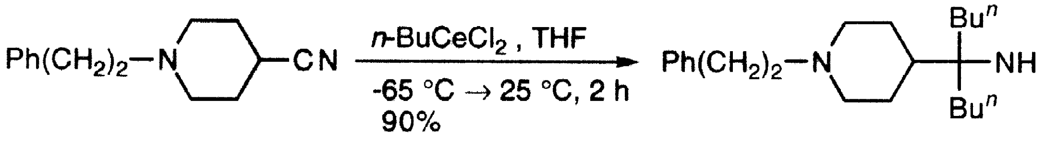
13

More recently, the addition of various organocerium reagents to imine-Fe(0) complexes proved to be effective for the preparation of secondary amines (Eq. 43).[55]

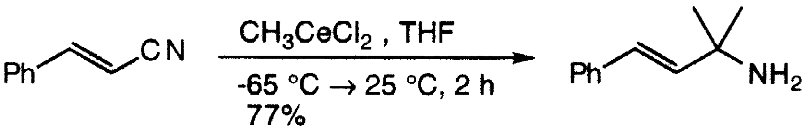


[Eq. 43]

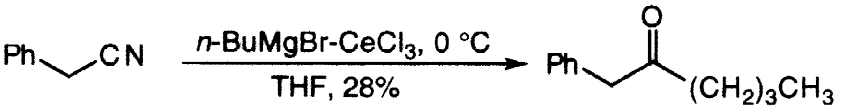
Saturated and α,β-unsaturated nitriles undergo efficient addition with organocerium reagents generated from the corresponding lithio compounds to give tertiary carbinamines (Eqs. 44 and 45).[56] Interestingly, with organocerium reagents derived from Grignard reagents, the addition gave mainly ketones albeit in low yields (Eq. 46).[20] Tertiary carbinamines can also be prepared in modest yields by addition of organocerium reagents to ketimines (Eq. 47).[56]



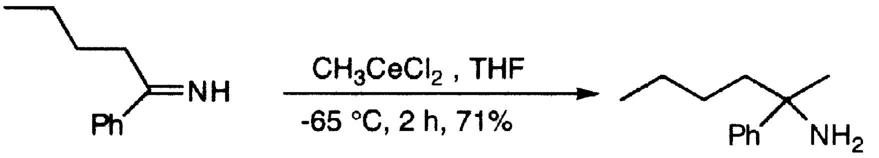
[Eq. 44]



[Eq. 45]

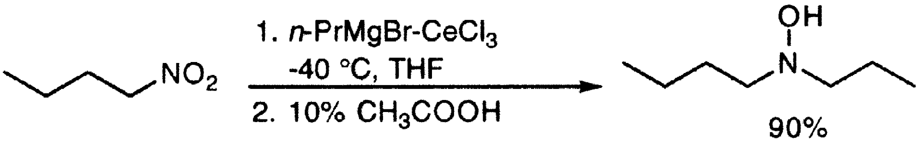


[Eq. 46]

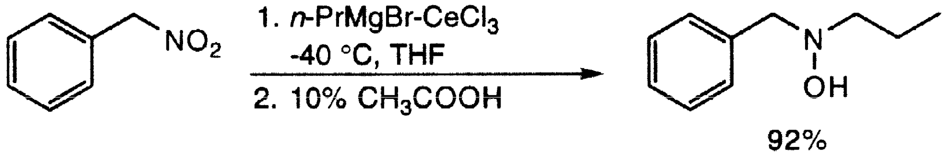


[Eq. 47]

N,N-Disubstituted hydroxylamines are difficult to synthesize by common methods. An efficient procedure for preparing these compounds has been developed recently, in which an organocerium reagent is generated *in situ* by addition of the corresponding Grignard reagent to a mixture of cerium chloride and a nitroalkane in THF. *N,N*-Disubstituted hydroxylamines were produced in good yields using this procedure (Eqs. 48 and 49).[57]

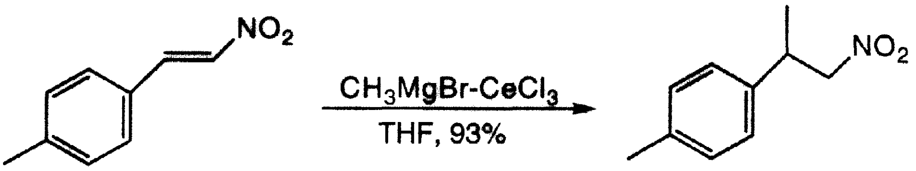


[Eq. 48]

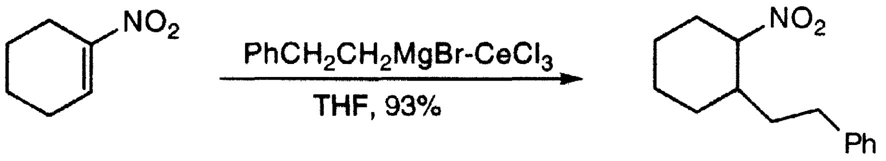


[Eq. 49]

Organocerium reagents normally do not undergo conjugate addition with Michael acceptors. One notable exception is the addition with α,β-unsaturated nitro compounds. The addition of organocerium reagents to this class of compounds occurred consistantly in a Michael fashion (Eqs. 50 and 51),[58] although their corresponding nitroalkanes could, in principle, lead to *N,N*-disubstituted hydroxylamines via a typical 1,2-addition process.



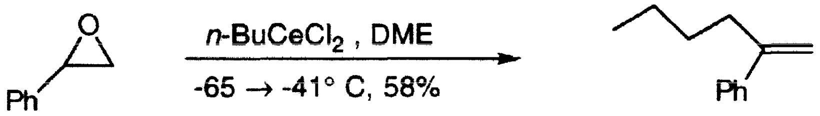
[Eq. 50]



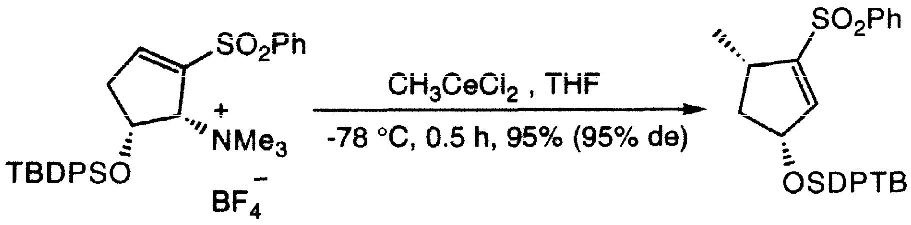
[Eq. 51]

c. Miscellaneous reactions

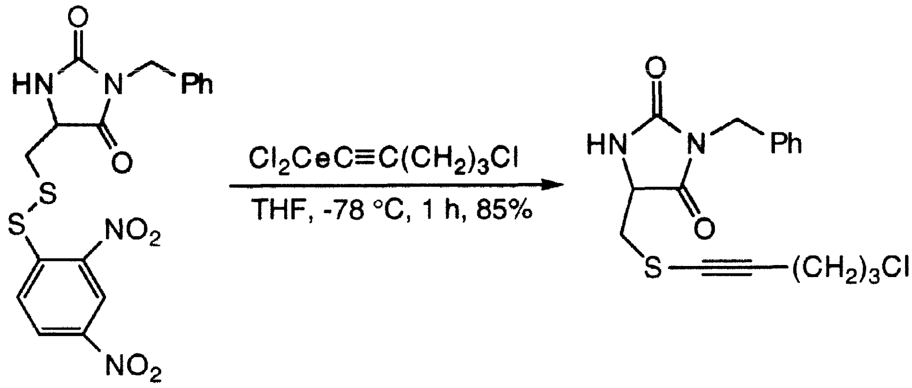
It is generally recognized that organocerium compounds do not undergo nucleophilic substitution with alkyl halides. With epoxides, however, the substitution reaction does occur to give olefins as a result of concomitant dehydration. An example is shown in Eq. 52.[59] Substitution was also observed for the reaction of methylcerium chloride and an allylic ammonium salt (Eq. 53).[60] As shown in Eq. 54,[61] the substitution reaction of an organocerium reagent and a mixed disulfide to facilitate the carbon-sulfur bond formation *en route* to (+)-biotin has also been demonstrated.



[Eq. 52]



[Eq. 53]

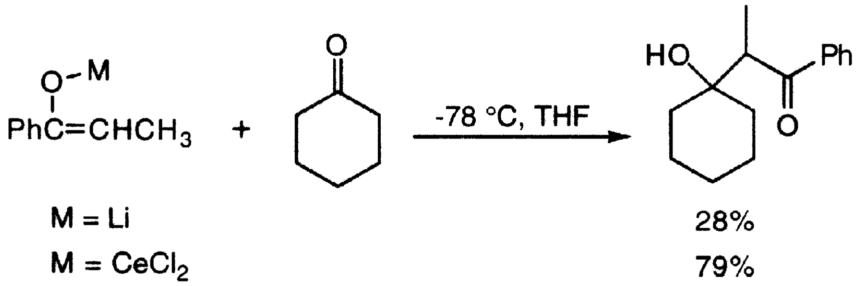


[Eq. 54]

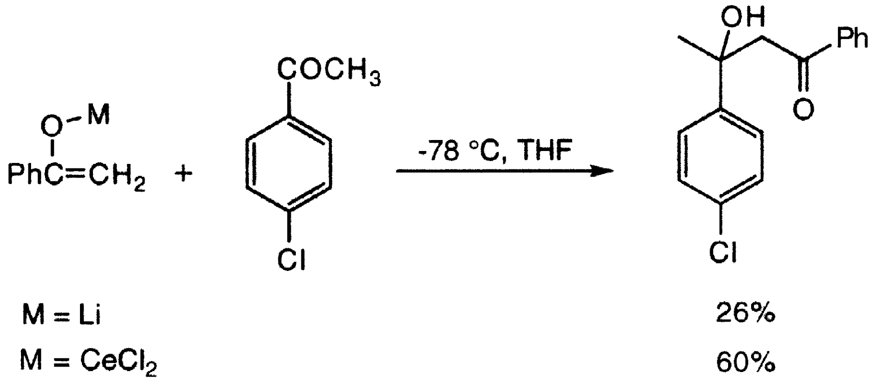
B. Cerium enolates

(a) Addition to carbonyl compounds

Aldol reactions are useful transformations which have been performed in various ways. Nevertheless, several side reactions, such as enolization and cross-aldol reaction, often accompany the normal aldol addition. An additional method via cerium enolates was described in 1983 by Imamoto *et al.* This new aldol process was found to effectively suppress retro-aldol and/or proton exchange reactions, resulting in considerably better yields than those obtained using the corresponding lithium enolates. Selected examples are shown in Eqs. 55 and 56.[21]

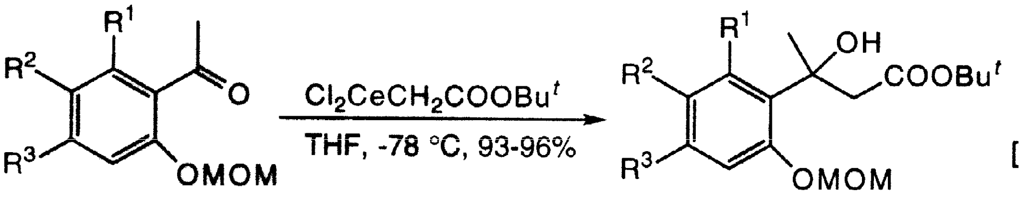


[Eq. 55]



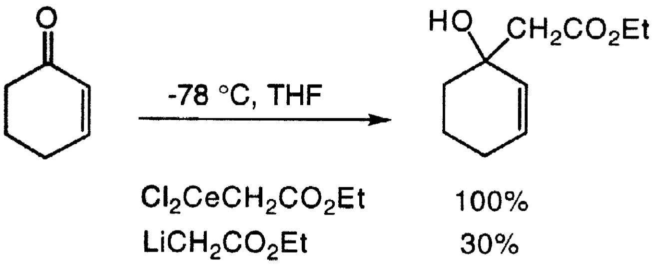
[Eq. 56]

In 1985, Nagasawa *et al.* reported the use of cerium(III) enolate $Cl_2CeCH_2COOCMe_3$ in reactions with a series of acetophenone derivatives to furnish β-hydroxy esters in excellent yields (Eq. 57).[62] In comparison, the use of the lithium enolate of *t*-butyl acetate or the Reformatsky type reactions under a wide variety of conditions afforded only recovered starting materials. More recently, various cerium enolates have been prepared from ethyl esters with different substitution patterns (acetate, propionate and isobutyrate). These enolates are apparently superior to the corresponding lithium compounds on the basis of several comparison addition reactions studied (e.g., Eq. 58).[8] All of these cerium reagents were found to undergo facile addition reactions with ketones including highly enolizable ones (e.g., Eq. 59)[8] and α,β-unsaturated ones. With the latter compounds, the addition was shown to occur in a 1,2-fashion exclusively. An example is provided in Eq. 60.[8] In this case, complete stereoselectivity was also observed.

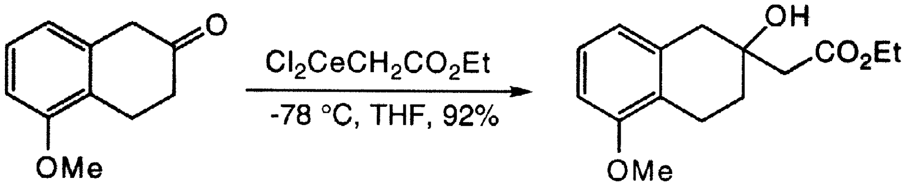


[Eq. 57]

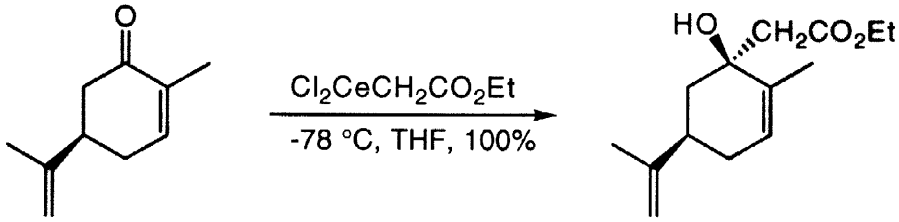
a: $R^1 = R^3 = CH_3$, $R^2 = H$
b: $R^1 = CH_3$, $R^2 = R^3 = H$
c: $R^1 = R^3 = CH_3$, $R^2 = Cl$



[Eq. 58]

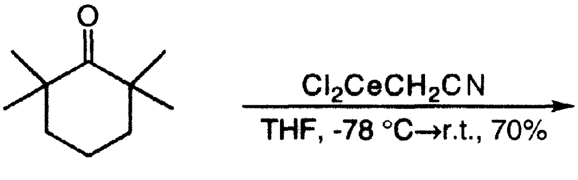


[Eq. 59]

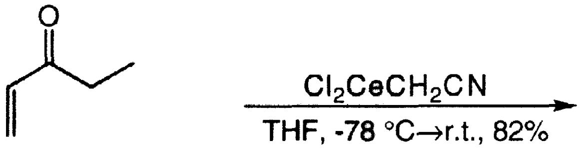


[Eq. 60]

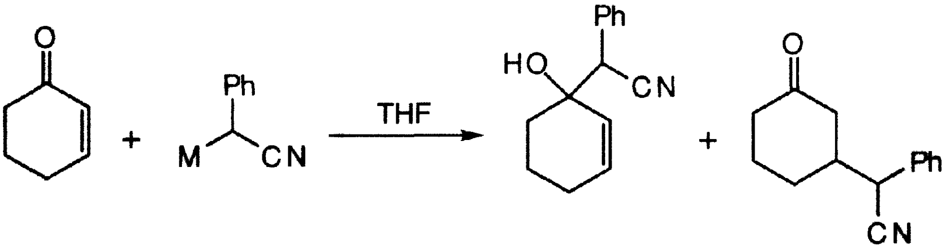
The cerium derivative of acetonitrile also undergoes addition with ketones efficiently. It adds effectively to hindered ketones (e.g., Eq. 61)[22] and gives 1,2-adducts exclusively with conjugated enones (e.g., Eq. 62).[22] It has been noted that cerium derivatives of nitriles are considerably less reactive than those derived from the corresponding esters. While various types of cerium ester enolates add readily to ketones even at -78°C, the addition of the cerium derivative of propionitrile requires prolonged treatment at room temperature and the cerium derivative of isobutyronitrile does not undergo addition at room temperature. At higher temperature, a complex mixture was invariably produced probably due to the instability of the reagent. The addition of the cerium reagent prepared from phenylacetonitrile to 2-cyclohexenone has also been studied. The reaction gave exclusively 1,2-addition product regardless of the reaction time, in sharp contrast to the addition reaction involving the corresponding lithium reagent which gave an increasing amount of the 1,4-adduct with extended reaction time (Eq. 63).[63] These results suggest that with the cerium reagent the reaction is kinetically controlled, whereas with the lithium reagent the reaction is thermodynamically controlled.



[Eq. 61]



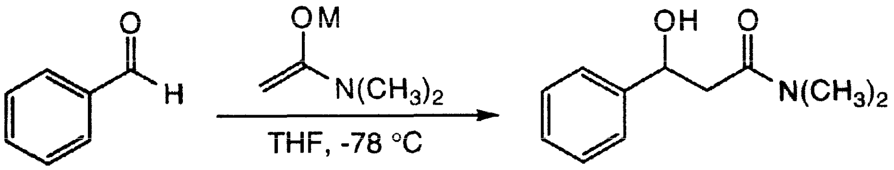
[Eq. 62]



[Eq. 63]

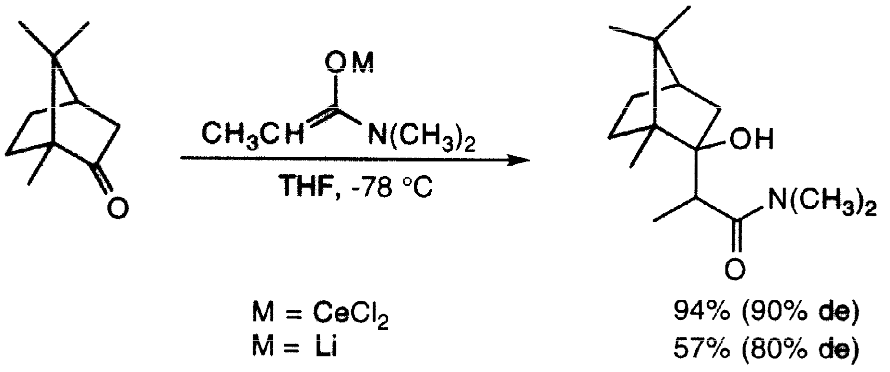
M = Li, -70 °C, 15 min	21%	49%
M = Li, -70 °C, 3 h	0%	90%
M = $CeCl_2$, -78 °C, 15 min	60%	0%
M = $CeCl_2$, -78 °C, 4 h	62%	0%

Recently the cerium enolates of *N,N*-dimethylacetamide, *N,N*-dimethylpropionamide and *N,N*-dimethylisobutyramide with an increasing number of α-substituents were prepared and their reactivity examined using a variety of aldehydes and ketones. In general, better yields of the expected adducts were obtained with the cerium enolates than with the corresponding lithium enolates. As illustrated by the following selected examples, this improvement is especially profound with aldehydes (Eq. 64),[23,24] sterically hindered ketones (Eq. 65)[23,24] and compounds with greater acidity (Eq. 66).[23] However, neither the cerium enolate nor the lithium enolate derived from *N,N*-dimethylisobutyramide was found to undergo addition with carbonyl compounds efficiently, presumably due to the steric congestion.

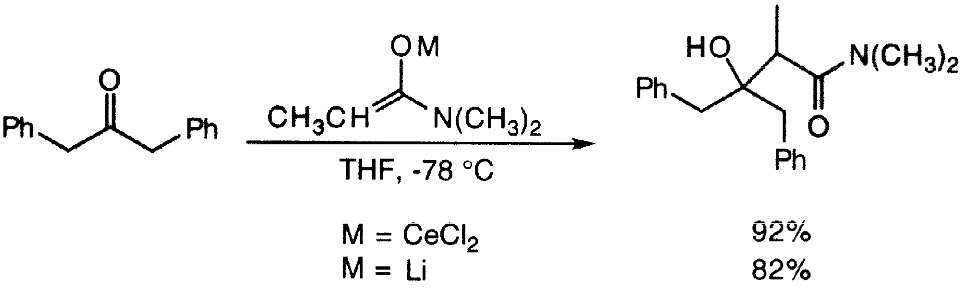


[Eq. 64]

M = $CeCl_2$	99%
M = Li	68%

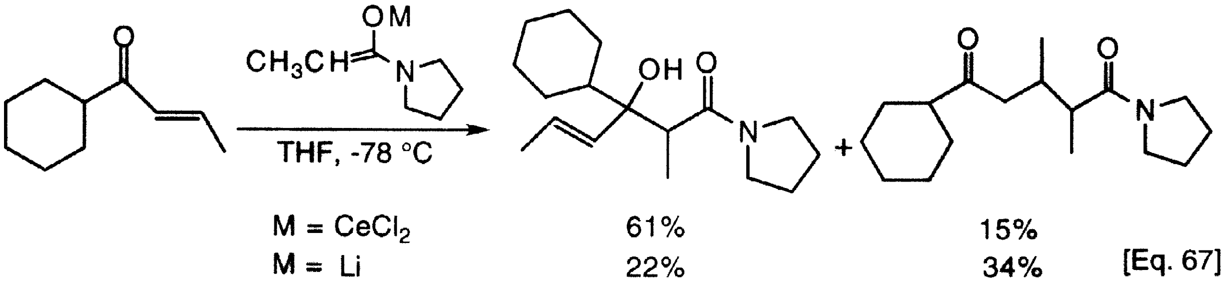


[Eq. 65]



[Eq. 66]

It has been shown that the addition of lithium enolates of hindered amides to α,β-unsaturated ketones gave predominantly 1,4-adducts (Eq. 67).[64] Improvement to varying degrees in the selectivity of 1,2-addition over 1,4-addition has been achieved using the corresponding cerium enolates (Eq. 67). To further improve the 1,2-selectivity, cation-chelating agents, such as HMPA and 12-crown-4 were applied.[24] Neither of these chelating agents, however, was found to enhance the desired selectivity. In fact, both agents, HMPA in particular, appear to have an adverse effect, in agreement with the solvent effects observed previously for conjugate additions.

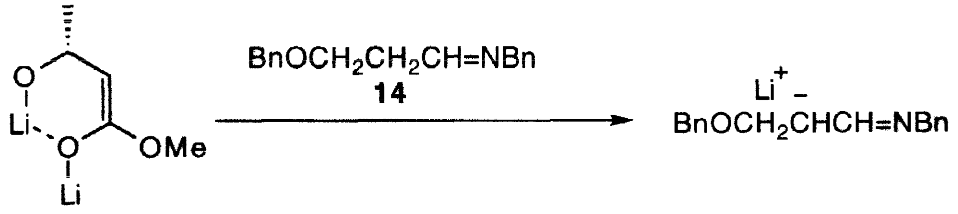


[Eq. 67]

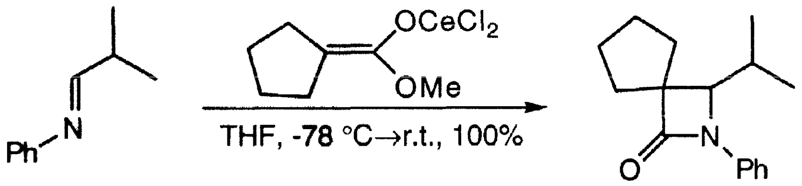
(b) Addition to imines

It is well known that lithium enolates do not react effectively with enolizable imines having a proton α to the carbon or nitrogen atom. Furthermore, in order to effect the addition, imines must be sufficiently electrophilic to accept the enolate nucleophile. If an electron-donating group is attached to the carbon-nitrogen double bond, no addition of the enolate to the imino group will occur. This is due to the much lower electrophilicity of imines compared with the carbonyl compounds which are more reactive towards organometallic reagents. In these cases, the lithium enolate simply acts as a base to deprotonate the imine.

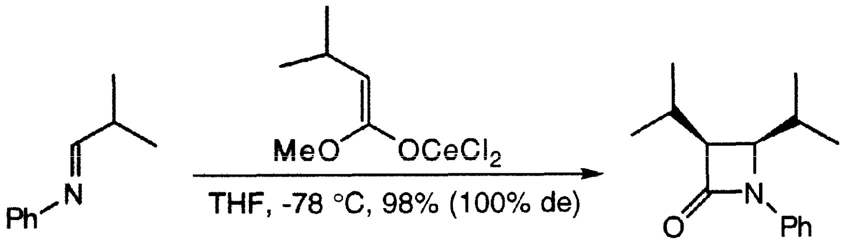
As an example, the addition of the lithium enolate of methyl 3-(*R*)-hydroxybutyrate with imine **14** did not afford any desired product probably due to proton exchange (Eq. 68).[65] Recent investigation on the addition of cerium ester enolates to imines has provided a simple solution to circumvent the above problems.[66,67] The addition occurred efficiently with both enolizable and nonenolizable imines in a highly stereoselective manner. More interestingly, as shown by the selected examples compiled in Eqs. 69-72,[66,67] in all cases studied the addition was followed by a concomitant cyclization, resulting in the direct formation of a β-lactam system. Apparently, in this newly developed procedure for the synthesis of azetidinones, both the addition and the lactam formation are facilitated by the cerium-containing species. A possible pathway which accounts for both the observed stereoselectivity and the facile lactam formation is illustrated in Eq. 73.[67]



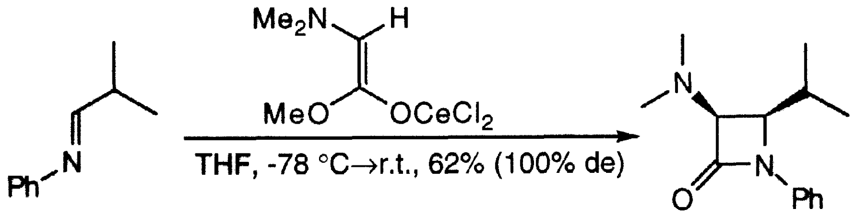
[Eq. 68]



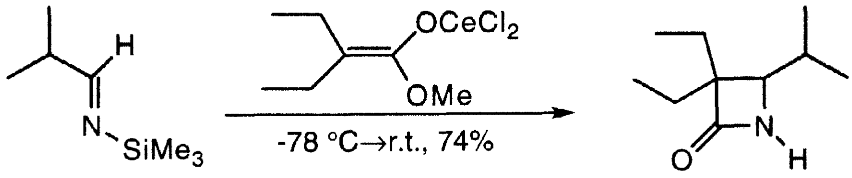
[Eq. 69]



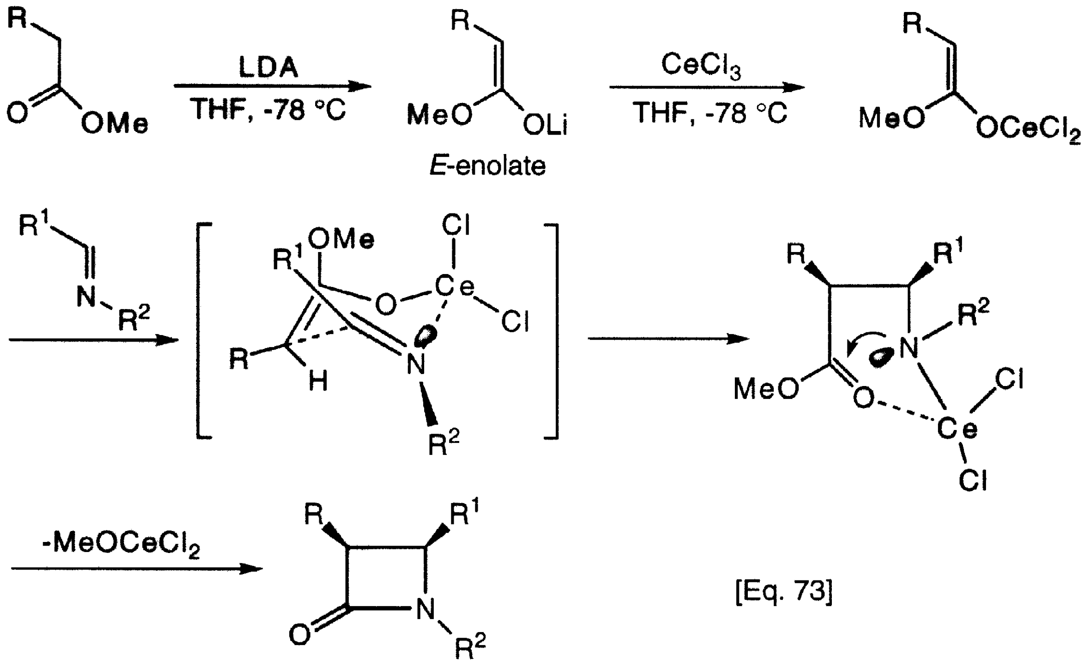
[Eq. 70]



[Eq. 71]



[Eq. 72]

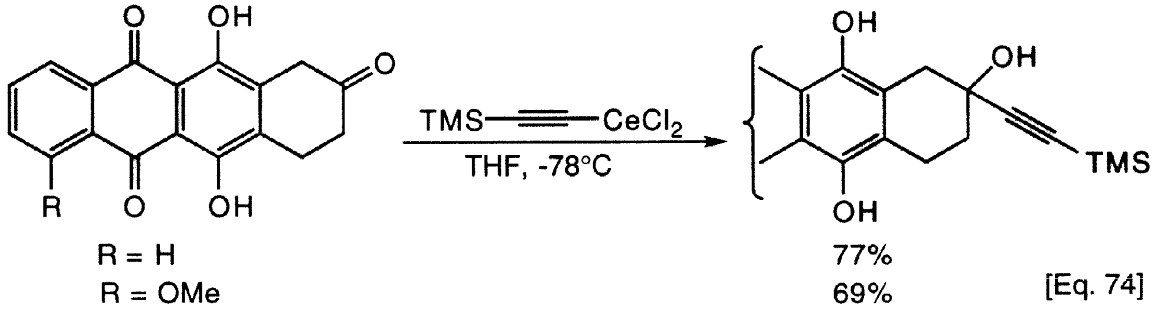


[Eq. 73]

IV. Application to the Synthesis of Complex Molecules

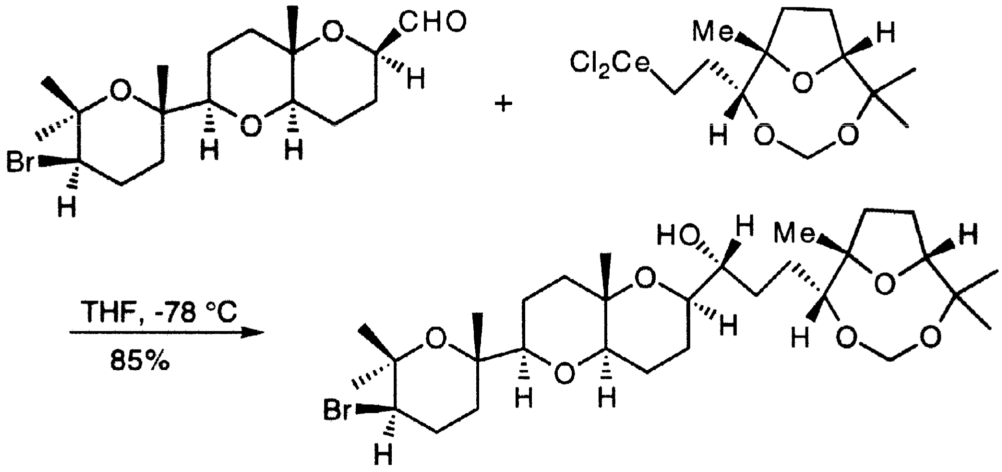
Since its inauguration about two decades ago, the field of organocerium chemistry has expanded remarkably rapidly, mainly due to the high practical utility of organocerium reagents. These reagents have been extensively applied to circumvent the problems often associated with the corresponding organolithium and Grignard reagents, namely, their inablity to react effectively with sterically hindered carbonyl compounds, imines possessing acidic α-protons and easily enolizable carbonyl compounds. Some early examples are illustrated below.

2-Trimethylsilylethynylcerium reagent, developed independantly by Terashima[33] and Tamura,[34,35] was found to react with the highly acidic tetralone system shown in Eq. 74, leading eventually to the synthesis of a number of antitumour agents of the daunomycin family.



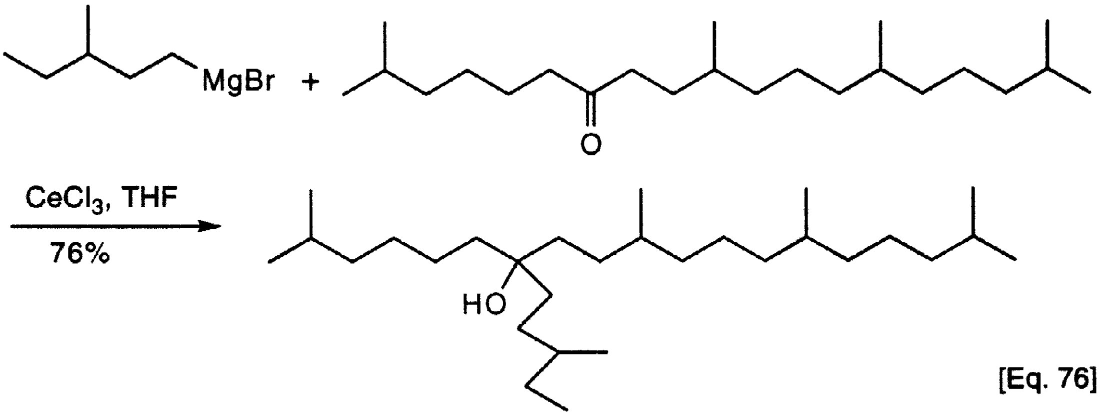
[Eq. 74]

Corey and Ha utilized a cerium-mediated nucleophilic addition to a chiral aldehyde successfully without epimerizing the adjacent chiral center to assemble the skeleton of venustatriol (Eq. 75).[68] The alcohol was isolated in satisfactory yield and with high stereoselectivity.



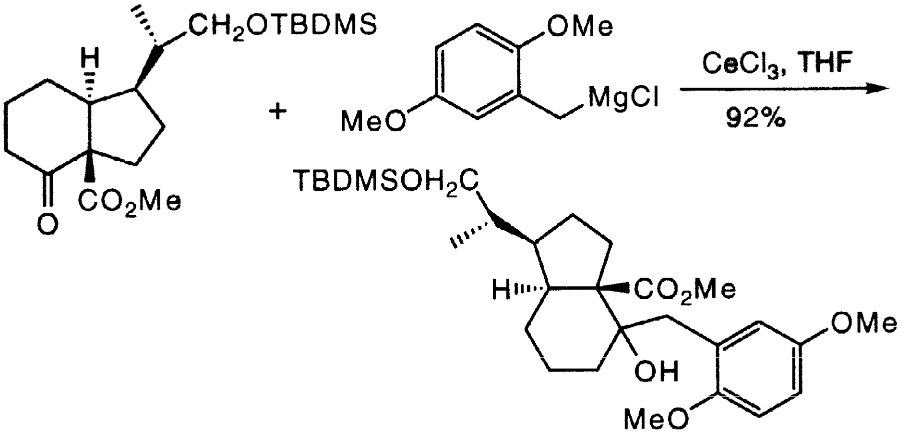
[Eq. 75]

Organocerium reagents were also used by Rowland *et al.* in 1988 in the synthesis of a highly branched C_{30} sedimentary hydrocarbon. Coupling of the ketone with a Grignard reagent in the presence of cerium chloride produced the alcohol in 76% yield, compared to 2% yield without $CeCl_3$ (Eq. 76).[69]



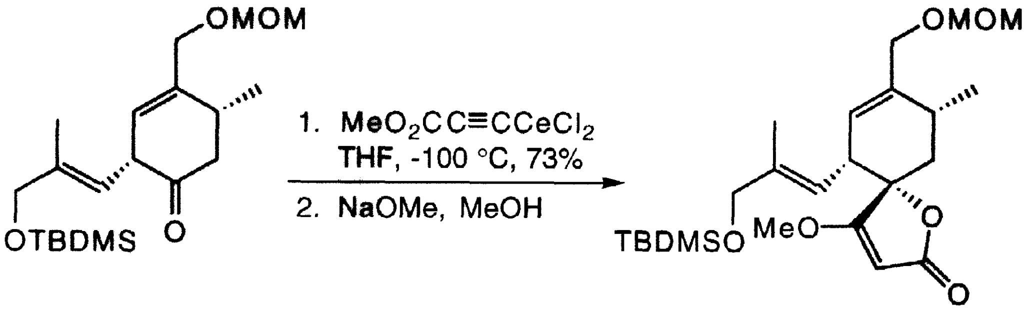
[Eq. 76]

The following Cerium mediated Grignard addition to a sterically hindered ketone was applied by Hart *et al.* in the synthesis of (±)-pleurotin and (±)-dihydropleurotin acid (Eq. 77).[70]



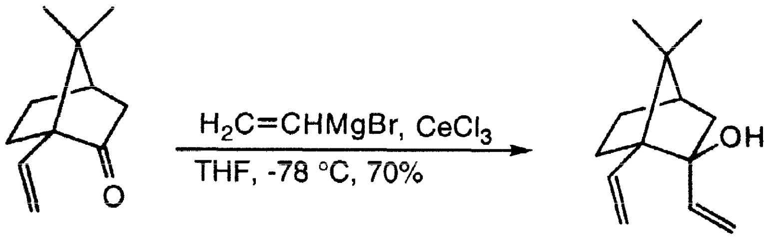
[Eq. 77]

In the synthesis of (±)-28,29-bisnorkijanolide, Yoshii in 1988 employed the acetylenic organocerium reagent, dichlorocerium methoxycarbonylacetylide, which underwent facile addition with a highly epimerizable β,γ-unsaturated ketone for the construction of the key intermediate spirotetronate (Eq. 78).[71]

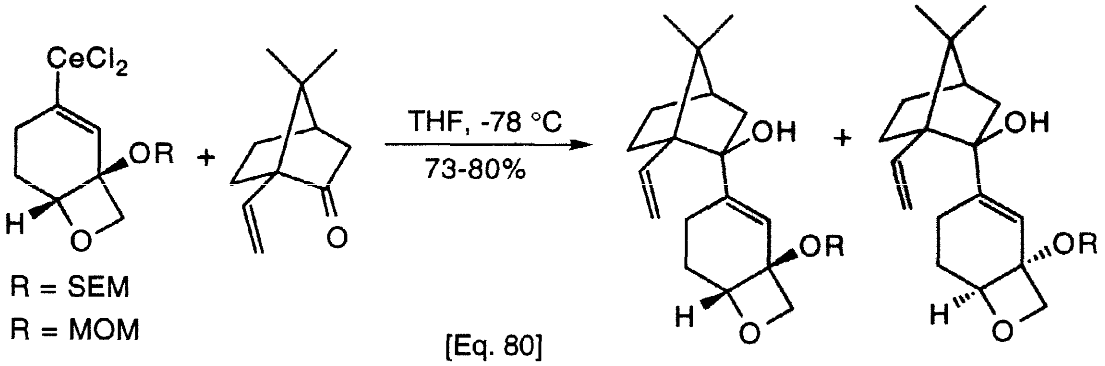


[Eq. 78]

Some of the more interesting recent examples are as follows. Paquette and coworkers have extensively investigated the anionic oxy-Cope rearrangement for the asymmetric induction of C-C bond formation. The requisite intermediates were normally produced by the efficient nucleophilic addition of alkenylcerium reagents to β,γ-unsaturated ketones. A more interesting example is given in Eq. 79.[72] Addition of vinylmagnesium bromide to the optically pure ketone simply induced deprotonation. Both vinylcerium reagents derived from vinylmagnesium bromide and vinyllithium proved to be effective for the desired reaction. However, the reagent prepared from vinyllithium was shown to be superior to that obtained from the Grignard reagent. An attempted application of their anionic oxy-Cope rearrangement strategy to the synthesis of taxol made use of addition of the bicyclic cerium reagent to the 2-norbornanone as shown in Eq. 80.[73,74]

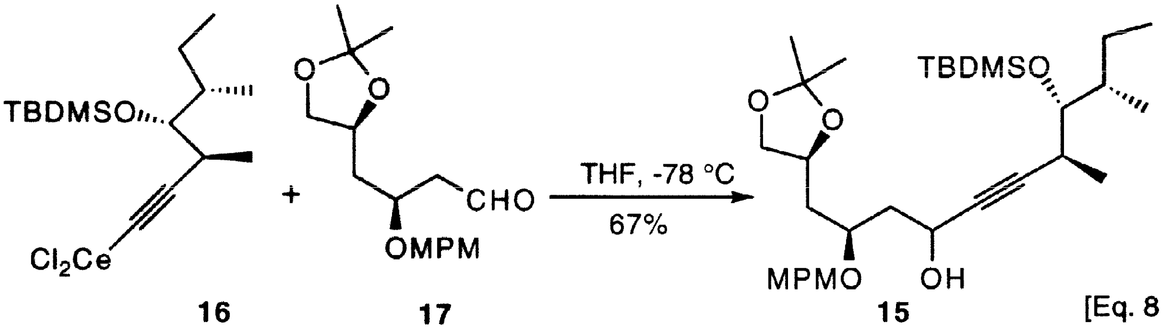


[Eq. 79]

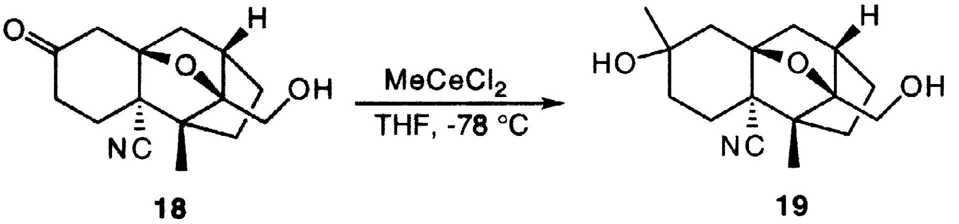


[Eq. 80]

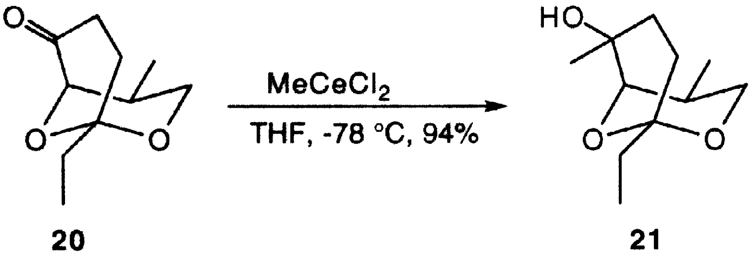
In the area of macrolide synthesis, compound **15** was conceived as an intermediate towards the total synthesis of avermectin B_{1a}. This compound was effectively prepared in 67% yield by addition of alkynylcerium **16** to aldehyde **17** (Eq. 81).[75] In contrast, the use of the corresponding alkynyllithium gave **15** in poor yield along with recovery of the starting alkyne. Similar observations were made in connection with the total synthesis of sporol and neosporol. The addition of $MeCeCl_2$ to ketone **18** gave a diastereomeric mixture of diols **19** (Eq. 82),[76] whereas the use of methyllithium and methylmagnesium bromide resulted mainly in enolization of the ketone. As another example, the addition of methylcerium chloride to ketone **20** gave, in high yield, the bicyclic alcohol **21** (Eq. 83),[77] a projected intermediate in a synthetic approach to erythronolides A and B.



[Eq. 81]

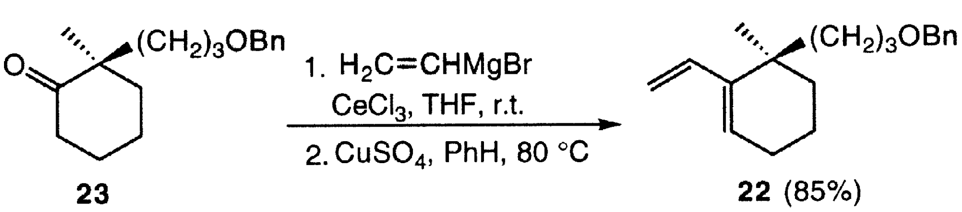


[Eq. 82]

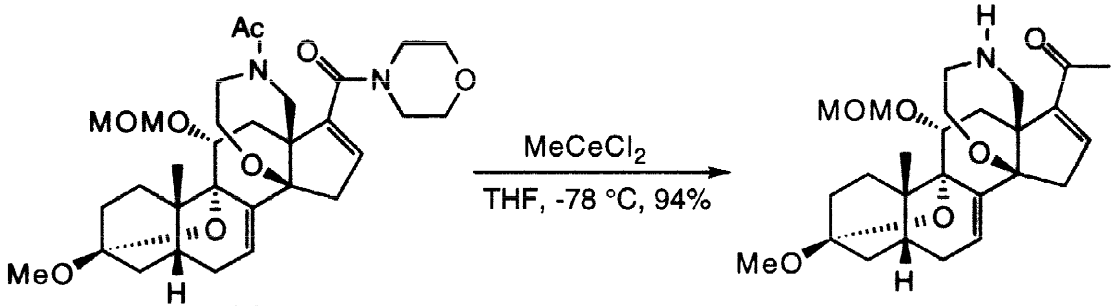


[Eq. 83]

Two recent applications of cerium reagents are shown below. In the total synthesis of (+)-dysidiolide via a Diels-Alder approach, the optically active diene **22** was efficiently produced by addition of the vinylcerium reagent to ketone **23** followed by dehydration (Eq. 84).[78,79] In another case, the preparation of methyl ketone **25**, an advanced intermediate leading to (±)-batrachotoxinin A, was effected by treatment of amide **24** with methylcerium chloride (Eq. 85)[80] while many other methods failed.



[Eq. 84]



24 25 [Eq. 85]

V. Conclusion

Their ease of preparation, low basicity and strong nucleophilicity make organocerium compounds reagents of choice in addition reactions involving ketones, aldehydes and carbon-nitrogen double bond compounds. These reagents have proven to be superior to the corresponding lithium and Grignard reagents, and are now routinely used in place of the latter reagents, especially when the electrophiles are considered to be sterically hindered or susceptible to enolization.

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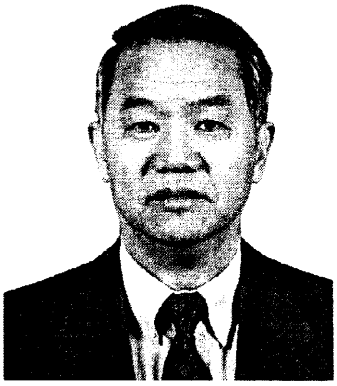
Biographical sketch



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Kak-Shan Shia

Xiao Sha

Bing-Yan Zhu

Hsing-Jang Liu was born in mainland China in 1942 and raised in Taiwan. He received his B.Sc. degree in chemistry from National Taiwan Normal University in 1964. In the subsequent year, he began his graduate work at the University of New Brunswick under the direction of Professor Z. Valenta. Following the completion of his Ph.D. degree in 1968, he carried out postdoctoral studies at UNB (1968-69) and Columbia University (1969-70) under Professors Z. Valenta and G. Stork, respectively. He returned to UNB as a Teaching and Research Associate in 1970. After one year he joined the faculty at the University of Alberta where he served until his recent move to National Tsing Hua University. He is currently a Professor Emeritus at U of A and a Distinguished Professor at NTHU sponsored by the Foundation for the Advancement of Outstanding Scholarship. Hsing-Jang served as an Editor of the Canadian Journal of Chemistry (1995-98), the 1993-94 Chairman of the Organic Division, Canadian Society for Chemistry, and has been an elected Fellow of the Chemical Institute of Canada since 1983. His research interests are in the general area of synthetic organic chemistry with emphasis on the development of new synthetic methodology and the total synthesis of naturally occurring compounds.

Kak-Shan Shia received his B.Sc. in chemistry from National Taiwan Normal University in 1982 and M.S. degree (under Professor Hsien-Jen Wu) from National Chiao Tung University in 1987. He undertook graduate studies in organic chemistry at the University of Alberta, where he obtained a Ph.D. degree in 1995 under the supervision of Professor Hsing-Jang Liu. After two and one-half years at the National Tsing Hua University as a Lecturer, he began his research career at National Health Research Institutes as an Assistant Principal Investigator. His current research interests include the synthesis of natural molecules and the design of new drugs based on combinatorial chemistry.

Xiao Shang received his B.Sc. degree in chemistry in 1984 from Peking University and then moved to the Institute of Materia Medica, Chinese Academy of Medical Sciences, to study organic synthesis and medicinal chemistry under the supervision of Professor Xiao-Tian Liang. In 1988, he went to work with the late Professor Gunther Snatzke as a Visiting Researcher at Ruhr University, studying the CD and ORD spectra of chiral organometallic complexes and natural products. He pursued his Ph.D. studies in natural product synthesis under the direction of Professor Hsing-Jang Liu at the University of Alberta. Upon receiving his Ph.D. degree in 1995, he joined Professor J. Bryan Jones' group at the University of Toronto as a Postdoctoral Fellow. Currently, he is with Rhône Poulenc Ag Company, conducting pesticide research at the Discovery Chemistry Department.

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