Applications of $CeCl_3$ as an Environmental Friendly Promoter in Organic Chemistry

Giuseppe Bartoli,[‡] Enrico Marcantoni,*[,†] Mauro Marcolini,[†] and Letizia Sambri[‡]

School of Science and Technology, Chemistry Division, University of Camerino, via S. Agostino 1, I-62032 Camerino (MC), and Department of Organic Chemistry "A. Mangini", University of Bologna, viale Risorgimento 4, I-40156 Bologna, Italy

Received March 8, 2010

Contents

Giuseppe Bartoli graduated from the University of Bologna in 1967 with a Laurea in Industrial Chemistry. He was Assistant Professor of Organic Chemistry at the University of Bari (Italy) from 1968, moving to the University of Bologna (Italy) as Associate Professor and then to the University of Camerino in 1986 as Full Professor. In 1993 he returned to the University of Bologna, where he is currently Professor of Organic Chemistry. From 2001 to 2006 he has held the position of Head of the Department of Organic Chemistry "A. Mangini", and now he is chairman of the Industrial Chemistry degree course. His research interests include studies on the reactivity of organometallic compounds with aromatic systems, the use of dianions derived from enamino carbonyl compounds, the stereoselective reduction of various classes of ketones, and the development of new Lewis acid systems. Currently, he is interested in enantioselective organocatalysis.

1. Introduction

Long considered the forgotten elements of the periodic table and sometimes thought of merely as atomic number place holders, the lanthanides, in the last decades, are easily changing their status from disregarded to indispensable. Ever since the pioneering work by Kagan and Luche in the past decade, lanthanide reagents have experienced an extensive growth in organic chemistry.[1] Applications of lanthanides cover almost every aspect of organic transformations, and they represent ideal promoters for being applied widely. Lanthanides are often called the rare earths; however, these elements are not really rare, with the exception of *prometium*, which is radioactive and does not occur naturally. For example, cerium, which is the most abundant in the lanthanide series, is more abundant than cobalt, tin, and zinc.

The most stable oxidation states of cerium are +4 and +3. Cerium(IV) compounds have been extensively utilized as convenient and effective one-electron oxidants for a variety of transformations.[2] However, the trivalent state is the most common oxidation state for cerium, and cerium(III) chloride heptahydrate ($CeCl_3 \cdot 7H_2O$) is the most common source of Ce^{3+} commercially available. For this, $CeCl_3$ has been widely used in a large number of applications realized in academic and industrial laboratories. Figure 1 shows the steady increase in the citation statistics in the field of "$CeCl_3$ in organic chemistry", thus demonstrating this topic is a growing area of research, which connects chemistry with other disciplines, such as material sciences,[3] physics,[4] and biology.[5] Furthermore, in producing organic molecules, there are increasing requirements for green and efficient promoters, with particular attention to several environmentally friendly[6] and atom-economical organic transformations.[7] The use of promoters, then, has received increasing attention, as it allows great advantages, such as energy savings, waste minimization, and high-purity delivering products, and recent reports have highlighted the applications of cerium trichloride as a green and efficient Lewis acid in modern organic synthesis,[8] and they are powerful approaches to realize synthetic procedures with great chemical efficiency and reduced environmental impact.

* To whom correspondence should be addressed. Phone: +39 0737 402255. Fax: +39 0737 402297. E-mail: enrico.marcantoni@unicam.it.
† Chemical Sciences, University of Camerino.
‡ Organic Chemistry, University of Bologna.

10.1021/cr100084g
Published on Web 08/23/2010

Enrico Marcantoni was born in 1963. He is currently Full Professor of Organic Chemistry at the University of Camerino (Italy). In 1994/1995 he served as a research collaborator in the group of Prof. Meyers (Colorado State University, Fort Collins, CO), and in 1999 he was the recipient of the "Ciamician" Medal by the Organic Chemical Division of the Italian Chemical Society, for his contribution as a young scientist in the field of organocerium compounds. He is a member of the Italian Chemical Society and the American Chemical Society, and from 2004 to 2009 he has held the position of Ph.D. Coordinator for Chemical Science Graduate Courses. At this time, his efforts focus of new on the development of efficient and selective chemical reactions promoted by Lewis acids for the creation of new heterocyclic molecules.

Mauro Marcolini was born in Italy in 1982. He graduate in Industrial Chemistry from the University of Bologna in 2006, studying enantioselective catalysis. From 2006 to 2008 he worked in the development of low density materials in collaboration with plastic industries. He is currently pursuing his Ph.D. in organic chemistry under the guidance of Prof. Enrico Marcantoni at the University of Camerino. His research interests include organic synthesis using the promoter system $CeCl_3 \cdot 7H_2O-NaI$ and studies of APIs impurities in collaboration with pharmaceutical industries. As part of his Ph.D. program, he is currently spending a period in Pfizer research groups Pfizer Global Manufacturing in Kalamazoo, Michigan.

In general, the lanthanide family is characterized by 4f electrons, and the existence of these shells allows for unique physical[9] and chemical properties which differ from those of main group elements and d-block transition elements. The cerium atom has an extended Xe-core electronic configuration with $5s^25p^6$ outer shell electrons and $4f^2$ deep-lying electrons (Table 1). The inert 4f shell lies inactive deep in the interior of the cation and is well-shielded by the filled $5s^2$ and $5p^6$ orbitals. Ce^{3+} ion is commonly thought to have a tripositively charged, closed shell with a noble-gas electronic configuration. Therefore, no s-donor−p-acceptor bonding mode occurs.[10]

The trivalent cerium ion, located between Sr(II) and Ti(IV), is, undoubtedly, a "hard cation" according to the HSAB terminology of Pearson.[11] As a consequence, $CeCl_3$ shows a strong affinity toward "hard bases" such as oxygen and nitrogen donor ligands. In particular, the ionic bond contributions in combination with the high Lewis acidity cause the strong oxophilicity of the cerium(III) cation.[12] However, given that the Lewis acidity is affected by the charge density (Z/r; Z = charge and r = ionic radii), this is particularly low in complexes derived from the large Ce^{3+} cation;[13] of consequence, $CeCl_3$ is considered in organic chemistry to be a mild Lewis acidic promoter. The rationale behind this beneficial feature of cerium(III) salts is the

Letizia Sambri graduated from the University of Bologna in 1993 with a Laurea in Industrial Chemistry, and she obtained her Ph.D. degree in 1998 in the group of Prof. G. Bartoli. During her thesis she spent a research period at the University of Nijmegen (NL) in the group of Prof. Zwanenburg. Since 2000 she has been Assistant Professor at the Dept. of Organic Chemistry, University of Bologna. During 2009, she spent four months as visiting scientist in the group of Prof. L. De Cola at the University of Münster (D). Her research interests included the application of Lewis acid activators in organic reactions and the development of new methods for the synthesis of useful intermediates. Currently her research interests focus on the synthesis and the properties of organic materials for molecular electronics.

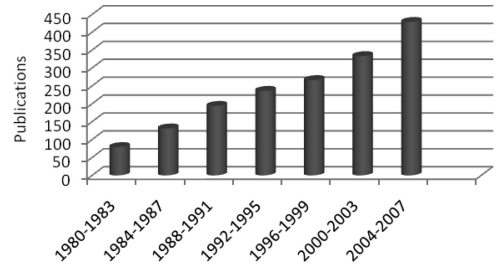
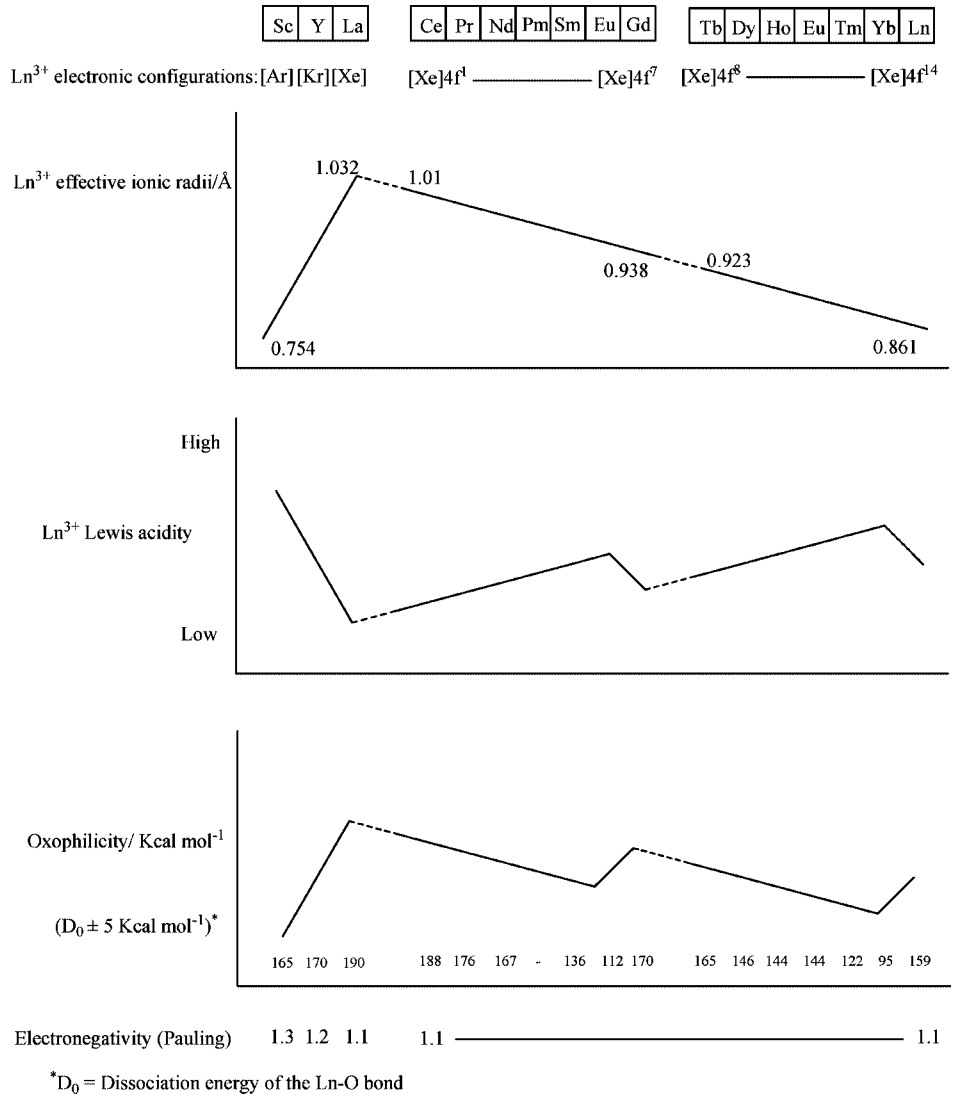


Figure 1. Number of publications using the term "$CeCl_3$" in the abstract (source SciFinder).

Table 1. Characteristic Features of Lanthanide Elements

		configuration of outer electron shell		
element	atom	Ln^{2+}	Ln^{3+}	Ln^{4+}
La	$5d^16s^2$	$5d^1$	[Xe]	
Ce	$4f^26s^2$	$4f^2$	$4f^1$	[Xe]
Pr	$4f^36s^2$	$4f^3$	$4f^2$	$4f^1$
Nd	$4f^46s^2$	$4f^4$	$4f^3$	$4f^2$
Pm	$4f^56s^2$	$4f^5$	$4f^4$	
Sm	$4f^66s^2$	$4f^6$	$4f^5$	
Eu	$4f^76s^2$	$4f^7$	$4f^6$	
Gd	$4f^75d^16s^2$	$4f^75d^1$	$4f^7$	
Tb	$4f^96s^2$	$4f^9$	$4f^8$	$4f^7$
Dy	$4f^{10}6s^2$	$4f^{10}$	$4f^9$	$4f^8$
Ho	$4f^{11}6s^2$	$4f^{11}$	$4f^{10}$	
Er	$4f^{12}6s^2$	$4f^{12}$	$4f^{11}$	
Tm	$4f^{13}6s^2$	$4f^{13}$	$4f^{12}$	
Yb	$4f^{14}6s^2$	$4f^{14}$	$4f^{13}$	
Lu	$4f^{14}5d^16s^2$		$4f^{14}$	

Scheme 1. Characteristic Features of Lanthanide Ions and Elements



preference of this large cation toward coordination numbers (contraction phenomenon) of preferring high coordination numbers (formal coordination number in the range 8−12 is common)[14] (Scheme 1).

Among the several cerium(III) salts that can be used, the cerium(III) halides, cerium(III) nitrate, and cerium(III) triflate are the more common reagents in organic synthesis. On the other hand, the strong complexation of doubly charged anions (CO_3^{2-} and SO_4^{2-}) causes a considerable decrease in solubility of the corresponding Ce_2X_3 and, hence, precludes their broad use as synthetic promoters.[15] Even if to a small extent nitrate ligand coordinates slightly more strongly to the cerium center compared to halides, pseudoinorganic salts derived from superacids, in particular derivatives of triflate, contain weakly coordinating anions, and were often found to be superior to cerium halide.[16] The triflate hydrolyzes slowly, and the small amount of cations produced is generally not enough to promote catalysis. By using cerium(III) triflate in aqueous/organic solvent systems (especially in THF/H_2O mixtures), the quantity of water can influence both the yield and the stereoselectivity of the reaction. There is a THF/H_2O ratio at which the water, rather than THF, preferentially coordinates the cerium triflate to form the active cerium cation.[17] However, generally, metal triflate promoters are rather expensive, and their uses, especially for the large-scale synthetic operation, may not be economical. Thus, the experimental issues associated with the use of the above-mentioned reagents shifted the attention toward $CeCl_3$, which has found wide applications in organic synthesis in both hydrated and anhydrous forms. These reasons, combined with the oxophilic character, a crucial factor in governing chemo-, regio-, and streoselectivities in cerium(III) promoted transformations,[18] increased the interest throughout the scientific community due to its low toxicity,[19] ease of handling, low cost, stability, and recoverability from water.[20,21]

Despite the large amount of relevant literature on $CeCl_3$-promoted organic reactions, there are only a few recent reviews dedicated with particular emphasis to the practical use of $CeCl_3$, as demonstrated by the number of reviews[22] and books[23] on the subject. However, these reviews are mainly microreviews or book chapters that either investigate focused areas or describe esclusively one synthetic methodology. Thus, an overview, covering the mechanisms and applications in total synthesis of both bond-forming reactions and functional group transformations in which $CeCl_3$ plays a fundamental role, could be considered as complementary to the existing literature.

This review covers the literature reports on the following topics: (i) aptitude of the organocerium reagents derived from anhydrous $CeCl_3$ and an organolithium or Grignard reagent

in transferring a carbon framework to a readily enolizable substrate, (ii) aptitude of $CeCl_3$ in promoting the reduction of carbon−heteroatom and heteroatom−heteroatom multiple bonds by metal hydrides, and (iii) aptitude of the $CeCl_3$ in conjunction with iodide ion to act as an efficient Lewis acid promoter in important carbon−carbon and carbon−heteroatom bond forming reactions under mild conditions. Particular emphasis is given to the citations reported in the past decade.

The object of the review is to demonstrate that the usage of $CeCl_3$, applying the related synthetic methodologies cited in the literature, can lead to results which are both exciting and, more importantly, useful to the organic chemistry community. Often references are generally obtained from the journals that specialize in new organic reaction methodologies; as a consequence, it is not unusual for an article on the topic to appear in an unfamiliar journal. For this reason, certain important manuscripts may have been overlooked, and the authors apologize for such inadvertent omissions.

2. Organocerium Compounds in Organic Chemistry

The nucleophilic addition of an organometallic reagent to multiple bonds is one of the most important strategies to obtain new bonds. In particular, the addition of organomagnesium (Grignard reagents, RMgX)[24] or organolithium compounds (RLi)[25] to an electrophilic carbon represents one of most important methods for introducing a carbon framework in a given substrate. The usefulness of RMgX and RLi is of marked importance not only for organometallic chemists but also in organic chemistry and in the synthesis of complex organic molecules.[26] However, in spite of its broad utility, their basicity and redox potential sometimes cause serious drawbacks to these organometallic reagents.[27] For example, in the reaction with carbonyl compounds, side reactions such as enolization, self-condensation, and reduction can compete with, and in several cases prevail over, the expected addition process. Because of this reason, in the last years, many efforts were devoted to the development of more selective organometallics, which tolerate a wide range of functionalities.[28] Unfortunately, this goal was often achieved at the expense of the reactivity, availability of the reagent, and toxicity and of their byproduct too. In this scenario, lanthanide(III) salts, when used as additives in combination with organolithium or Grignard reagents, emerged as reagents of choice in metal-promoted reactions allowing straightforward formation of carbon−carbon bonds.[29] This reaction is now one of the most frequently used organolanthanide(III)-promoted transformations either in academic institutions or in industry. Furthermore, given that the most interesting feature of these reagents and their byproduct is their low toxicity, making these compounds environmentally sound compared to other organometallic reagents, this has been an important aspect of their continued development. Since cerium(III) occupies an unusual position in the periodic table, providing a bridge between group 3 and the lanthanides, organocerium reagents represent an ideal class of reagents when they are seen from the point of view of the organolanthanide complexes.

Organocerium derivatives were discovered and first exploited in organic synthesis by Imamoto.[30,31] After his pioneering work, these reagents have extensively been used as organocerium species able to add to electrophilic substrates having a high reduction potential or containing acidic hydrogens.[23b,32] In addition, organocerium reagents displayed

Scheme 2

significant scope, allowing their use with functionalities traditionally incompatible with Grignard reagents and organolithium compounds. Their broad utility in nucleophilic additions is possible because they can be easily prepared from the corresponding RMgX and RLi derivatives (Scheme 2) and the most convenient way to prepare these organocerium reagents is to use anhydrous $CeCl_3$. Although anhydrous $CeCl_3$ is commercially available, it can also easily be prepared by the dehydration of the heptahydrate form in vacuo.[33] It is desirable to use the Grignard reagents as the source of a transferable alkyl group, since this is generally the more valuable part of the reagent, which can be purchased as a solution in THF and titrated before use.[34]

An interesting concern about this procedure is the stability of cerium chloride during the thermal dehydration. It is known that $CeCl_3$ can decompose to HCl and its corresponding oxychloride is produced in the presence of water at elevated temperature. This elevated drying temperature can cause a reverse reaction between $CeCl_3$ and water that generates CeOCl and 2 equiv of HCl. However, when finely ground $CeCl_3 \cdot 7H_2O$ is heated gradually to 135−140 °C under high vacuum (<0.5 mmHg), excellent mass accountability is observed with correct stoichiometry of metal to chloride (1:3). During the thermal dehydration of $CeCl_3 \cdot 7H_2O$, the oxidation of Ce^{3+} to Ce^{4+} can occur as a side reaction; this possible drawback has been ruled out, since the thiosulfate titration method has shown that under these conditions the amount of Ce^{4+} found is generally less than 0.5% (w/w) throughout the drying process.[35]

Organocerium compounds feature low basicity and high nucleophilicity and, in some cases, superior characteristics to those of the parent grignard or lithium compounds. Two classes of cerium reagents are known: those prepared from RLi and those from RMgX. Their preparation according to the original methods of Imamoto follows:

(i) from RLi: a solution of RLi (1 equiv) in THF or Et_2O is added dropwise to a vigorously stirred suspension of anhydrous $CeCl_3$ (1 equiv) in THF at −78 °C under argon atmosphere, and the stirring is continued for 30 min. The reaction mixture usually results in a yellow or brownish red suspension;

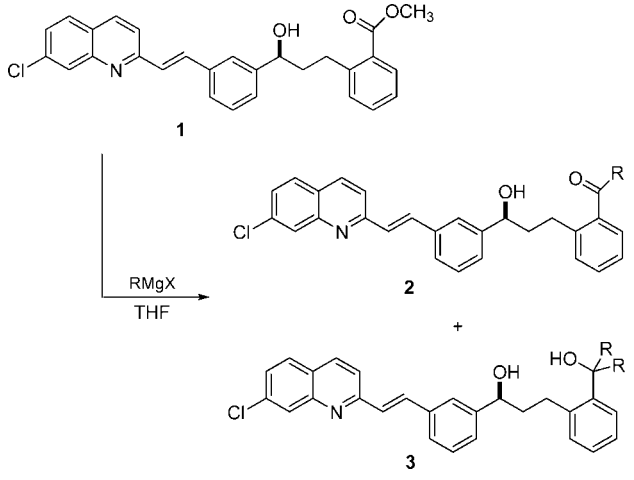
(ii) from RMgX: a solution of RMgX (1 equiv) in THF or Et_2O is added dropwise to a vigorously stirred suspension of anhydrous $CeCl_3$ (1 equiv) in THF at 0 °C under argon atmosphere, and the stirring is continued for 1.5 h. The reaction mixture usually results in a dark gray suspension.

Compounds derived from RLi are stable only at low temperature,[36] and they are generally used at −78 °C. Compounds derived from RMgX are more stable and are prepared at temperatures ranging from −20 to 0 °C, with the exception of alkenyl and alkynyl derivatives, which require reaction temperatures below −60 °C. In both cases, compounds containing a large variety of carbon frameworks are available, including primary, secondary, and tertiary alkyl groups as well as alkynyl, alkenyl, and aromatic moieties.

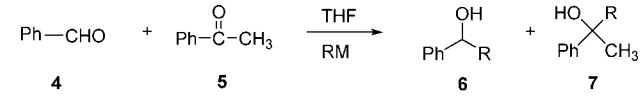
Organocerium reagents cannot be stored for a long time and must be prepared immediately before use. Generally, the reactions are carried out by adding the THF or Et_2O solution of a given electrophilic substrate to a freshly prepared suspension of organocerium compound in THF at

the appropriate temperature. Alternatively, the electrophilic substrate, dissolved in THF, is added to a stirred suspension of dry $CeCl_3$ at room temperature. The mixture is stirred for 1 h and then cooled to −40 °C, and a THF or Et_2O solution of the Grignard reagent is added dropwise. Interestingly, the two different solvents (THF or Et_2O) may affect the same reaction to different extents even under similar experimental conditions, and then, the reaction is best controlled by an appropriate choice of the solvent. Generally, the use of THF leads to improved yields and reduced reaction times, compared to the use of Et_2O. In fact, 10 years ago, the crystal structure of a THF solvate of anhydrous cerium chloride was reported to have a polymeric structure previously not identified for THF-solvated lanthanide halides.[37] The incorporation of THF into the crystal structure may indicate why the reactions perform better in THF than other ethereal solvents. THF is more basic than Et_2O and strongly coordinates metals, especially oxophilic cerium.[38] In the same period, W. J. Evans and co-workers proposed that the crystal forms are hydrates and reported a crystal structure for $[Ce(\mu\text{-}Cl)_2(H_2O)(THF)_2]_n$ formed from a cerium chloride that contains water.[39] This structure accommodates an eight-coordinate cerium, and all the chlorides are of the less reactive bridging type. Even if the material obtained after thermal drying of $CeCl_3 \cdot 7H_2O$ contains water, the suspension of anhydrous $CeCl_3$ in THF is highly efficient without the need for a large excess of organolithium or Grignard reagent. Recently, Dimitrov and co-workers published an alternative procedure and found an improved efficacy for removing any adventitious moisture that might be detrimental toward nucleophilic additions.[40] Generally the amount of detrimental water present is <0.1%, and thus, it has no effect on the overall course of the reactions investigated. Although the actual nature of an organocerium reagent is not yet well-known, it is common opinion that those derived from RLi should have a structure resembling that of a true organocerium species ($RCeCl_2$), while those derived from RMgX are supposed to be *ate*-complexes; it must be noted that, despite extensive efforts, the solution structure of the reagent formed from $CeCl_3$ and Grignard reagents is still obscure.[41] Recent insights into the $CeCl_3$-promoted Grignard addition to hydroxyl ester **1** indicated that the nature of the reactive species is dependent on the manner in which the $CeCl_3$ is activated and on the water content of the system.[42] The possible compositions are the *ate*-complex $RMgX \cdot CeCl_3$ and the σ-alkyl species (Scheme 3).

Scheme 3



Scheme 4. Chemoselective Reactions of Organocerium with 4 and 5 in THF



RM	Yield (%)	6:7
$CH_3Li/CeCl_3$	99	50:50
$CH_3Ce(OPr^i)_3Li$[a]	90	82:18
$CH_3Ce(OPr^i)_3MgCl$[b]	80	99:1
$PhLi/CeCl_3$	95	50:50
$PhMgBr/CeCl_3$	81	99:1
$PhCe(OPr^i)_3MgBr$[c]	80	99:1

[a] From CH_3Li and $Ce(OPr^i)_3$.
[b] From $CeCl_3 \cdot 3Pr^iOH$ and four equivalents of CH_3MgCl.
[c] From PhMgBr and $Ce(OPr^i)_3$.

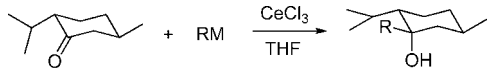
$RCeCl_2$ formed by transmetalation, but the study did not indicate which of these possibilities was occurring. In the case of the regioselective allylation reactions using crotyl and prenyl Grignard reagent-$CeCl_3$ systems,[43] IR spectra suggest a η^3-allylcerium complex and indicate that the organocerium species, written as "$RCeCl_2$", are produced with allyl-type Grignard reagents and $CeCl_3$. The difference between $RLi/CeCl_3$ and $RMgX/CeCl_3$ complexes in reactions with electrophilic substrates was also shown by Reetz.[44] The extent of selectivity in the carbonyl addition reactions to **4** and **5** organocerium reagents depends significantly on the nature of the coordinating anion of the cerium(III) salt. The first indication of synthetically meaningful ligand effects came about in a simple study regarding chemoselectivity (Scheme 4). The study has been first concentrated on *ate*-complexes produced by reacting cerium triisopropoxide[45] with RLi and RMgCl. These organocerium *ate*-complexes selectively react with aldehydes when they are derived from Grignard reagents, and it is also significant that $RLi/CeCl_3$ behaves chemorandomly, in contrast to the >99% aldehyde-selectivity displayed by $RMgX/CeCl_3$.

In general, problems can often be encountered during the preparation of organocerium reagents. A solution has been provided by Greeves and co-workers, who have shown that use of ultrasounds can greatly aid the preparation of active cerium(III) salt.[46] The more convincing evidence supporting the existence of two different structures for organocerium reagents is that the $RLi/CeCl_3$ complexes are better nucleophiles and poorer bases than the $RMgX/CeCl_3$ complexes.[47]

2.1. Addition to Carbonyl Compounds

The organocerium addition to a carbon−oxygen double bond has found a broad utility in carbon−carbon bond-forming reactions.[22c] These addition reactions usually occur much more smoothly than those of the parent organolithium or organomagnesium reagents. Various carbonyl compounds are converted to alcohols in high yields even in the presence of substrates susceptible to enolization, metal−halogen exchange reduction, and pinacol coupling reaction.[48] The aptitude of highly active anhydrous $CeCl_3$ to afford improved yields of the corresponding tertiary alcohols from ketones has been exploited in the addition of several organometallic reagents to (−)-menthone (Scheme 5).[49] The reaction provided neomenthol derivatives, important auxiliaries[50] or ligands[51] for the asymmetric synthesis, in high yields. The stereoselectivity of the addition provided **9**, the result of equatorial attack. Only in the case of $PhMgBr/CeCl_3$ has a

Scheme 5. Addition of Organometallic Reagents to (−)-Menthone in the Presence of Dry $CeCl_3$



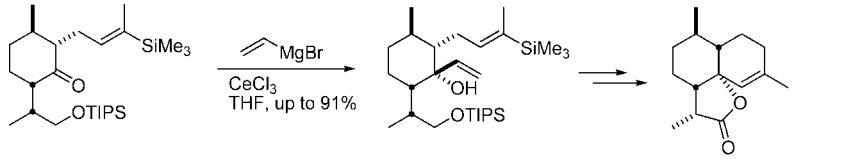
8 **9** (65-75%)

small amount of the axial addition product (5%) been obtained. The experimental evidence might be rationalized by the increased steric hindrance between the phenyl *ortho*-protons of the reagent and the axial protons of (−)-menthone.[52] When different organometallics species are used, however, products of exclusive equatorial-addition[53] of the reagents have been obtained, providing useful enantiomerically pure compounds on a preparative scale also. The fact that the related problems with nucleophilic addition of the hindered menthone core are resolved by using organocerium nucleophiles has suggested to Dudley and co-workers[54] a study for providing insights into the reactivity and synthetic processing of the artemisinin sesquiterpenes[55] (Scheme 6). The intermediate **10** is obtained from silyloxymenthone (Z = OTIPS)[56] by Noyori's procedure,[57] and despite its steric congestion, the organocerium reagent derived from freshly prepared vinylmagnesium bromide and activated $CeCl_3$ provides the corresponding tertiary alcohol **11**. Alternatively, a three-step sequence starting with the addition of lithium trimethylsilylacetylide and subsequent Lindlar's reduction provided **11** in reduced yield. The organocerium solution developed to overcome initial difficulties in the addition of vinylorganometallic reagents to menthone derivatives has served as a valuable methodology to obtain building blocks for synthetic artemisinin and related compounds,[58,59] such as (+)-dihydro-*epi*-deoxyarteanunin B (**12**).[60]

Another example of the superiority of an organocerium reagent over alternative organometallic reagents in the synthesis of hindered substrates is reported in Scheme 7.[61] When (*2S*,*5S*)-2,5-disubstituted pyrrolidine **13**, easily prepared through the formation of a pyrrolidine ring by reaction of the dimethyl-2,5-dibromoadipate with (*S*)-(−)-1-phenylethylamine as chiral auxiliary, is treated with in situ-generated phenylcerium reagent, the corresponding tertiary alcohol **14** is obtained in very high yield. If phenylmagnesium bromide is used in the same reaction, only complete degradation of diester **13** is observed.[62] Hydrogenolysis of **14** affords pyrrolidine derivative **15a**, and tertiary hydroxyl groups at the benzylic positions can be reductively removed *via* conversion to trimethylsilyloxy groups followed by the use of $Me_3SiCl-NaI-CH_3CN$ reagent and water. The four steps and 54% overall yield provided 2,5-disubstituted pyrrolidines with a *C*2 axis of symmetry,[63] without the use of lipase-catalyzed kinetic resolution,[64,65] and the key steps involve the nucleophilic addition of an organomagnesium reagent to a carbonyl compound promoted by $CeCl_3$.

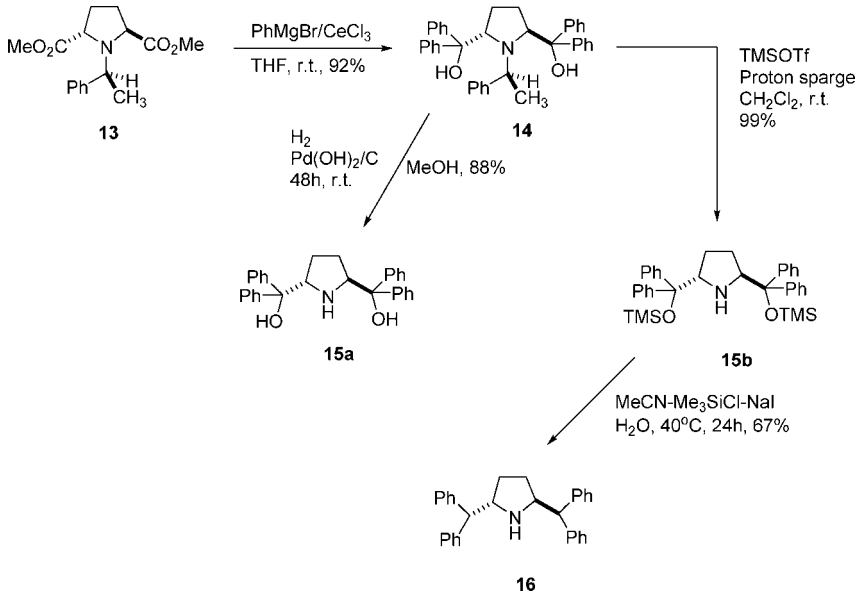
The construction of quaternary centers is a major contemporary challenge in organic chemistry, in particular when stereogenic centers are involved.[66] During their study on identification and characterization of new steroids,[67] in particular of series of unidentified aliphatic compounds with 27 to 29 carbon atoms, found in fossil organic materials,[68] Christoffers and co-workers reported an elegant introduction of the fully saturated 1,5-dimethylhexyl side chain onto an cholestane skeleton using a transmetalation of organolithium to organocerium reagent as a first step (Scheme 8). After a lithium−halogen exchange of 2-bromo-6-methylhepta-1,5-diene and *t*-BuLi, the organolithium was transmetalated with anhydrous $CeCl_3$ and then added to ketone **17**. The tertiary alcohol **18** was obtained without formation of any byproduct and in good yield. Attempts of adding simple alkenyllithium reagent have again not been successful. Subsequent dehydra-

Scheme 6. Addition of Vinylcerium Derivative to Intermediate 10



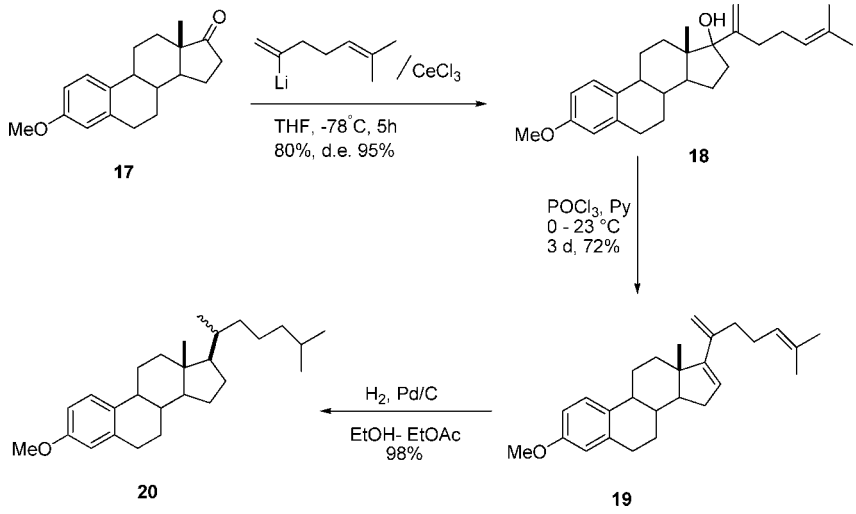
10 **11** (+)-dihydro-*epi*-deoxyarteanunin B (**12**)

Scheme 7. Synthesis of *trans*-(*2S*,*5S*)-(1,1-Diphenylmethyl)pyrrolidine

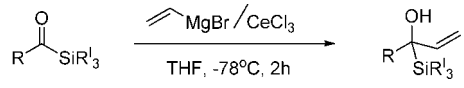


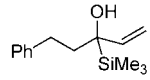
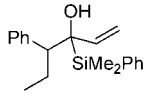
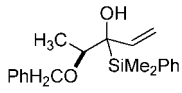
13 **14** **15a** **15b** **16**

Scheme 8. Synthesis of 19-Norcholestane Derivative 20



Scheme 9. Synthesis of Silylated Allylic Alcohols

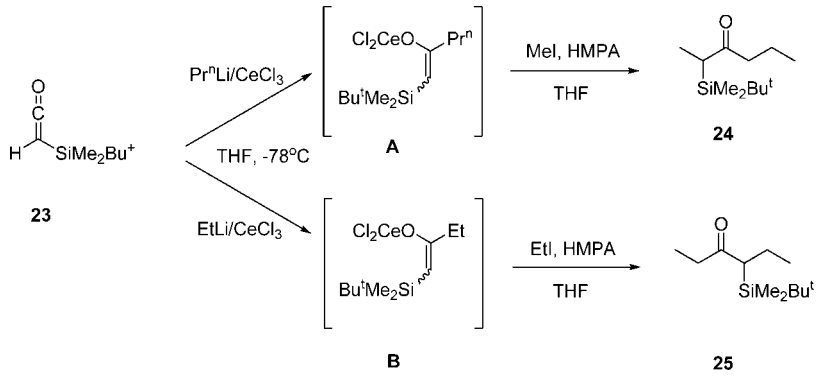


R	Product	Yield(%)
$PhCH_2CH_2$-		98
$PhHC(CH_2CH_3)$—		95
H_3C, OCH_2Ph		60

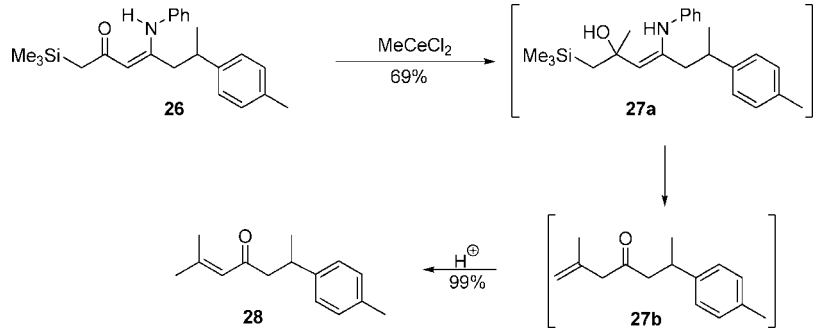
tion and carbon−carbon double-bond hydrogenation provided the target compound without requiring multistep syntheses to introduce cholesterol side chains.[69]

Allylic alcohols are easily accessible by addition of vinyl metallic reagents to carbonyl compounds. The importance of polyfunctionalized allylic alcohols as versatile intermediates for the synthesis of biologically active compounds has supported a vinylation strategy for preparation of acylsilanes.[70] The combination of vinylmagnesium bromide with $CeCl_3$ works very well, and silylated allyl alcohols are obtained in satisfactory yields (Scheme 9).[71] In this strategy, Ricci has marvelously exploited the aptitude of trivalent cerium to be strongly oxophilic and able to chelate more tightly to the carbonyl than magnesium, thus inhibiting the magnesium alkoxide−homoenolate equilibration, which is responsible for the formation of (*Z*)-isomer silyl enol ethers as byproduct. Substituted and functionalized allylsilanes have been obtained from Li also, who has exploited this aptitude of $CeCl_3$ to promote the addition of a (trialkylsilil)methyl Grignard to ketones.[72] Similar reaction of silyl derivatives with organocerium reagents has been reported by Kita et al.,[73] who have developed a convenient synthetic method for various types of α-silylketones by addition of organocerium carbanions to the carbonyl moiety of silylketenes **23** (Scheme 10).[74] The reaction of **23** with an organolithium resulted in a complicated mixture without formation of any carbonyl compounds. On the other hand, the organocerium reagent selectively added to the carbonyl group of **23** to generate silylated enolate anions (A or B), which after quenching with alkyl halides in the presence of hexamethylphosphoramide (HMPA) as cosolvent afforded the corresponding α-silylketones **24** and **25**. This methodology allows for regiocontrolled synthesis of the two isomeric α-silylketones **24** and **24** and provides an alternative preparation of O-silyl enol ethers of corresponding asymmetric ketones.[75] It is interesting to note that the use of the cerium reagents generated from organolithium compounds is preferable for this reaction, since cerium reagents generated from Grignard reagents gave α-silylketones in low yields. The observation that cerium reagents derived from organolithium represent a prerequisite for the positive outcome of the reaction while cerium−

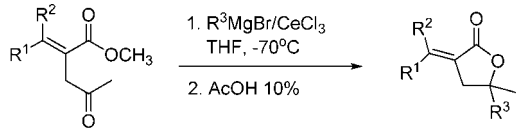
Scheme 10. Preparation of α-Silylketones 24 and 25



Scheme 11. Synthesis of (±)-*ar*-Turmerone

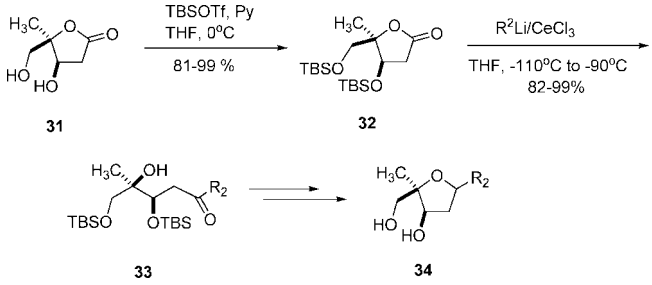


Scheme 12. Synthesis of γ,γ-Dialkyl-α-(alkylidene)-γ-lactones



R^1	R^2	R^3	Yield (%)
$-(CH_2)_5-$		CH_3	75
$CH_3(CH_2)_2$	H	$PhCH_2$	65
CH_3	CH_3	CH_3	65

Scheme 13. Preparation of 4′-Quaternary 2′-Deoxy-3′-*epi*-β-C-nucleoside 34

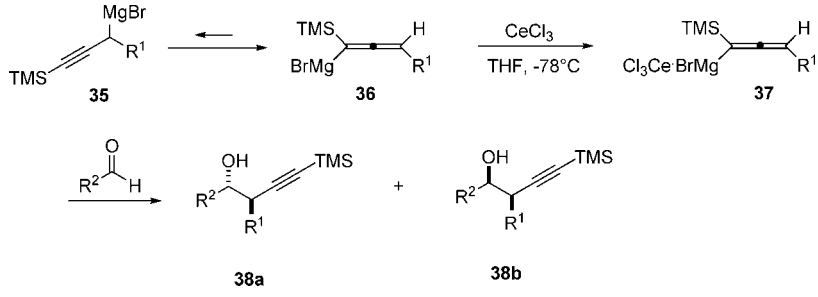


magnesium complexes are ineffective has been confirmed by our group in the examination of the addition of organocerium reagents to α′-(trimethylsilyl)enaminones **26**.[76] The silanol adducts **27** undergo hydrolysis to the β,γ-unsaturated ketones **28** (Scheme 11).[77] To ensure 1,2-addition to the carbonyl moiety at the α′ position of the (trimethylsilyl)enaminone **26**, a phenyl substituent at the nitrogen is required,[78] in agreement with the results previously reported for the organocerium addition to enaminones.[79]

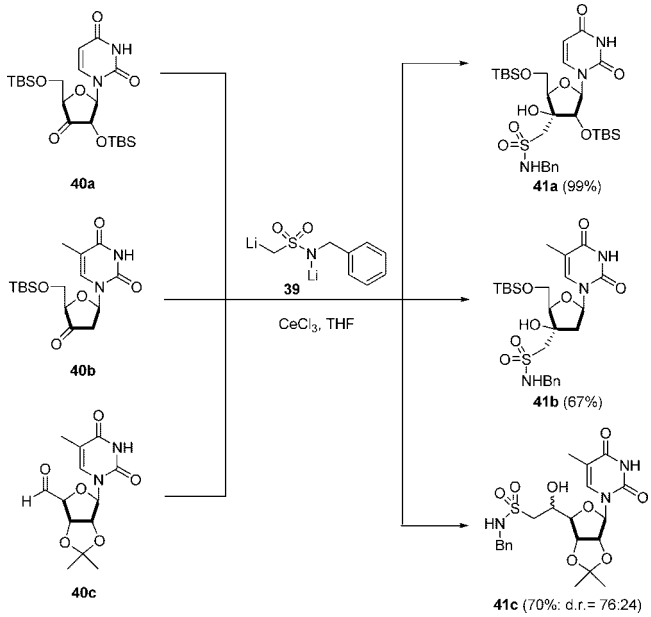
The chemoselective addition of the organometallic species to the ketone functionality[80] promoted by dry $CeCl_3$ allowed us to develop a new strategy for the synthesis of γ,γ-dialkyl-α-(alkylmethylene)-γ-butyrolactones **30** (Scheme 12).[81] The keto esters **29** can be conveniently prepared by Michael addition of nitroalkanes to commercially available methyl *trans*-4-oxo-2-pentanoate catalyzed by bases.[82] Adding the Michael adduct **29** to a suspension of dry $CeCl_3$ in THF, followed by subsequent addition of the organomagnesium reagents, provided substituted butyrolactones **30** in satisfactory yields. The success of this strategy can be attributed to the important role that $CeCl_3$ plays in increasing the nucleophilicity of the Grignard reagents.[83] The chemoselectivity of the reaction can be controlled by carrying out the experiment at low temperature (−70 °C) and with only a slight excess of the organometallic reagents. In fact, the reaction temperature is very important for the addition of an organolithium compounds/$CeCl_3$ combination to O-protected lactones **32** also (Scheme 13).[84] The temperature must be kept below −105 °C to prevent a second addition to the new keto functionality, and the reaction mixture is then allowed to warm up to −99 °C to allow ring-opening to desired product **33**. Finally, the reduction and deprotection steps provided β-C-nucleotides **34**, where the substituent at the 4′-position can vary from alkyl and allyl to aromatic. The importance of γ-butyrolactones in synthetic organic chemistry[85] is the foundation of a useful method for the synthesis of *threo*-homopropargylic alcohols **38**, key intermediates for the synthesis of heterocyclic targets (Scheme 14).[86] The authors found that, after formation of allenyl Grignard compounds/$CeCl_3$ complexes **37**, these reacted with various aliphatic and aromatic aldehydes to give the corresponding homopropargylic alcohols. The alcohol adducts have been obtained with *threo*/*erythro* ratios ranging from 65:35 to >98:2, and higher regio- and diastereoselectivities have been achieved in reactions promoted by $CeCl_3$ than other cerium(III) salts such as $Ce(OPr^i)_3$.[87]

The ability of $CeCl_3$ to mediate high yielding and highly diastereoselective transfer of carbon frameworks to base sensitive carbonyl compounds has been utilized by Widlanski in the addition of dianions to aldehydes and ketones of

Scheme 14. Reaction of Organocerium Allenyls with Aldehydes



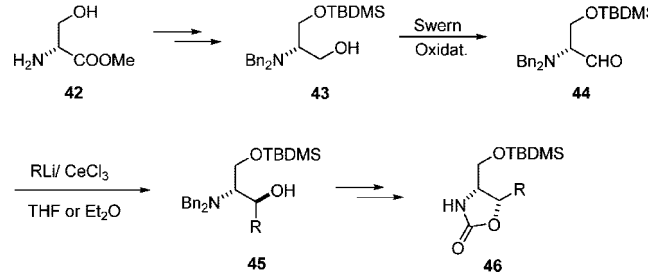
Scheme 15. $CeCl_3$-Promoted Addition of *N*-Benzyl-α,*N*-Dilithiomethanesulfonamide to Aldehyde- and Ketouridines



biological relevance.[88] Generally, ketonucleosides give moderate yields of addition product to the carbonyl group upon reaction with Grignard,[89] organolithium,[90] and organoaluminum[91] reagents. In this context, the usage of $CeCl_3$ mitigates the basicity of heterofunctional dianions[92] such as *N*-benzyl-α,*N*-dilithio methanesulfonamide (**39**), thus facilitating addition to the carbonyl group with 2′-deoxy-3′-ketonucleosides in good yields (Scheme 15). The reagent combination of dianion **39**/$CeCl_3$ has general utility for the addition to a variety of carbonyl compounds, such as steroids and sugars, and it demonstrates the high potential for important synthetic applications[93] associated with the combination of preformed enolates/$CeCl_3$. It is possible that in these reactions the kinetic order in cerium is quite high, so that the $CeCl_3$ promoted enolate anions condensation is compatible with a range of substrates, including those having base-epimerizable centers adjacent to carbonyl groups, as well as those possessing other base sensitive functionality. Furthermore, the yields of addition products observed, unlike the results obtained with other types of dianions such as the dialkoxide of TADDOL[94] and the dialkoxide of binaphthol,[95] suggest that ligation to the nitrogen and oxygen functionalities of the nucleobase is not operative. This is in agreement with the findings reported by Denmark that chelating ligands curtailed the reactivity of organocerium reagents.[96]

Highly functionalized, optically pure compounds are in strong demand in the pharmaceutical and agricultural industries. In a study aimed at the identification of powerful tools for providing such complex molecules, it has been found that γ-hydroxy-β-amino alcohols are key structural units in bioactive natural products[97] and also play an important role in modern organic chemistry as a class of versatile chiral ligands.[98] As chiral building blocks, N-protected amino aldehydes have found numerous applications in the synthesis of amino alcohols.[99] In particular, N-protected serinal has special importance, as the presence of a β-hydroxy group in the side chain of serine gives rise directly to γ-hydroxy-β-amino alcohols. Among the pool of protected serine aldehydes, Garner's aldehyde is probably the most popular synthon.[100] The configurational stability at room temperature

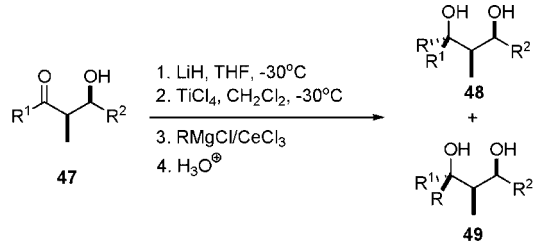
Scheme 16. Reaction of *N*,*N*-Dibenzylserine Aldehydes with Organocerium



of *N*,*N*-dibenzylamino aldehydes and their high diastereoselectivity observed with different organometallics[101] have prompted Zhu and co-workers[102] to study the addition to the carbonyl group of *N*,*N*-dibenzylserine aldehyde **44** (Scheme 16). The *tert*-butyldimethylsilyl (TBDMS) group has been selected as a protective group mainly for the ease of introduction and the nonchelating property of the resulting TBDMS ether. This type of aldehyde has scarcely been reported in the literature because the reaction with alkyllithium gives rise to a complex reaction mixture. Only when $CeCl_3$ is added is the efficiency of the desired transformation recovered to give protected amino alcohol **45** in good chemical yield and with excellent *anti* diastereoselectivity. The stereochemistry can be verified by conversion of **45** into oxazolidinone **46**, where the coupling constant ($J_{H4-H5} = 6.5$ Hz) together with the observation of a NOE cross-peak between H-4 and H-5 indicated a *cis* relationship for the two protons and, consequently, the *anti* stereochemistry of adduct **45**. To evaluate the usefulness of this procedure, attention has been focused on the synthesis of an important β-hydroxy-α-amino acid such as (2*S*,3*S*)-β-hydroxyleucine.[103]

Because of the outstanding diastereoselectivities often reached with organocerium compounds in addition reactions to carbonyl compounds, we investigated the suitability of these organometallics for a highly efficient and stereoselective addition to *syn*-β-alkyl-β-hydroxy-α-methyl ketones.[104] The introduction of an alkyl group into O-protected β-hydroxy ketone systems with stereocenters in α-positions, using RLi or RMgX, has been studied by Guanti and co-workers.[105] The authors found that the reaction proceeds with high selectivity, but often in very low yields due to the extensive occurrence of an enolization process, especially when a saturated alkyl chain is bound to the prochiral carbonyl group. These drawbacks can be circumvented by conversion of β-hydroxy ketones such as **47** (Scheme 17) into the corresponding titanium alkoxide, followed by in situ treatment with a Grignard reagent/$CeCl_3$ complex. The conversion of the starting material into a trichlorotitanium alkoxide is necessary because the obtained intermediate can assume a cyclic half-chair conformation, which can provide great stereofacial discrimination in the nucleophilic attack of RMgCl/$CeCl_3$.[106] The methodology allows the introduction of a variety of aliphatic and aromatic moieties in high yields and with good stereoselectivities shown by diols **48/49**. The presence of $CeCl_3$ in the reaction mixture has improved the efficiency of the reaction without affecting the stereochemical course. Moreover, the treatment of β-hydroxy ketones **47** with only an excess of RMgCl/$CeCl_3$ gave the expected diols **48** in poor yields and with moderate diastereoisomeric excess. Then, despite the strong coordinating properties, the ability of cerium(III) compounds to form six-membered cyclic chelation complexes has been questioned in the last few

Scheme 17. Reaction of Enolizable *syn*-β-Hydroxy Ketones with RMgCl/$CeCl_3$ Complexes by Way of Their Titanium Alkoxides

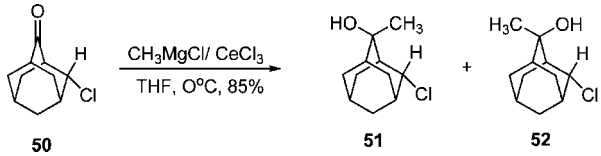


R	R^1	R^2	Yield (%)	48/49 ratio
CH_3	CH_3CH_2	Ph	77	93:7
$PhCH_2$	CH_3CH_2	Ph	85	96:4
PhC≡C	CH_3CH_2	Ph	95	92:8
Ph	CH_3CH_2	CH_3CH_2	93	99:1

years.[107] Furthermore, given that the construction of an alcoholic unit with a stereodefined geometry represents an important target in organic synthesis, it seemed of great synthetic interest to apply this protocol for the $TiCl_4$-mediated addition of RMgX/$CeCl_3$ complexes to β-keto amides, of the bidentate carbonylic substrates in which the formation of a covalent bond with the Lewis acid is not possible.[108] The reaction proceeded with very high diastereoselectivity with exclusive formation of the diastereoisomer derived from the attack of the carbanionic opposite to the α-alkyl group. The choice of the carbanionic moiety is a crucial point, and β-hydroxy amides[109] with stereodefined geometry are obtained when organocerium is employed.[110]

The important role that $CeCl_3$ plays in increasing the nucleophilicity and decreasing the basicity of the alkylorganometallic reagents has been observed in the manipulation of the bicyclic precursor to the permethylpentalene ligand.[111] For this reason, $CeCl_3$ has been used for promoting the alkylmethylation of equatorial 4-chloroadamantan-2-one (**50**).[112] The rigid structure of adamantanone can be viewed as two cyclohexanones sharing one carbonyl group. On the basis of the cage structure, substituted adamantanones are considered free of steric and torsional bias to either side of the carbonyl group. Experimentally, it has been shown that the *syn* π-methylation of 5-haloadamantan-2-one is well studied; the same reaction on 4-chloroadamantan-2-one is less frequent. It is known that **50** is highly reactive with organometallic reagents for giving halogen−metal exchange,[113] and we have tested the effectiveness of methyllithium with poor results. The only major products identified by GC-MS were a dehalogenated compound and a tetracyclic compound. To overcome these drawbacks, we planned a different methylation that involves the addition of organocerium species (Scheme 18).[114] The organometallic compound was prepared from dry $CeCl_3$ and methylmagnesium chloride stereoselectively added to 4(*eq*)-chloroadamantan-2-one for producing an alcohol mixture of diastereoisomers

Scheme 18. Diastereoselective $CeCl_3$ Promoted Methylation of 4-Chloroadamantan-2-ones



(**51** with *eq*-OH and **52** with *ax*-OH). NMR results show that the main component is identified as 4(*eq*)-chloro-2(*eq*)-hydroxy-2(*ax*)-methyladamantan-2-one (**51**) and that a selective preference for *syn*-addition[115] results when the chloro substituent is in the 4-equatorial position (**50**).

2.2. Addition to Acid Derivatives

In the course of programs aimed to explore the importance of ketones as key intermediates for the synthesis of biologically active natural substances, a procedure for the preparation of ketones starting from inexpensive substrates was needed. The addition of organocerium to carboxylic acids and to their derivatives allowed in many cases circumventing the problem of overalkylation of the reaction products to tertiary alcohols. Examples involving acids,[116] acyl chlorides,[117] anhydrides,[118] lactones,[118] and esters[119] are known. In the past decade the most common synthetic route is the nucleophilic addition of an RMgX or RLi in the presence of $CeCl_3$ to *N*-methoxy-*N*-methylamides (Weinreb amides). The reaction leads to the corresponding ketones in good yields with no formation of tertiary alcohols due to overaddition.[120] A recent interesting application of an organocerium for ketone synthesis *via* a saturated Weinreb amide is the stereoselective construction of the intermediate **61**[121] to obtain one of five fragments of a new possible synthetic approach toward Azaspiracid **53** (Figure 2).[122] The strategy utilizes the addition of a precooled solution of Weinreb amide **62** in THF to the organocerium suspension at low temperature (Scheme 19). The desired acetylenic ketone **61** is obtained in 63% yield from lithiation of the acetylenic **60** using *n*-BuLi followed by addition to the amide **62** in the presence of $CeCl_3$.

The versatility of the addition of organocerium compounds to Weinreb amides for obtaining carbonyl compounds has suggested to Kojima[123] the application of $CeCl_3$ as an additive for an efficient conversion of (*Z*)-α,β-unsaturated Weinreb amides to (*Z*)-α,β-unsaturated ketones (Scheme 20). The use of a Wittig-type reaction to prepare (Z)-α,β-unsaturated Weinreb amides,[124] and treatment of these amides with RLi and $CeCl_3$, completes the transformation. Not only has the treatment of **63** with only organolithium reagents been found to be rather messy and to give the desired α,β-unsaturated ketones arising from 1,2-addition, but also the crude reaction mixtures showed the presence of multiple saturated products in varying amounts, making purification somewhat tedious. The presence of $CeCl_3$ secures crude reactions that rather were clean, where the desired 1,2-product was principally obtained with minimal change in *E*/*Z* ratio.[125] Unfortunately, the high cost of starting materials such as MeONHMe·HCl, which is needed to make the Weinreb amides, excluded their use on a large scale. A more suitable and general synthetic approach is designed for the synthesis of ketones; therefore,

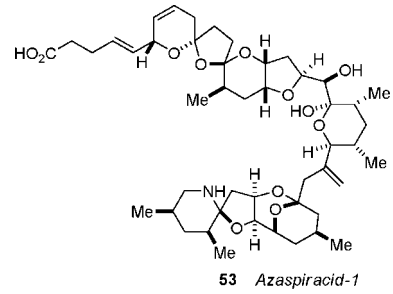
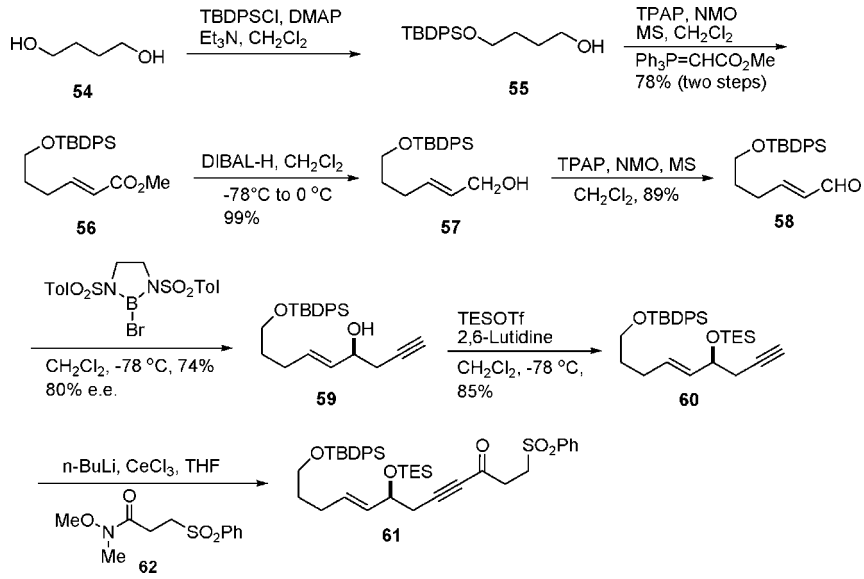
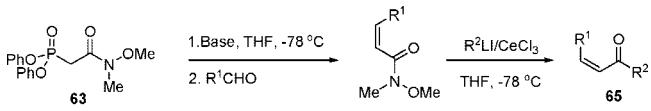


Figure 2. Azaspiracid structure.

Scheme 19. Synthesis of Intermediate 61 of Fragment A of Azaspiracid



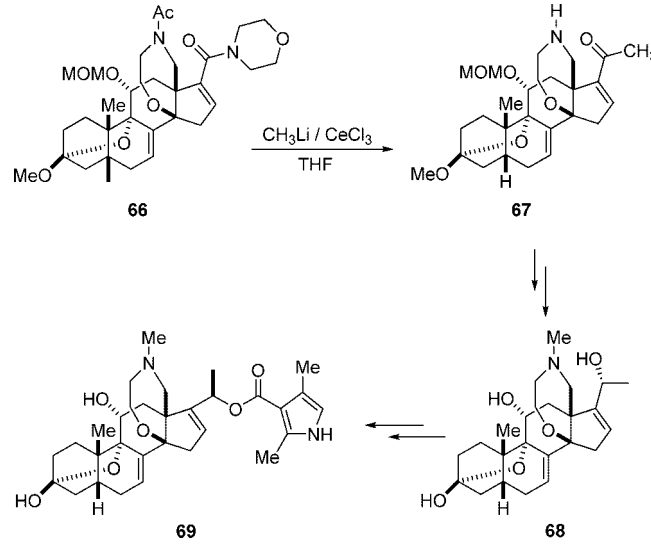
Scheme 20. Reaction of Unsaturated Amides with RLi/$CeCl_3$



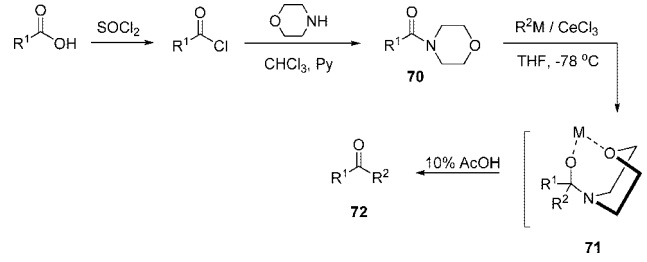
R^1	R^2	Yield (%)	Z:E
Ph	Ph	93	94:6
$Ph(CH_2)_2$	n-Bu	95	99:1
c-Hexyl	Me	90	95:5

organic chemists looked for new carboxylic acid derivatives and have developed the corresponding morpholine amides as an effective alternative. In the morpholine amides replacement of Weinreb amides in ketone synthesis,[126] there is an important limitation to the preparative use because the reactions are susceptible to steric hindrance, on the part of both the organometallic reagents and the starting amides, and the undesired enolization is observed in addition of organocerium compounds.[127] However, Kishi and co-workers found in their Batrachotoxin synthesis (Scheme 21)[128] that the morpholine amide **66** is readily converted to the desired methyl ketone, and the *N*-acetyl protecting group is simultaneously removed upon reaction with the organometallic reagent prepared from dry $CeCl_3$ and methyllithium. After methylation of the secondary amine, diastereoselective reduction of the α-enone moiety, and acidic deprotection, the authors arrived at **68**. Since the chemical transformation of **68** into **69** is known, the strategy constitutes a formal total synthesis of (±)-Batrachotoxin (**69**), a steroidal alkaloid that is an extremely potent neurotoxin, which acts as a selective and irreversible Na^+-channel activator.[129] Kishi's method is limited to organocerium species, supposedly as "CH_3CeCl_2", since with tertiary amides the organocerium species with an increased steric bulkiness presented a poor reproducibility. The efficiency of the ketone synthesis by the organocerium strategy could be influenced by the temperature, and, in fact, as a solution to Kishi's problem, running the reaction at low temperature, such as −78 °C (Scheme 22),[130] is an effective solution to the issue of reproducibility. Under these conditions, the enhancement of reactivity is attributed to the fact that the R″M/$CeCl_3$ complex acts as a Lewis acid, coordinating to the morpholine oxygen atom, decreasing the basicity of the morpholine nitrogen and thereby increasing the electrophilicity of the amide carbonyl group. Even in the presence of an excess of R″M/$CeCl_3$ complex, no tertiary alcohol has been detected, indicating that a metal-chelated tetrahedral intermediate **71** precludes further addition of the organocerium. Our study further demonstrates the reduced basicity and higher oxophilicity of organocerium species, if compared to the precursors from which they are derived.

Scheme 21. Transformation of the Morpholine Amide 66 into the Corresponding Methyl Ketone 67



Scheme 22. Reaction of Morpholine Amides 70 with Organolithium or Organomagnesium Reagents in the Presence of $CeCl_3$

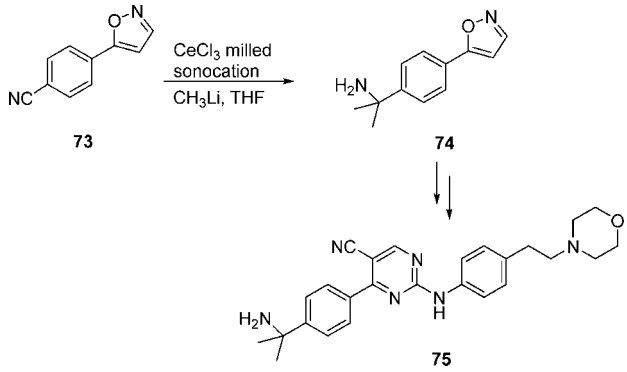


2.3. Addition to Carbon−Nitrogen Multiple Bonds

The characteristic structural features of primary amines are present both in natural products and in pharmacologically active compounds,[131] and this warrants continued method development for their preparation by addition of various organometallic compounds to the carbon−nitrogen multiple bond. In particular, the double addition to RC≡N of a RMet is generally problematic because of poorly electrophilic carbon−nitrogen triple bonds. The use of organocerium reagents appeared to be appropriate, as the double addition of these reagents to nitriles and tertiary carbinamines (that is compounds in which the amino group is bounded to a tertiary carbon atom) has been achieved in often excellent yields.[132] Recently, a modification to Ciganek's method has been described in the efficient synthesis of potent VEGF-R2 kinase inhibitor **75**, a pyrimidine carbonitrile derivative[133] that exhibits significant oral activity in suppressing tumor growth in murine models (Scheme 23).[134] The pivotal step in the reaction sequence is a stirred-ultrasound-assisted cerium-mediated preparation of a key cumyl amine intermediate **74**. This high-yielding $CeCl_3$ mediated transformation is robust, reproducible, and readily scalable based on a requirement for the anhydrous $CeCl_3$ to be milled and subjected to ultrasound treatment prior to the addition of methyllithium.

In recent years efforts have been applied to studies of the stereoselective synthesis of optically active amines. The nucleophilic addition of organometallic reagents to azomethine moieties is of considerable interest in asymmetric synthesis.[135] However, the reaction between RMgX or RLi and imines or related compounds is synthetically useful only when carried out on nonenolizable substrates. In the cases of poorly electrophilic carbon−nitrogen double bonds, the substrate undergoes α-metalation rather than addition. The strong propensity of cerium(III) salts in being coordinated with Lewis bases permits the addition of functionalized carbanions to the imine function and its derivatives for the generation of amino functions. In particular, organocerium reagent, prepared from the corresponding organolithium or Grignard compounds and dehydrated $CeCl_3$ using standard conditions, adds to chiral hydrazones in good yield and with high diastereoselectivities.[136] In this chemistry, Enders has marvelously exploited the SAMP/RAMP hydrazone methodology for the synthesis of chiral amines.[137] To illustrate the utility of this diastereoselective nucleophilic 1,2-addition of various organocerium compounds to the CN double bond of hydrazones, the nitrogen−nitrogen bond of the unprotected hydrazines is cleaved by hydrogenolysis. As part of the continuous interest in the asymmetric synthesis of sulfur heterocycles,[138] the asymmetric preparation of 3-substituted γ-sultams **80** through the 1,1-asymmteric 1,1-addition of RLi or RMgX in the presence of dry $CeCl_3$ to the CN double bond of ω-SAMP-hydrazonosulfonates **76** (Scheme 24) has also been reported.[139]

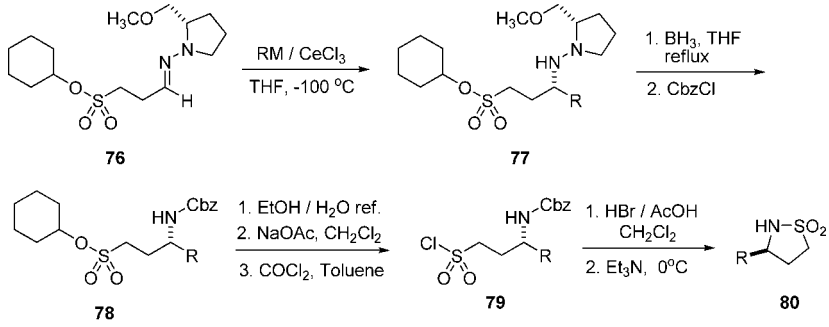
Scheme 23. Preparation Cumylamine Derivative 74



2.4. Addition to Carbon−Carbon Multiple Bonds

Addition of organometallic reagents to a carbon−carbon double bond has always represented an unreachable target for organic chemists, since carbon−carbon double bonds are generally inert toward nucleophilic attack. For this reason, this type of reaction has not yet found general synthetic applications, especially for the extreme reaction conditions required.[140] Even though organocerium reagents are reactive toward acidic hydrogen, some reaction conditions have been reported allowing an efficient cross-coupling between various $RLi/CeCl_3$ complexes and a range of allyl, homoallyl, and propargyl alcohols.[141] The combination of both organolithium compounds and lithium hydride with dry $CeCl_3$ works very well (Scheme 25), and products are obtained in moderate to good yields and without chromatographic purification of the crude product. The formation of a negatively charged oxygen-containing species is essential for

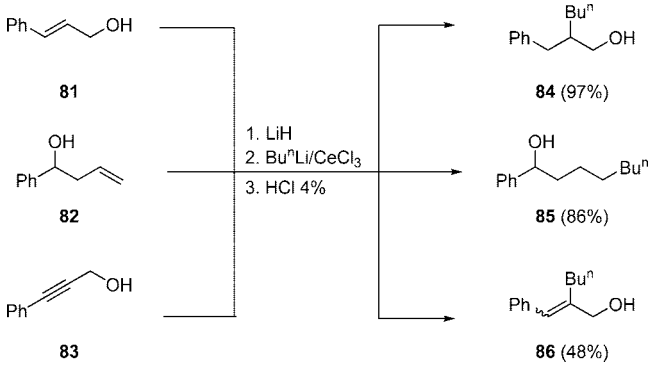
Scheme 24. Synthesis of 3-Substituted γ-Sultams 80



Diastereoselective 1,2-addition

R	Product 77	Yield (%)	d.e. (%)
Ph	(*S*,*S*)-**77a**	99	96
-Me	(*R*,*S*)-**77b**	78	96
n-Bu	(*R*,*S*)-**77c**	94	96
n-Hex	(*R*,*S*)-**77d**	75	96

Scheme 25. Addition of RLi/$CeCl_3$ to Unsaturated Lithium Alcoholate



the reaction to proceed. In fact, the corresponding allyl ethers do not react under these conditions, and starting material is quantitatively recovered. It should be noted that when cerium reagent is prepared from $CeCl_3$ and an excess of a Grignard reagent instead of an alkyllithium, the reaction proceeds more slowly and less efficiently.

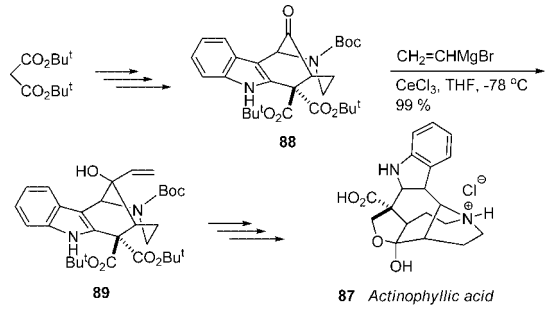
2.5. Application in Organic Synthesis

The utility of organocerium reagents throughout organic synthesis is seen by their use as key intermediates in the preparation of a wide range of synthetic targets. Although several total syntheses reported in the past decade display the use of organocerium reagents, this review highlights key steps in which $CeCl_3$ promotes organometallic addition to a carbonyl function for a novel synthetic approach.

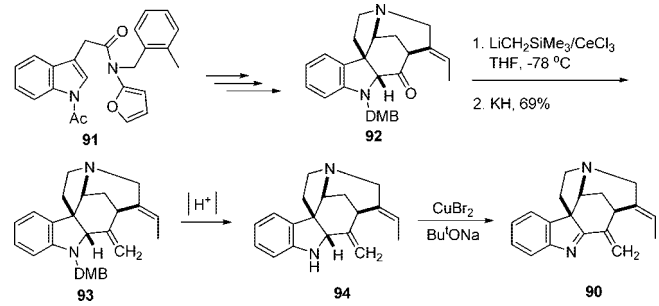
Overman and co-workers have recently reported the first total synthesis of (±)-Actinophyllic acid (**87**) by a route that is sufficiently concise for being suitable for the production of gram quantities of the natural product.[142] The synthesis (Scheme 26) has been accomplished from di-*tert*-butyl malonate in an overall yield of 8% by a concise sequence that proceeds by way of only isolated intermediates. Of the eight stages of the synthesis, the key bond formation included the addition of a vinyl nucleophile to ketone **88**. The presence of bulky groups shielded the *Si*-face of the ketone, and when premixing **88** with $CeCl_3$, followed by reaction with vinylmagnesium bromide at −78 °C in THF, the reaction provided a single allylic alcohol product **89** in nearly quantitative yield.

In the same year, Padwa reported[143] the importance of the use of organocerium in the total synthesis of (±)-Valparicine (**90**), an alkaloid isolated from the stem bark extracts of *k. arborea*, a member of the *kopsia* family.[144] Starting from an indolyl-substituted amidofuran derivative **91** (Scheme 27), it has been shown that aza-penatcycle **92** can be prepared in 61% yield. Having this intermediate, the author has treated with trimethylsilylmethyllithium and $CeCl_3$, and this has been

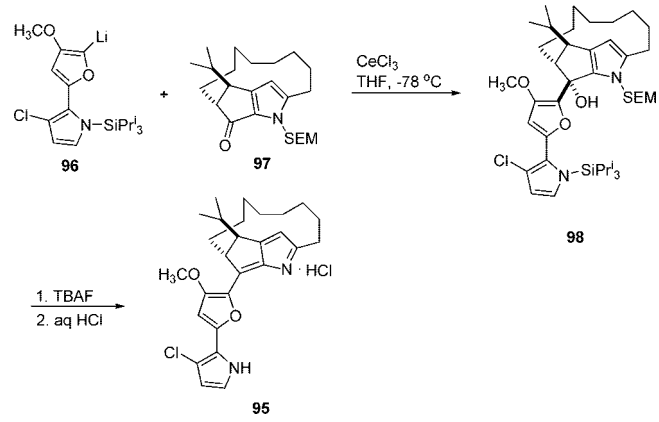
Scheme 26. Synthesis of (±)-Actinophyllic Acid (87)



Scheme 27. Synthesis of (±)-Valparicine (90)



Scheme 28. Synthesis of (±)-Roseophilin (95)



followed by heating of the resulting alcohol with potassium hydride in THF, which delivered the C-16 methylene unit of **93** in 69% yield. Removal of the DMB protecting group and successive oxidation of the carbon−nitrogen single bond between the C-2 and N-1 positions gave the (±)-Valparicine (**90**) together with recovered starting material, thereby completing the first total synthesis of the alkaloid target.

The capacity of dry $CeCl_3$ to promote carbon−carbon bond forming reactions when used as additive in reactions of RLi reagents has been masterfully exploited by Fürstner in his first total synthesis of racemic Roseophilin.[145] For this synthesis of (±)-Roseophilin (**95**), a novel antibiotic isolated from *Streptomyces griseoviridis*, the author chose an organometallic strategy for the condensation of segments **96** and **97** (Scheme 28), since previous attempts in this direction were unsuccessful.[146] Deprotonation of the parent compound of **96** with *n*-BuLi at low temperature proceeded exclusively on the furan ring. Subsequent transmetalation of the resulting lithium compound with anhydrous $CeCl_3$ provided a highly nucleophilic organocerium species. Although the resulting tertiary alcohol **98** could be isolated by flash chromatography, it turned out to be rather sensitive, and it has therefore been processed without delay. Addition of aqueous HCl and the instantaneous appearance of an intense red-orange fluorescent color indicated the formation of the protonated azafulvene chromophore of **95** by loss of water.

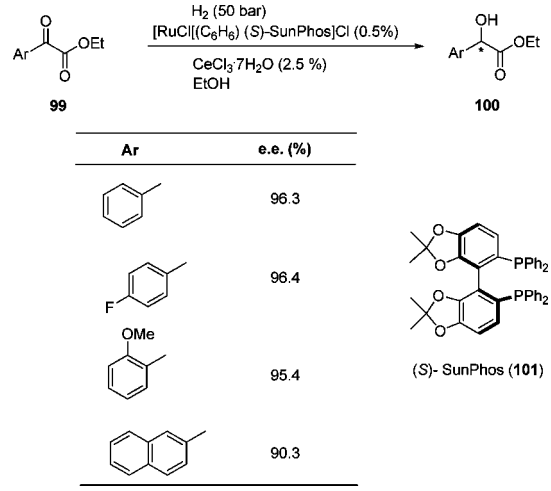
3. $CeCl_3$ Mediated Reductions

Reductions by metal hydrides are at the center of the important chemical research and synthetic method development. Their impact on industrial production can hardly be overestimated and is likely to increase further.[147] A high degree of sophistication is always needed in preparative organic chemistry, especially related to multiple bonds reductions.

In synthetic organic chemistry, reduction usually has the meaning of the removal of oxygen and/or the addition of hydrogen to a molecule. Complete reduction of an unsaturated compound can generally be achieved without excessive difficulty, but the aim is often selective reduction of one group in a molecule in the presence of other unsaturated groups. Furthermore, the method of choice in a particular case will often depend on the selectivity required and on the stereochemistry of the desired product. In fact, the stereochemical course of reduction has long been studied. Studies of the behavior of different structural series of unsaturated groups (such as a carbon−carbon double bond, a carbonyl group, or a heteroatom−heteroatom multiple bond) in concert with different reducing agents have led to several rationalizations, which have proven their usefulness for predicting new results. However, much controversy about factors controlling the observed stereochemical induction is going on, and many questions remain unresolved.

In general, most of the common unsaturated groups in organic chemistry can be reduced under appropriate conditions, although they are not all reduced with equal ease. The order is influenced to some extent by the structure of the compound being reduced and by the catalyst employed. Its choice is governed by the activity and selectivity required. As a general rule, the more active the catalyst, the less discriminating it is in its action; and equally for greatest selectivity, reactions should be run with the least active catalyst and under the mildest possible conditions, consistent with a reasonable rate of operation. Frequently, small amounts of additives have been attributed to eliciting remarkable changes in conversion rate, yield, stereoselectivity, and even reaction pathway.[148] In the presence of additives, improvements in reactivity and stereoselectivity of the catalyst can be observed, but also enhancements in terms of stability might occur too. In general, both Brönsted acids and Lewis acids could be used as additives, but when Lewis acids have been used, dramatically improved selectivities have been obtained.[149] A variety of lanthanide salts proved effective in this context, and for all reasons already described, $CeCl_3 \cdot 7H_2O$ has been chosen as the preferred additive. Among the possible methods available for reduction of organic compounds, catalytic hydrogenation is one of the most convenient.[150] Reduction is carried out easily by simple stirring or shaking of the substrate with the catalyst system in a suitable solvent and in an atmosphere of hydrogen gas. The ability of catalytic hydrogenation to reduce multiple bonds in a chemo- and stereocontrolled manner is of central importance in organic synthesis. The enantioselective hydrogenation of a carbon−carbon double bond is mainly accomplished by the use of transition metal catalysts containing metals such as Pd, Rh, or Ru in the presence of chiral ligands. Noyori's hydrogenation of β-dicarbonyl compounds[151] is developed to a fine level of understanding, and it predicts that catalysts are available for the selective production of either enantiomer of hydroxyl esters. Recently, Zhang and co-workers investigated the function of catalytic amounts of $CeCl_3 \cdot 7H_2O$ in the ruthenium-catalyzed asymmetric hydrogenation of aromatic α-keto esters **99** (Scheme 29).[152] The procedure provided a highly efficient synthesis of a variety of ethyl α-hydroxy-α-arylacetates **100** in up to 95% enantiomeric excess, which are important structural motifs in numerous biologically interesting compounds.[153] In the course of their study of this enantioselective hydrogenation by employing $CeCl_3 \cdot 7H_2O$ additive and chiral

Scheme 29. Enantioselective Hydrogenation of α-Keto Esters in the Presence of $CeCl_3 \cdot 7H_2O$



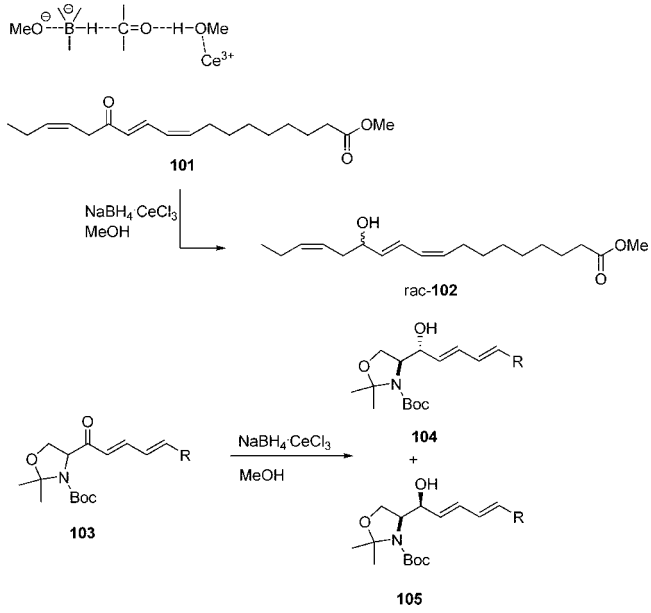
diphosphine,[101] they found that the cerium salt hydrate not only improved the reaction activity and enantioselectivity but also stabilized the Ru-catalyst in preparative and scale-up experiments. Unfortunately, attempts to isolate and identify the catalytic intermediates have not been successful. Certainly, $CeCl_3$ would not undergo hydrolysis or ethanolysis to produce hydrogen chloride under these conditions.[154] Probably, $CeCl_3$ activates aromatic α-keto esters by forming adducts with carbonyl groups mainly through σ-coordination.

However, the most visible contribution to organic synthesis in the field of reductions of multiple bonds is that of the reactions with metal hydrides. Reactions that proceed by transfer of hydride ions are more widespread in organic chemistry, and they are important also in biological systems. The enantioselective reduction of a prochiral substrate by metal hydrides associated with a chiral ligand has been successfully employed for a broad variety of unsymmetrically prochiral compounds.[155] The presence of $CeCl_3$ can play a key role in promoting these reductions of multiple bonds by metal hydrides.

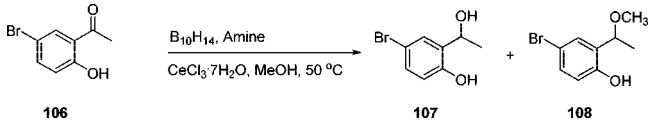
3.1. Reduction of Carbon−Oxygen Double Bond

The reduction of carbonyl groups is a general synthetic method for the preparation of hydroxyl compounds in organic synthesis. Even if a wide variety of reagents is available, the development of adequate methods with regard to economic and ecological considerations and associated with high chemoselectivity is of great interest in organic chemistry. For example, reduction of α-enones by $NaBH_4$ alone is usually accompanied by 1,4-reduction, affording a mixture of allylic alcohols and saturated alcohols. Over 30 years ago, Luche reported the effectiveness of lanthanide(III) salts in selective reduction of carbonyl compounds by $NaBH_4$.[156] He found that $CeCl_3$ exhibits the highest efficacy, although other lanthanide(III) salts were equally efficient. The reaction mechanism accounting for the regio- and diastereoselectivity has been proposed on the basis of the Pearson's hard−soft principle.[157] Sodium borohydride (Scheme 30) is rapidly converted to the $[BH_{4-n}(OMe)_n]^-$ species in methanol by the action of $CeCl_3 \cdot 7H_2O$. The carbonyl function is activated by hydrogen bonding, and this carbonyl carbon, being harder than the nonactivated one, is attacked by hard borohydride to give allyl alcohols. This transformation did not change the stereochemistry of conjugated polyenic systems such as

Scheme 30. Regioselective 1,2-Reduction of α,β-Unsaturated Ketones



Scheme 31. Chemoselective Reduction of Ketones to Alcohols in the Presence of Amines and $CeCl_3 \cdot 7H_2O$

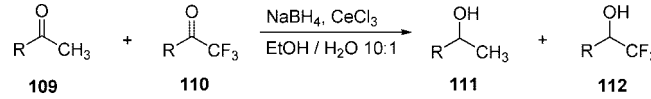


Amine (equiv)	$CeCl_3 \cdot 7H_2O$ (equiv)	107 (%)	108(%)
—	0.1	30	30
Pyridine (0.3)	0.1	84	Traces
Triethylamine (0.3)	0.1	85	Traces
Piperidine (0.3)	0.1	97	—
Pyrrolidine (0.3)	0.1	95	—

hydroxypolyenoic fatty acid derivative **102**[158] and diastereomers **104** and **105**,[159] which are important intermediate ceramide analogues.[160] It is worth noting that during reduction of certain α,β-unsaturated ketones with Luche's system in alcoholic solution, alkyl allylic ethers were formed.[161] In the first step, ketones are reduced to allylic alcohols, which react further with aliphatic alcohols to give ethers. The composition of the product depends on the structure of allylic alcohols. This drawback of the reductive etherification side product is also possible in the reduction of ketones in the presence of $CeCl_3 \cdot 7H_2O$ as promoter. However, when amines as bases are added at the reaction of ketones with the decaborane/$CeCl_3$ system in methanol, the yield of the corresponding secondary alcohols is improved (Scheme 31).[162] In these studies, secondary amines proved to be more cost efficient than pyridine.

Even if an unusual $NaBH_4/CeCl_3 \cdot 7H_2O$ reduction of the carbon−carbon double bond of enones has been observed,[163] Luche's protocol has been widely applied for the chemoselective reduction of ketones in the presence of other reducible functional groups such as aldehyde moieties.[164] Thus, the reduction occurs at the less reactive functionality, leaving intact the more reactive one. The explanation of this attractive reversed reactivity is very simple: $CeCl_3 \cdot 7H_2O$ is an efficient catalyst for acetalization or emiacetalization of aldehydes, but not of ketones, and an immediate *in situ* protection of −CHO groups occurs. This idea has been applied from

Scheme 32. Reduction of a Mixture of 109 and 110 with $NaBH_4$ and $CeCl_3$

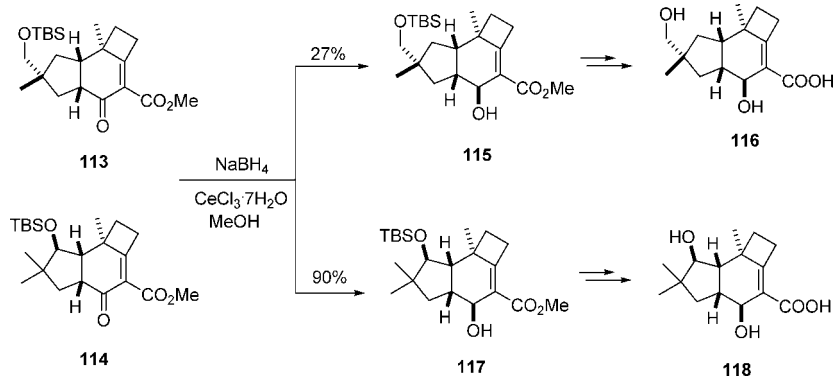


R	Ratio of 111/112
Ph	99:1
4-$MeOC_6H_4$	72:28
4-MeC_6H_4	83:17
4-ClC_6H_4	93:7
4-CF_3CH_4	99:1
c-Hex	99:10

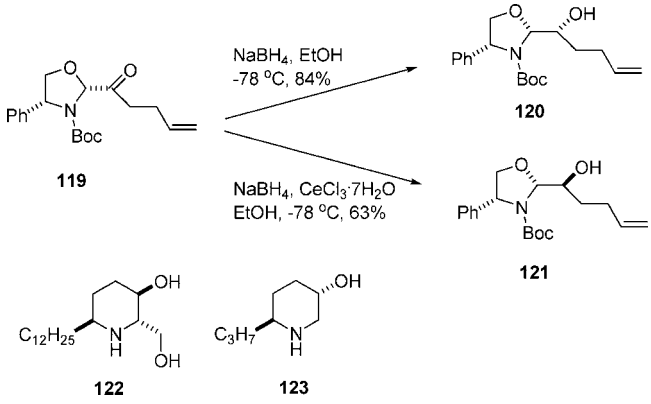
Higashiyama and co-workers for the successful chemoselective reduction of methylketone derivatives **109** in the presence of trifluoromethylketones **110** (Scheme 32).[165] These organofluorine compounds are highly reactive and readily susceptible to nucleophilic attack,[166] and for a long time they have been useful as building blocks for the synthesis of complex organic molecules with biological activity.[167] The presence of a powerful electron-withdrawing group such as CF_3 makes trifluoromethylketones **110** so highly reactive that they probably are $CeCl_3$-converted into their corresponding hydrates, and these ones provided adequate protection during the $NaBH_4$ reduction step. For this reason, the selectivity is lower when an electron-donating group such as a methoxy group is directly linked with the aromatic ring. On the other hand, the presence of an electron-withdrawing group such as CF_3 linked with the aromatic ring facilitates the hydrate stabilization.

After the amazing works of Luche, the use of $CeCl_3$ in the reduction of carbonyl compounds to the corresponding alcohols under mild conditions holds promise in organic synthesis, particularly in the synthesis of natural products.[168] High stereocontrol in the reduction step is remarkable and must be due to prior complexation of the carbonyl group with $CeCl_3$,[169] as shown in the first total synthesis of two novel Protoilludane Sesquiterpenoids, named Pasteurestins A and B (**116** and **118** in Scheme 33) reported by Mulzer and co-workers.[170] The authors assume that the cerium complex is formed between the C-4 carbonyl and the C-3 ester groups on the less hindered *exo* face, so that the hydride attacks from the more hindered *endo* face. The level of stereoselectivity is particularly high for the presence in the molecule of hard donor groups such as oxygen atoms. In fact (Scheme 34), the reduction of ketone **119** with $NaBH_4$ at low temperature afforded alcohol **120** in a high diastereomeric ratio (dr = 95:5, as determined by NMR spectra on the crude mixture). Alternatively, when an analogous reduction was performed in the presence of $CeCl_3 \cdot 7H_2O$, diastereomer **121** is produced (dr = 15:85).[171] Alcohols **120** and **121**, respectively, can be separated from their minor stereoisomer by flash chromatography. Under chelating conditions promoted by the presence of cerium(III) cation, the reaction affords alcohol **121**, whereas its diastereomer **120** is the major product in the absence of any cerium additive. A Felkin−Ahn model[172] proposed by Scolastico[173] and Hoppe[174] for nucleophilic attacks on N-protected-2-acyloxazolidines[175] could provide a possible explanation for the opposite stereochemical outcomes (Scheme 35). The Felkin−Ahn model **119A** orientates the hydride attack onto the *Si* diastereoface, whereas the chelated structure **119B** directs

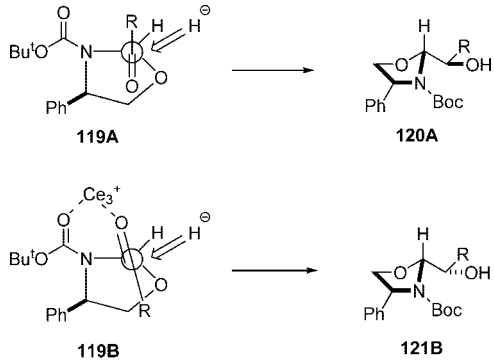
Scheme 33. Reduction Step in the Synthesis of Pasteurestins A and B



Scheme 34. Diastereoselective Reduction of Ketoxazolidine 119

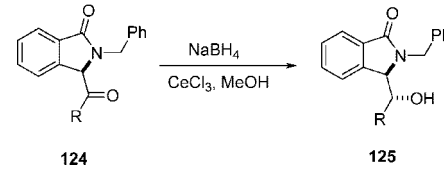


Scheme 35. Chelated Model and Felkin−Ahn Model Applied for the Reduction of 119

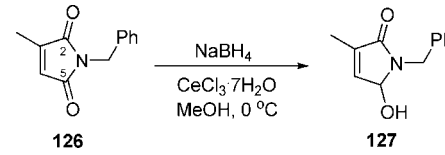


the nucleophilic addition to the least hindered *Re* diastereoface. This diastereoselective reduction to the stereomeric compounds **120A** and **121B** is well suited for the construction of the hydroxyl bearing stereogenic center (C-3) of substituted piperidine heterocycles at the β-position.[176] The strategy has successfully been used for the synthesis of (−)-Desoxoproposopinine (**122**)[177] and of (+)-Pseudoconhydrine (**123**),[178] respectively. Given that the common oxazolidine precursor is easily prepared using a three-step sequence starting from (*R*)-phenylglycinol, the stereodefined construction of *threo*- or *erythro*-heterocyclic moieties with a hydroxyl-containing side chain attracts considerable attention due to their presence in the framework of natural products.[179] For this, Yoda studied stereoselective reduction of N-protected keto amides.[180] As shown in Scheme 36, the use of $CeCl_3$ in the $NaBH_4$ reduction of N-benzyl keto amides **124**[181] produces *threo*-compounds **125** as the sole product. The beneficial effect of $CeCl_3$ on this reduction has been established in reactions employing different keto amides, and

Scheme 36. Stereoselective Reduction of Keto Amides 124 in the Presence of $CeCl_3$



Scheme 37. Regioselective Reduction of Citraconimide (126)



again the exclusive formation of the corresponding *threo*-isomers is possible by attack of anion hydride on the carbonyl group from the top face of the *cis*-fused cerium-chelate. The presence of a benzyl function is fundamental for a high diastereofacial differentiation, and this role is observed in the regioselective reduction of Citraconimide (**126**) with the $NaBH_4/CeCl_3$ system (Scheme 37).[182] The methanol−Ce^{3+} complex preferably coordinated with the less hindered carbonyl group in **126** and activated the C-5 atom. Then, the hydride anion approaches from the more hindered carbonyl group and attacks the C-5 atom, as predicted by Speckamp and co-workers.[183] The method represents a convenient synthesis of 5-hydroxy-1,5-dihydropyrrol-2-one derivatives **127**, which are important building blocks for the preparation of a wide variety of natural products with potential pharmaceutical applications.[184]

In order to exploit the ability of cerium(III) to control the stereochemical outcome of any given reaction, the $CeCl_3$-mediated reduction of a series of sterols was investigated. Due to their rigid framework and potential for varying levels of functionalization, broad biological activity profile, and ability to penetrate the cell membrane and bind to specific hormonal receptors, this noteworthy architecture has become preferred for synthons for the development of diverse bioconjugates. The possibility of obtaining polyhydroxylated sterols with a definite stereochemistry allows one to derive a correlation of molecular structure versus biological activity when using these compounds as standards in the broader study of steroid metabolism disorders.[185] In regard to this relationship between configuration and physiological activity, Cui and co-workers found that polyhydroxylated **129** exhibits moderate cytotoxicity toward human gastric carcinoma cells and cervical carcinoma cells, whereas its epimer **128** shows only a very weak cytotoxicity toward these two tumor cells

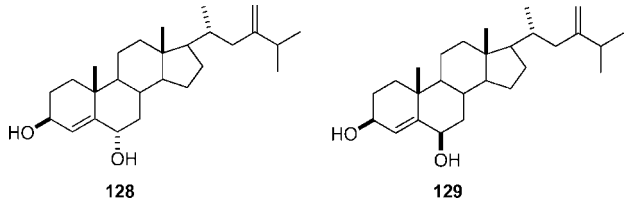
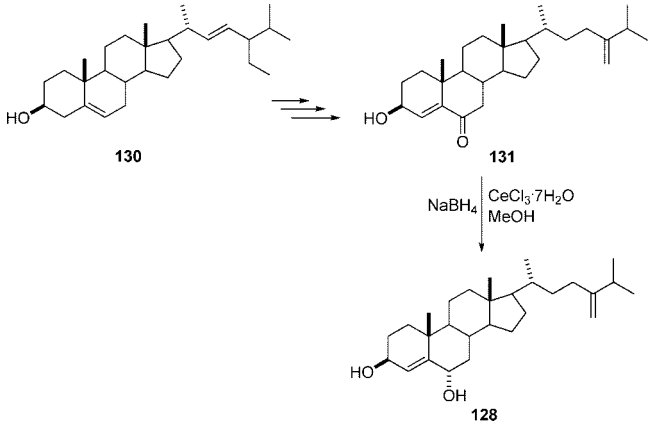


Figure 3. Examples of polyhydroxylated sterols.

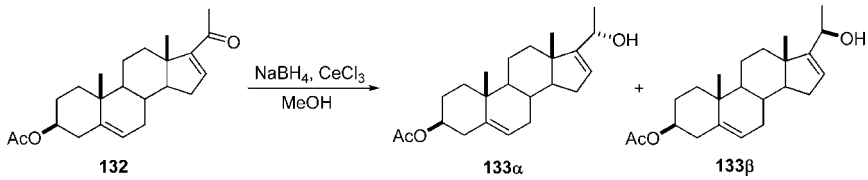
Scheme 38. Synthesis of the C-6 Epimer 128



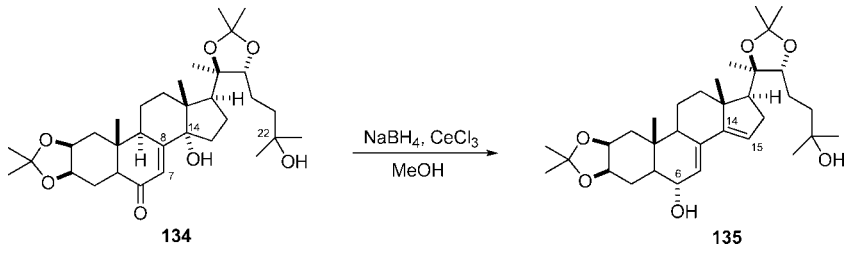
(Figure 3).[186] For the synthesis of **128** (Scheme 38), the Stigmasterol (**130**) commercially available is chosen as the starting material and after seven steps is transformed into the steroidal nucleus intermediate **131**. The preparation of the target product **128** is completed by the reduction of **131** with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ in methanol at room temperature. When the reduction is carried out with $NaBH_4$ alone in methanol, the 3β,6α-diol **128** and the other C-6 epimer 3β,6β-diol **129** are obtained; in contrast, in the presence of $CeCl_3 \cdot 7H_2O$, the reduction afforded **128** as the sole product. In contrast, in the synthesis of epimeric 20-hydroxy pregnane derivatives, considered new types of potent enzyme inhibitors,[187] Brodie and co-workers showed that the reduction of 16-dehydropregenelone acetate (**132**) with $NaBH_4$ in methanol and in the presence of $CeCl_3$ gave the allyl alcohols **133α** and **133*β*** in a ratio of 1:2:7.[188] It is possible to obtain pure 20β-ol-3-acetate derivative (**113*β***) by recrystallization (Scheme 39). Certainly, the reduction in the presence of $CeCl_3$ gave better stereoselectivity for 20β-ol than Meerwein−Pondorff reduction of **132** as described by Marker.[189] The presence of a double bond (C^{16}=C^{17} bond) in the steroid nucleus not only enhances the biological activity but should also force the reduction with $NaBH_4$/$CeCl_3$ to proceed in a stereoselective fashion.

Treatment of 2,3:20,22-di-*O*-isopropylidene-20-hydroxy-ecdysone (**134**) with $NaBH_4$ in the presence of $CeCl_3$ in alcohol at −5 °C resulted in stereoselective reduction of the 6-oxo group to give the corresponding 6α-hydroxy derivative (Scheme 40).[190] This stereoselective reduction of the 6-oxo group with the $NaBH_4$/$CeCl_3$ system requires the presence of a hydroxyl group and an additional double bond (apart from the existing C^7=C^8 bond). Presumably, the C^{14}=C^{15} bond, which is formed by dehydration during the reduction of **134**, together with the Δ^7-bond and hydroxy group on C-25, create favorable conditions for stereoselective reduction of the 6-oxo group. Formation of a complex with cerium at the α-side of the intermediate ensures β-orientation by hydride attack on the carbonyl moiety to afford the 6α-alcohol. In the absence of $CeCl_3$, the reaction is not stereoselective and the hydride attack on the 6-oxo group is likely to occur preferentially from the less sterically hindered α-side, leading to predominant formation of the 6β-alcohol. No stereoselectivity in the reduction of the 6-oxo group is observed when the hydroxyl groups on C-14 and C-25 in **134** are protected by silylation.[191] However, treatment with the $NaBH_4$/$CeCl_3$ system gives rise to a mixture of 6α- and 6β-hydroxy derivatives at a ratio of about 3:2, in accordance with the 6-H signal intensities in the ^{1}H NMR spectrum. Unlike from $NaBH_4$/$CeCl_3$, the reduction of **134** with the $LiAlH_4$/$CeCl_3$ system is not selective, and a complex mixture of products is obtained. Even in the absence of $CeCl_3$, the reduction with $LiAlH_4$ afforded a mixture of 6α- and 6β-epimers. Under these conditions no dehydration occurred in the reduction of diacetonide **134**, despite the presence of an additional double bond. The reduction of steroids reveals that to have a 3-acetate group is a stable protecting group in the synthesis of complex steroid[192] with metal hydride reductions in the presence of $CeCl_3$. This fundamental role of $CeCl_3$ in the reduction of polyfunctionalized molecules has been observed in the synthesis of Enprostil (**136**),[193] a highly effective analogue of prostaglandin E2 (Scheme 41).[194] The authors tried to extend the procedure of Myers and co-workers[195] for one-step synthesis of allenes from acetylenic alcohols. In order to obtain a precursor of compound **136** with a 2-propynyl alcohol moiety in the α-chain starting from bis-silyl ether **137**, reduction of enone **138** with the $NaBH_4$/$CeCl_3 \cdot 7H_2O$ system in MeOH afforded the desired epimeric

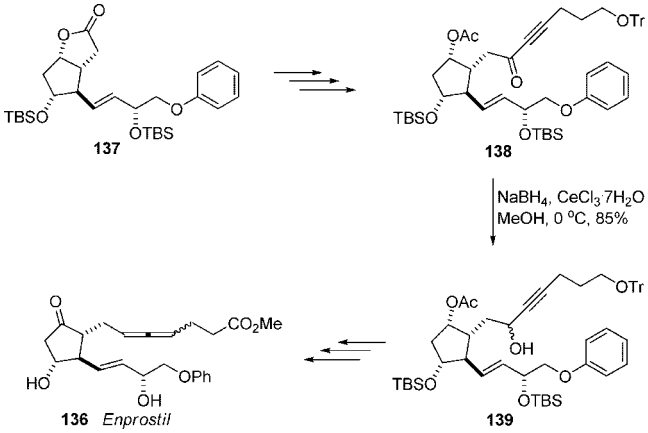
Scheme 39. Stereoselective Reduction of 16-Dehydropregenolone Acetate



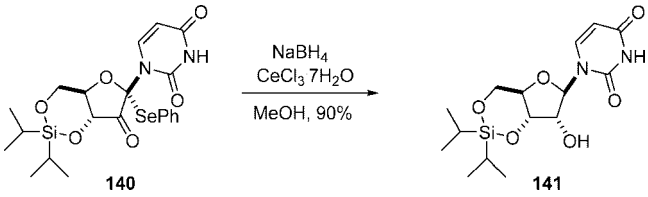
Scheme 40. Reduction of the Δ^7-6-Oxo Group in Ecdysteroids



Scheme 41. Synthesis of Acetylenic Alcohols by Reduction of Corresponding Enones with the $NaBH_4/CeCl_3 \cdot 7H_2O$ System



Scheme 42. Diastereoselective Reduction of 1′a-Phenylselenouridine Derivative 140



acetoxy alcohols **139** in good yield. The same reduction in the absence of $CeCl_3 \cdot 7H_2O$ is accompanied by hydrolysis of the acetoxy group on C-9 to give the corresponding diol.

Highly π-facial diastereoselective reduction of ketones by using metal hydrides is an efficient procedure in organic chemistry if $CeCl_3$ is used as additive. In particular, reduction of substituted acyclic ketones by a σ-electron withdrawing substituent has demonstrated that a probable chelation-controlled reaction pathway is involved.[196] An extension of this concept has successfully been applied in the stereoselective reduction at the 2′-carbonyl of the 1′-α-phenylseleno-2′-ketouridine **140** (Scheme 42).[197] The 1′-α-phenylseleno product **140**, obtained in pure form starting from natural nucleosides, is subjected to reduction at the 2′-keto moiety with hydride reagents, such as $NaBH_4$, $LiBH_4$, $NaBH_3CN$, DIBAL-H, or $LiAl(OEt)_3H$. However, the 2′-carbonyl group of **140** is chemo- and stereoselctively reduced from the β-face only when the reaction is carried out with $NaBH_4$ in MeOH at very low temperature and in the presence of $CeCl_3$. The desired sugar-protected 1′α-phenylselenouridine **141** is obtained in good yield as the sole product,[198] and this sugar-modified nucleoside analogue represents a useful precursor for the synthesis of 1′-α-branched-chain sugar nucleosides having biological importance.[199,200] The stereoselective reduction with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ has successfully been applied in the synthesis of carbocyclic nucleosides[201] in which the sugar ring of a natural nucleoside is replaced by a cyclohexene ring (Figure 4).[202] Typically, reduction of enone **142** with the $NaBH_4/CeCl_3$ system gave the α-alcohol **143** (Scheme 43), and after introduction in the

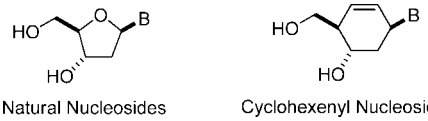
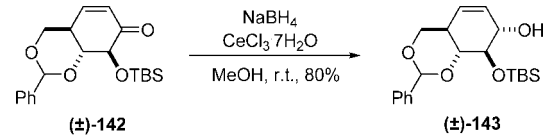
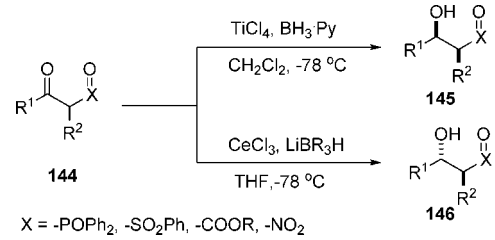


Figure 4. Structure of representative examples of cyclohexenyl nucleosides.

Scheme 43. Allylic Hydroxyl Group Introduction *via* Reduction with the $NaBH_4/CeCl_3$ System



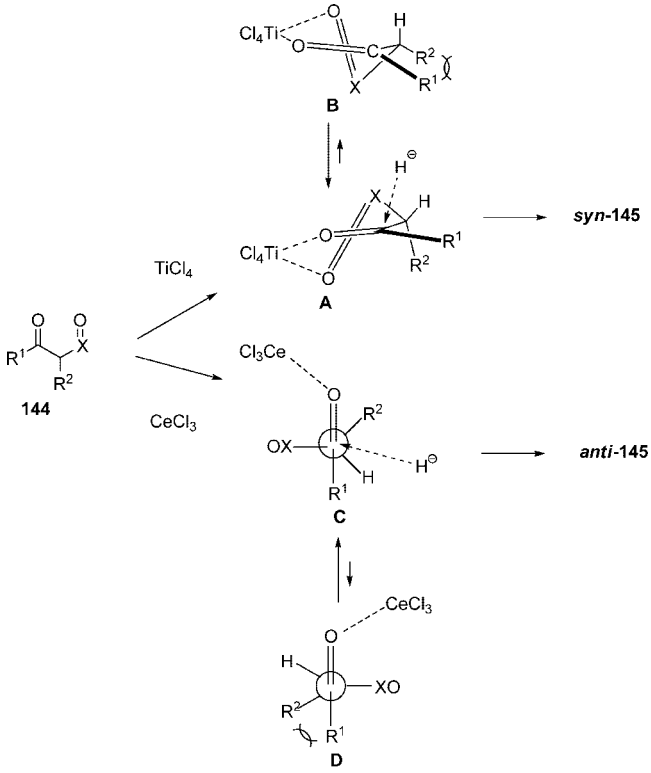
Scheme 44. Diastereoselective Reduction of β-Functionalized Ketones 144



allylic position of the base moiety using the Mitsunobu methodology,[203] it is possible to isolate cyclohexenyl nucleosides. They possess the properties of carbocyclic nucleosides, but on account of the absence of an anomeric center they are stable against chemical and enzymatic degradation.[204]

These highly stereoselective results continue to be commonly explained in terms of "chelate-controlled" processes, even if the π-facial diastereoselection is the subject of intense debate.[205] In fact, this interpretation was modified in our group,[22a] by arguing that in many cases an open chain mechanism can better account for the observed results. In the course of our studies to develop new synthetic Lewis acid-mediated reductions of functionalized carbonyl compounds with chiral α-carbon, we took advantage of the nature of Lewis acid in determining the stereochemical outcome of these reactions (Scheme 44). The $CeCl_3$-mediated reduction of a series of α-alkyl-β-functionalized carbonyl compounds **144** with metal hydrides in various solvent mixtures was investigated. The results have been compared to those obtained in reactions carried out under the same experimental conditions, but in the presence of $TiCl_4$, whose ability to give chelation complexes is well established.[206] These investigations led us to conclude that the reaction shows a stereochemical outcome fully consistent with a "chelation-controlled" pathway in the case of titanium and with an "open chain controlled" one the case of $CeCl_3$ (Scheme 45). In fact, the titanium-mediated reaction is prevalently *syn*-selective, with *syn*-selectivity increasing with increasing bulkiness of the α-substituent (R^2) and the residue bound to the carbonyl group. Moreover, high stereocontrol is favored by the use of noncoordinating solvents such as dichloromethane. On the contrary, the $CeCl_3$-promoted reduction is *anti*-selective. The *anti*-selectivity only increases with increasing bulkiness of the R^1 group and decreases or even reverses when R^2 becomes more sterically demanding than the XO group. When the electronic and steric repulsions exerted by the carbon moiety at the carbonyl group are similar to those exerted by a carbon−oxygen double bond, the diastereomeric induction vanishes. Certainly, a complex between $CeCl_3$ and the β-functionalized carbonyl compound is formed, since the addition of the substrate to a suspension of the cerium salt resulted in a clear solution. However, the paramagnetism of the cerium salt prevents the use of NMR to get information on the structure of this complex from being obtained.[207] We believe that no chelation occurs between the β-functionalized carbonyl compound and $CeCl_3$. There is the possibility that

Scheme 45. Stereochemical Control in the Reduction of α-Substituted-β-Functionalized Ketones

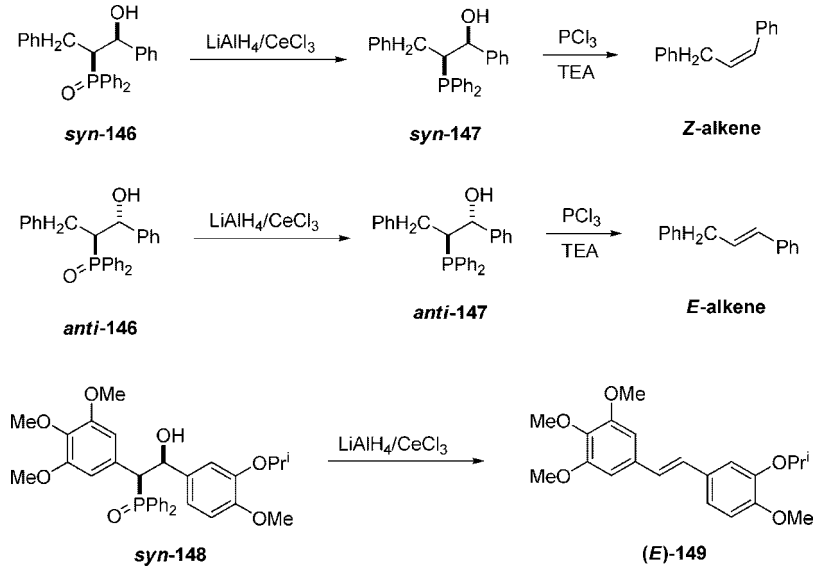


the true reducing agent is not the $(BH_4)^-$ anion, but rather CeH_nCl_{3-n} formed from reduction of $CeCl_3$ by a hydride of boron in a polar solvent. Fukazawa and co-workers[208] have suggested that such hydride species are unlikely to be the reducing agent in the reduction reactions with $LiAlH_4$ in the presence of $CeCl_3$. In spite of this, a similar behavior seems to be plausible in the $CeCl_3$-mediated reductions of α-alkyl-β-functionalized carbonyl compounds. Dry $CeCl_3$, then, is not able to give chelation with β-functionalized carbonyl compounds, but its presence is essential for obtaining high yields and diastereoselectivities. Shorter reaction times could be obtained at 0 °C, but to the detriment of the diastereomeric ratio, so reaction conditions at −78 °C are essential for high diastereoselectivities. The presence of $CeCl_3$ is then essential to obtain both high yields and high stereochemical efficiency, since the reaction can be carried out at lower temperature. Our studies on the reduction in the presence of $CeCl_3$ led to many applications in organic synthesis, since they represent efficient and general protocols for the reduction of various classes of functionalized ketones **144** (β-keto eters,[209] β-keto sulphones,[210] β-keto phopshine oxides,[107] β-nitro ketones,[211] and β-hydroxy ketones[212]) with *anti*-stereoselectivity.

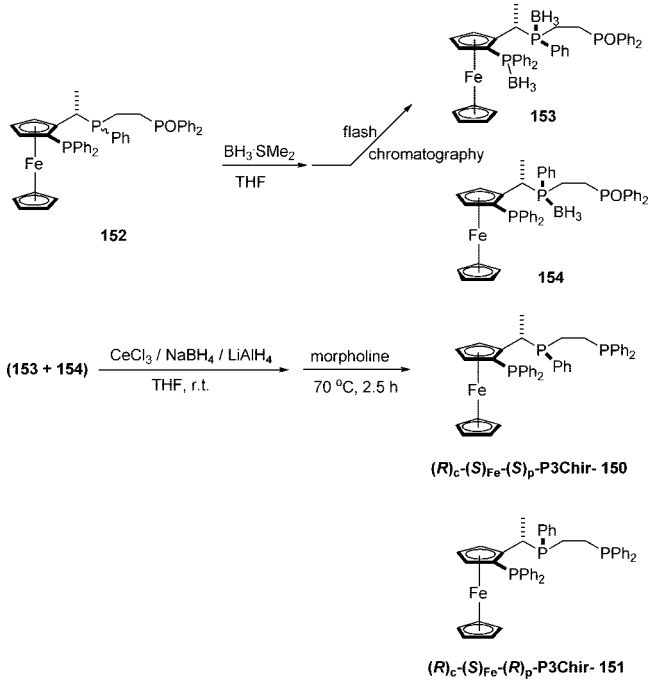
3.2. Reduction of Phosphorus−Oxygen Double Bond

The distinctive ability of the metal hydride/$CeCl_3$ system as a reducing agent is based on the assumption that the extremely hard Lewis acid character of cerium cation might so perturb oxygen and nitrogen[213] based functions to induce their reduction. This concept spurred Imamoto and co-workers to try the reduction of phosphine oxides using the $LiAlH_4/CeCl_3$ reagent system.[214,215] The $CeCl_3$ most likely activates phosphine oxides by coordination to the P═O functionality, so that the deoxygenation with $LiAlH_4$ proceeds readily. The authors did not comment upon a detailed mechanism of the reaction but showed that the reduction is very efficient and is especially suitable for the reduction of sterically crowded phopshine oxides. This mode of deoxygenation has been exploited for the reduction of 1,2-phosphinoyl alcohols to the corresponding 1,2-phosphinyl alcohols, useful intermediates for the synthesis of alkenes.[216] In fact (Scheme 46), with both the *syn*- and *anti*-diastereomers of the phosphinoyl alcohols **146** in hand, easily prepared by the methods of Warren[217] and our group[207,218] from substituted alkyldiphenylphosphine oxides, the authors were able to reduce these with an excess of $LiAlH_4$ and $CeCl_3$ to produce *syn*- and *anti*-1,2-phosphinyl alcohol, respectively. Reduction of other phopshinoyl alcohols worked equally well. Treatment of *syn*- and *anti*-**147** with phosphorus trichloride and triethylamine gave (*Z*)- and (*E*)-alkenes, respectively; the stereochemistry is consistent with the *anti*-elimination of the phosphorus and hydroxyl groups, after the conversion of this latter into a good leaving group. This is in marked contrast to the *syn* Horner−Wittig elimination of the corresponding 1,2-phosphinoyl alcohols.[219] It should be noted that when reduction of the P−O bond occurs more

Scheme 46. Diastereoselective Reduction of 1,2-Phosphinoyl Alcohols with the $LiAlH_4/CeCl_3$ System



Scheme 47. Synthesis of Ferrocenyl Triphosphine Ligands P3Chir 150 and 151



slowly than the deprotonation of the alcohol, as in the substrate *syn*-**148**, Wittig elimination of the lithium alkoxide intermediate gave the unexpected (*E*)-olefin **149**. This unexpected (*E*)-selective Horner−Wittig elimination during reduction in the presence of $CeCl_3$ of a 1,2-phosphinoyl alcohol led to the synthesis of the precursor required for the synthesis of the antimitotic agent (*E*)-Combrekastatin A-4, biologically less active than the (*Z*)-isomer.[220]

The ability of $CeCl_3$ to promote the reduction of the P═O function has allowed the synthesis of two diastereomerically pure tridentate ferrocenyl phosphine ligands P3Chir **150** and **151**, which constitute important classes of auxiliaries on asymmetric catalysis by metal complexes.[221] The synthetic approach (Scheme 47)[222] involved the chromatographic resolution/reduction of the epimeric phosphine oxides **153** and **154**, obtained by nucleophilic addition to (*R*)-(*S*)-diphenylphopshinoferrocenylamine.[223] The diastereomeric triphosphines **150** and **151** are obtained in 80 and 88% yield, respectively, and >99% de. The presence of $CeCl_3$ permits that the reduction step proceeds with retention of configuration at the ferrocenyl unit and at other phosphorus and carbon stereocenters.

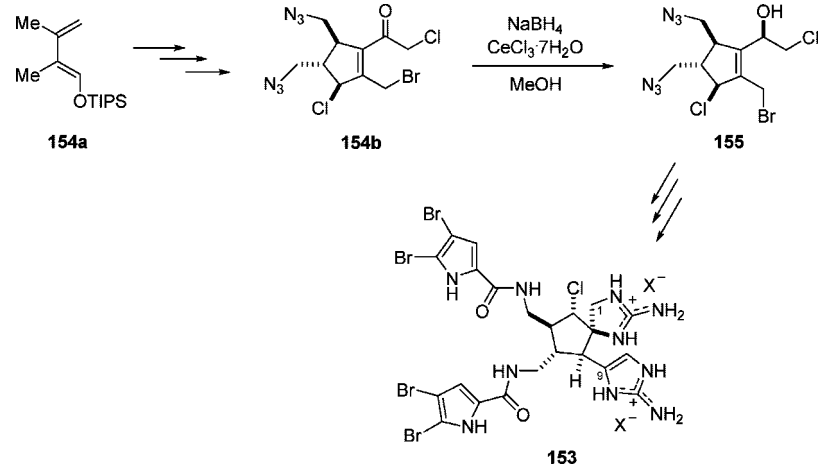
The reductive deoxygenation by $CeCl_3$ coordination to the P═O functionality is another demonstration of the strong propensity of $CeCl_3$ to be coordinated with oxygen donor ligands. In fact, in substrates where the sulfur atom replaces the oxygen atom, the reduction by metal hydrides in the presence of $CeCl_3$ does not attack the P═S functionality.[224]

3.3. Application in Organic Synthesis

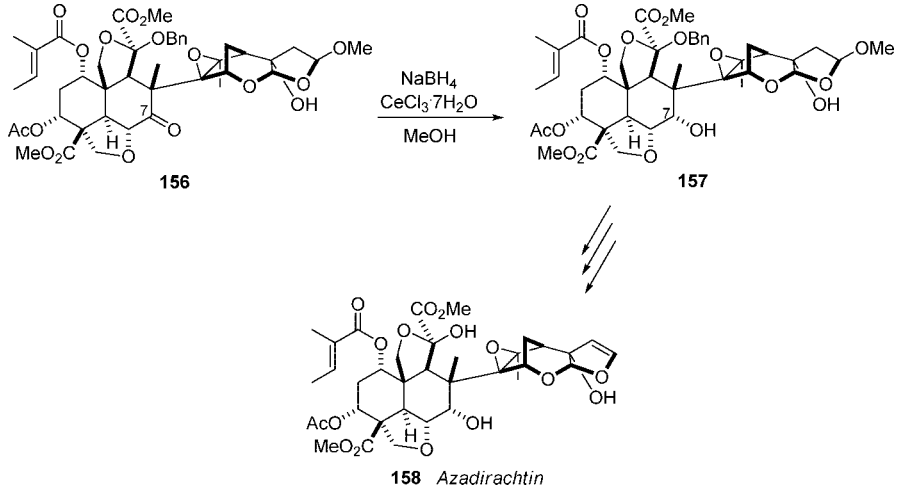
The synthetic versatility of the Luche reduction methodology has allowed the possibility of the use of metal hydride/$CeCl_3$ reductions for the synthesis of complex molecular structures. Marine-derived natural products such as dimeric pyrrole imidazole alkaloids[225,226] are characterized by a molecular structure with a fully substituted cyclopentane framework with spiro-fused and pendant guanidine-containing heterocycles. Baran and co-workers delineated a simple pathway to arrive at 1,9-deoxypreaxinellamine (**153**),[227] whereby the trihalogenated building block **154b**, obtained from diene **154a** by a robust, scalable, and reliable twelve-step route,[228] bears all the required functionalities and stereochemistry to be elaborated into **153** (Scheme 48). A regio-, chemo-, and stereoselective reduction of **154b** to provide the allylic alcohol **155** was the first step for a simple and reliable seven-step sequence to **153** from **154b**. The choice of $NaBH_4$ in the presence of $CeCl_3$ as reducing agent allowed successful conversion of **154b** to **155**, since the high covalent character of the oxygen−cerium bond makes the 1,2-reduction kinetically favored and irreversible.

The natural product Azadirachtin (**158**), a potent insect antifeedant and growth-disrupting agent,[229] represents an exceptionally challenging synthetic target by virtue of its sixteen contiguous stereogenic centers. During the investigation of the total synthesis and to define the structure−activity relationship of **158**,[230] Ley's group found that tiglate **156** is a key intermediate that, through a series of selective transformations, can be converted to **158** (Scheme 49).[231] The first objective has been the stereoselective reduction of the C-7 ketone present in **156** to provide the desired axial alcohol **157**. Owing to the high degree of steric hindrance about the C-7 center, it has not been possible to utilize bulky reducing reagents such as L-Selectride. Matters are complicated further by the presence of the C-1 tigloyl ester, which is also susceptible to conjugate reduction. Thanks to the

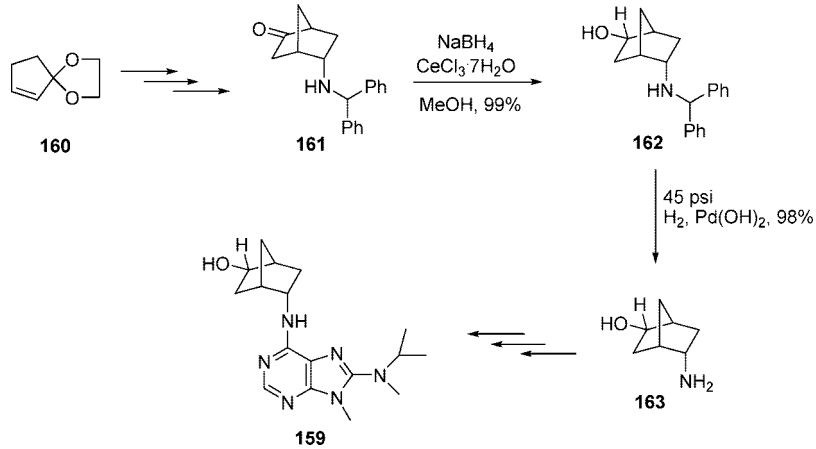
Scheme 48. Synthesis of 1,9-Dideoxy-pre-axinellamine (153)



Scheme 49. Synthesis of Axial Alcohol 157 a Key Intermediate for Azadirechtin 158



Scheme 50. Synthesis of WRC-0571, a Selective Antagonist for Adenosine A_1 Receptor



Luche conditions with the $NaBH_4/CeCl_3$ system in methanol, it has been possible to reduce the C-7 ketone, although a 1:1 mixture of diastereomers has been obtained.[232] The unwanted equatorial alcohol could, after separation, be reoxidized[233] and subsequently reduced to give yields of **157** up to 75% after one recycle. Adenosine is a purine nucleoside with an ample variety of physiological functions, and numerous adenosine receptor ligands have been synthesized and studied.[234,235] In particular, N^6-[*endo*-2′-(*endo*-5′-hydroxy)norbornyl]-8-(*N*-methylisopropylamino)-9-methyladenine (WRC-0571) (**159**) is one of the most potent and selective antagonists at the adenosine A_1 receptor.[236] The first reported synthesis exemplified several steps with low yields, especially the key $NaBH_4$ reduction of the carbonyl moiety to generate the corresponding *endo*-5′-hydroxy substituent.[237] Recently, Jin and co-workers have developed a new versatile synthetic approach to WRC-0571 (**159**) from commercially available cyclopent-2-en-1-one ethylene ketal (**160**) (Scheme 50).[238] After having prepared the *endo*-norbornan-5-one derivative **161** by a known procedure,[237,239] reduction of the carbonyl group to generate the *endo*-5′-hydroxy substituent has been investigated. Use of $NaBH_4$ or $LiAlH_4$ or the bulkier reducing agent 9-BBN did not give favorable results, and some side reactions occurred to give mixtures that were not easily separable. Fortunately, the addition of $CeCl_3 \cdot 7H_2O$ to the $NaBH_4$ in MeOH mixture afforded **162** quantitatively with very high stereoselectivity. Subsequent hydrogenolysis with palladium hydroxide of the *endo*-isomer isolated by recrystallization gave **163** in 98% yield, which after treatment with 6-chloro-9-methylpurine[240] and subsequent transformations provided the desired WRC-0571 target **159** in 14% overall yield.

4. $CeCl_3 \cdot 7H_2O$—NaI System in Bond-Forming Reactions

The above reactions are a demonstration that the strong aza- and oxophilicity are one of the most important characteristic features of $CeCl_3$. This characteristic is often utilized for a key aspect of organic chemistry such as new bond-forming reactions. It is worth noting that, like the common trivalent lanthanides, $CeCl_3$ in hydrate form has gained a lot of attention as a Lewis acid, since it is a mild reagent, and it is stable in an aqueous medium.[241] It is desirable, generally, to perform the reactions of compounds containing water of crystallization or other water-soluble compounds in aqueous media, because tedious procedures to remove water are necessary when the reactions are carried out in organic solvents. However, water often interferes with desired reactions, especially those using Lewis acids.[242] Even though various kinds of Lewis acid-promoted reactions have been developed and many of them are applied in industry, these reactions must be carried out under strict anhydrous conditions. The presence of even a small amount of water stops the reaction because Lewis acids immediately react with water rather than the substrates and are decomposed or deactivated. On the other hand, in the course of investigations targeting the development of new synthetic methods, it has

been found that lanthanide(III) salts can be used as Lewis acid promoters in water containing organic solvents (water-compatible Lewis acids).[243] The stability and catalytic activity of lanthanide trivalent compounds in water have been ascribed to their large ionic radii and to an equilibrium between the Lewis acids and water.[244] From the results, Kobayashi and co-workers noticed a correlation between the catalytic activity of the lanthanide metals and two kinds of constants: hydrolysis constants (K_h) and exchange rate constant for substitution of inner-sphere water ligands (water exchange rate constant: WERC).[245]

The Lewis acids play a vital role in regio-, chemo-, and stereoselective organic reactions,[246] and in this respect extensive efforts have been devoted to the exploration of new generations of these compounds. In particular, with increasing environmental concerns, it is imperative that the concept of searching for "environmentally friendly" reagents is developed. In this regard, the lanthanide(III) salts have become attractive candidates, and among these, $CeCl_3 \cdot 7H_2O$, a cheap and nontoxic Lewis acid, for example, is able to deprotect, in the chemoselective deprotection of alcohols, only the highly reactive methoxyethoxymethyl (MEM)[247] ethers, leaving intact other Lewis acid sensitive protecting groups, such as acetonide, *tert*-$BuMe_2Si$-, *tert*-$BuPh_2Si$-, and PMB (*p*-methoxybenzyl) ethers. However, moderate activation occurs when hydrated $CeCl_3$ is used alone.[248] These considerations allowed us about ten years ago to consider that $CeCl_3 \cdot 7H_2O$ in combination with sodium iodide (NaI) could act as a Lewis acid promoter able to facilitate a variety of useful organic transformations, whereby no precautions need to be taken to exclude moisture or oxygen from the reaction system. The addition of NaI to $CeCl_3 \cdot 7H_2O$ is a key additive that expanded the uses of $CeCl_3 \cdot 7H_2O$. Interestingly, it has been observed that different cerium(III) halides such as $CeBr_3$ and CeI_3 show a slightly reduced activity compared to $CeCl_3 \cdot 7H_2O$.[249] For this reason, the process of a halogen exchange reaction (eq 1)[250] leading to a more soluble species[251] could not be a plausible rationalization of the acceleration effect caused by addition of NaI. Moreover, the system $CeCl_3 \cdot 7H_2O - 3NaI$ is less efficient

$$CeCl_3 + n\text{NaI} \xrightarrow[n = 1 - 3]{} CeCl_{3-n}I_n + n\text{NaCl} \quad (1)$$

than a 1:1 combination, so that the iodide ion is not active as a promoter whereas cerium is. Certainly, this 1:1 combination of $CeCl_3 \cdot 7H_2O$ and NaI might give $CeCl_2I \cdot 7H_2O$ (eq 2), which might be a more powerful Lewis acid than its $CeCl_3 \cdot 7H_2O$ parent.[252] All the efforts into the structural characterization of this complex $CeCl_{3-n}I_n$ have been unsuccessful to date.

$$CeCl_3 \cdot 7H_2O + \text{NaI} \rightarrow CeCl_2I \cdot 7H_2O + \text{NaCl} \quad (2)$$

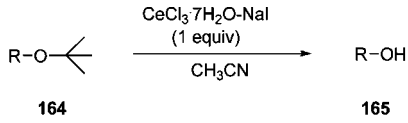
It might be likely that the interaction between $CeCl_3 \cdot 7H_2O$ and NaI gives a complex which exhibits a stronger Lewis acid character. The $CeCl_3$, being a hard Lewis acid, is suitable to form a weak and labile iodide ion−Lewis acid complex.[21] The nucleophile donor iodide ion can enhance the electrophilicity of cerium(III) Lewis acid promoter, a concept masterfully developed by Denmark.[253] This concept of the activation of a Lewis acid by a Lewis base may appear to contradict general chemical intuition,[254] as the reaction between a donor and an acceptor entity is expected to lead to the averaged rather than the polarized electron density of the molecule. There are, however, well-defined circumstances under which charge separation may operate and lead to decreased electron density at a particular central atom. This phenomenon can be considered as "ligand-accelerated catalysis", whereby the acidity of the active center is considerably enhanced after complexation with the Lewis base.[255,256] Even if it might be premature to speculate on the exact mechanism provided by the anion iodide, we have recently obtained some evidence that there is not direct interaction between the cerium(III) site and the iodide ion.[257] The interaction between $CeCl_3 \cdot 7H_2O$ and NaI has been analyzed by X-ray photoelectron spectroscopy (XPS), a valuable technique to quantify the chemical surroundings of the probed atom by means of the analysis of the chemical shift in the core level binding energies.[258,259] Though the XPS spectra were unable to determine the coordination environment of the Ce(III) ion because it was not possible to observe a variation within a few percent in the intensity of the f^2 satellite,[260] our results suggest that the activity of the $CeCl_3 \cdot 7H_2O - NaI$ system is mainly exerted in the heterogeneous phase, and above all, we believe that a chlorine-bridged oligomeric structure[39] of $CeCl_3 \cdot 7H_2O$ is easily broken by donor species such as the iodide ion. The resulting monomeric $CeCl_3 \cdot 7H_2O - NaI$ combination is a more active Lewis acid promoter. Consequently, various inorganic iodides have been examined, and the catalytic activity of inorganic iodide salts (MI_n) is directly dependent on their particle size and not on the nature of the metal M. In fact, when the $CeCl_3 \cdot 7H_2O - MI_n$ gives a fine powder, activity similar to that of the $CeCl_3 \cdot 7H_2O - NaI$ system is observed, whereas the systems that produce coarser powders are less effective. The NaI is optimal with regard to economic and ecological consideration as well, and overall, it is plausible to consider the use of the $CeCl_3 \cdot 7H_2O - NaI$ system as one of the most cost-effective and environmentally benign catalytic systems in contemporary organic chemistry.[261]

Water (from $CeCl_3 \cdot 7H_2O$) is another important component of our reaction system. It is known that catalysis in water depends on the ability of the catalysts to tolerate water, on the one hand, and to remain active, on the other hand; the $CeCl_3 \cdot 7H_2O - NaI$ promoted procedures proceed best in the presence of water, and the activity of the system is even amplified. This effect might be taken as a proof-of-principle that substrate interaction/cerium(III) Lewis acid and water are not mutually exclusive. When anhydrous $CeCl_3$[33] is employed in dry solvent, the activity of $CeCl_3 - NaI$ promoter is absent. However, by adding 1 equiv of water to the dry reaction mixture, the same reactivity as with cerium salt heptahydrate is observed. Thus, the cerium atom may require ligation by 1 or more equiv of water for generating fully active species.[258,262] Very probably (eq 3) the water preferentially coordinates the cerium chloride, promoting the dissociation of chloride anion to form a more active Lewis acid species.[263] As further evidence for this hydrophobic amplification effect[264] is provided, by our experience the yields decrease when the reaction is carried out by adding D_2O instead of H_2O. D_2O has a higher viscosity that

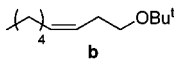
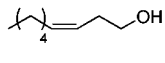
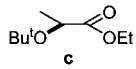
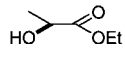
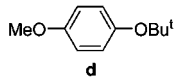
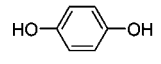
$$CeCl_3(\text{solvent})_m + H_2O \rightleftharpoons [CeCl_{3-n}(\text{solvent})_m(H_2O)]^{\oplus} + Cl^{\ominus} \quad (3)$$

makes mixing more difficult and reduces the hydrophobic effect.[265,266] Comparing the rate of reaction when the reaction mixture is exposed to air (through a $MgSO_4$ drying tube) to

Scheme 51. Cleavage of *tert*-Butyl Ethers 164 to the Corresponding Alcohols 165



164 165

Starting Material	Product	Yield (%)
C_8H_{17}-O-Bu^t **a**	$C_8H_{17}OH$	99
 **b**		98
 **c**		95
 **d**		95

the rate of the same reaction with the use of water added demonstrated that water, and not oxygen, accelerates the reaction.

A recent example supporting the differential activity between hydrated $CeCl_3$−NaI is reported in Scheme 51. The development of new protection and deprotection methodologies is still an important challenge in the synthesis of polyfunctionalized chemical structures, and the $CeCl_3 \cdot 7H_2O$−NaI system has proven to be an effective reagent for these transformations. A mild removal strategy for *tert*-butyl ethers has been designed and developed by us,[267] and this procedure should further contribute to the attractiveness of the *tert*-butoxy protecting group, since it is compatible with a series of other protecting groups and functionalities such as ethyl esters, hydroxyl moieties, nitriles, and carbonyls. It seemed appropriate to investigate if the amount of water present in the reaction mixture could vary the reaction rate.[268] Figure 5 shows a systematic study of the influence of the amount of water on the reaction rate, by drying $CeCl_3$ before use and then adding water in known amounts to the reaction mixtures. The reaction goes to completion (substrate **164a**) in less than 4 h when, at the most, 1 equiv of H_2O has been added. It is interesting to note that the reaction rate lightly decreases when three or more equivalents of water are present. In order to find the best reaction conditions, the effect of the amount of the promoters also has to be examined. The best results were found when an amount of $CeCl_3$ equivalent to that of the

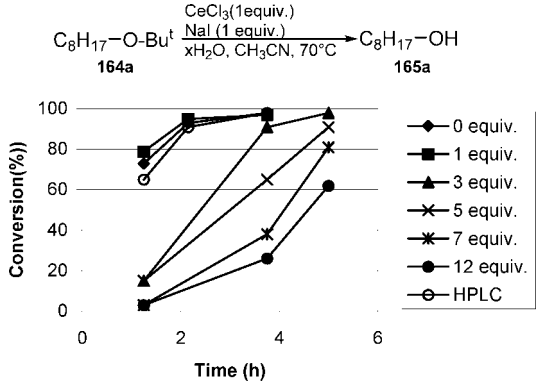
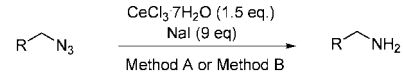
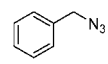
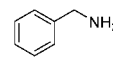
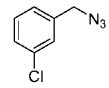
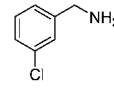
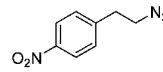
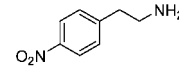


Figure 5. Rate of the cleavage of *tert*-butyl ethers in the presence of variable amounts of H_2O.

Scheme 52. Conversion of Azides into Primary Amines[a]



166 167

Starting Material	Product	Method	Yield (%)
		[A]	65
		[B]	86
		[A]	75
		[B]	91
		[A]	75
		[B]	96

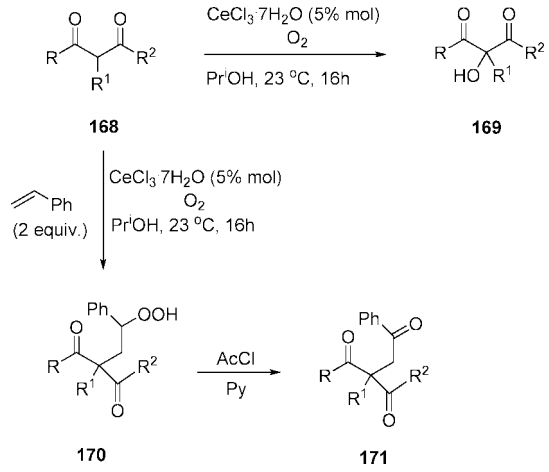
[a] Method A: Reactions performed in the presence of 9 equiv of NaI and 1.5 equiv of $CeCl_3 \cdot 7H_2O$ in refluxing acetonitrile (10 mL/mmol of azides **166**). Method B: Reactions carried out by irradiation in a PowerMax Cooling microwave oven (10 W, 100 °C, 20 min) of a mixture of **166** and the reagent system.

substrate was utilized. We have no evidence that the complex consists of one substrate molecule and one $CeCl_3$ molecule. We believe that an *n:n* complex of substrate and $CeCl_3$ would be the most effective species.[269] Furthermore, generally, the rate of the organic transformations studied decreases with less than 1 equiv of NaI, and in the absence of NaI the reaction does not occur at all. The use of a large excess of NaI does not increase the rate of the $CeCl_3$ promoted organic transformation. However, we have observed that in the case of a $[CeCl_3 \cdot 7H_2O]/[NaI]$ ratio of 1:9 an efficient promoter system for converting the azides to primary amines is working. The procedure is of considerable importance for the introduction of a primary amino group in organic synthesis for the remarkable consequence of primary amines as building blocks for the synthesis of biologically active compounds.[270] For its low cost and easy accessibility, this new $CeCl_3 \cdot 7H_2O$−NaI-promoted azide-transformation provides a practical method for producing exclusively primary amines (Scheme 52),[271] and it represents a valuable alternative to the existing protocols for the known difficulty of the synthesis of amine derivatives by Lewis acids promoted reactions, because the strong affinity of Lewis acids for the amino groups does not regenerate the Lewis acid in the reaction.

The rate and yield of the reaction are greatly influenced by the application of focused microwave irradiation, a common technique in organic synthesis[272] and already exploited in reactions promoted by $CeCl_3 \cdot 7H_2O$.[273] The study has established the optimal conditions for synthesizing amines by reduction of azides under microwave irradiation in the presence of the $CeCl_3 \cdot 7H_2O$−NaI system (method B, Scheme 52).

Even though we have obtained evidence for a not direct interaction between Ce^{3+} and I^-, it is not possible to exclude situations where the iodide anion could promote the *in situ* formation of a Ce^{3+}/Ce^{4+} redox system. In fact, an electron-transfer process may be involved either in the aromatic iodination by NaI using $CeCl_3 \cdot 7H_2O$ as catalyst and H_2O_2 (35%) as the terminal oxidant,[274] or the oxidation of thiols to disulfide by I_2/ $CeCl_3 \cdot 7H_2O$ in graphite.[275] This assumption of radical intermediates has marvelously been proved (Scheme 53) in the aerobic oxidative cerium-α-hydroxylation

Scheme 53. Aerobic Oxidative Process Promoted by $CeCl_3 \cdot 7H_2O$



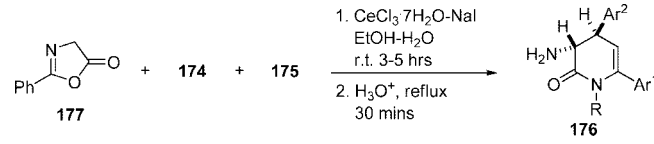
of 1,3-dicarbonyl compounds **168**,[276] and in cerium-catalyzed carbon−carbon coupling with formation of 1,4-diketones **171**.[277] However, in the reactions promoted by $CeCl_3 \cdot 7H_2O$−NaI system carried out in the presence of cerium(IV) sulfate for creating the Ce^{3+}/Ce^{4+} redox system under the same conditions, no catalytic effect has been observed.[278] On the other hand, the use of cerium(IV) ammonium nitrate (CAN), a strong Lewis acid and powerful oxidizing agent,[2] led to the formation of consisting of numerous and inseparable components. Thus, the Ce^{3+} acts only as Lewis acid promoter for coordinating the reactants, and the NaI enhances the electrophilicity of $CeCl_3 \cdot 7H_2O$ Lewis acid promoter.

In recent years, the $CeCl_3 \cdot 7H_2O$−NaI system as an efficient Lewis acid activator has found a wide range of interesting applications in many important organic reactions and in the formation of new carbon−carbon and carbon−heteroatom bonds. This intense activity has allowed a large variety of protocols to be developed which are in several cases superior to pre-existing procedures in terms of practicability, selectivity, and efficiency.

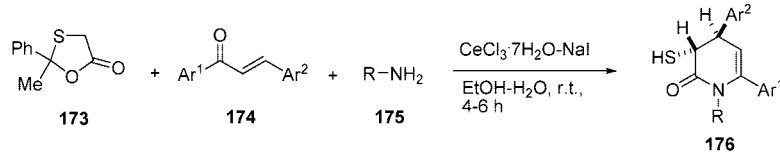
4.1. Formation of Carbon−Carbon Bonds

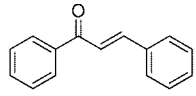
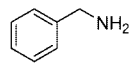
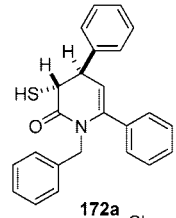
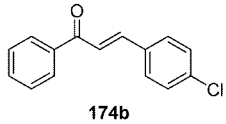
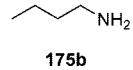
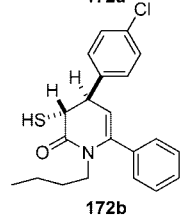
More than ever, the industry demands from organic chemists the development of new methodologies to obtain novel compounds in an efficient way. Among these methodologies, the multicomponent reaction (MCRs)[279] involving one-pot domino processes[280] offers the opportunity of building up molecules from simple and easily available starting materials.[281] MCRs are of significant academic, economic, and ecological interest because they address fundamental principles of synthetic efficiency and rational design. The development of novel MCRs has become an increasingly active area of research, that offers a variety of chemical scaffolds in drug discovery efforts.[282,283] Lewis acid-promoted multicomponent organic transformations are gaining increasing popularity.[284] A novel $CeCl_3 \cdot 7H_2O$−NaI-catalyzed three-component diastereoselective procedure for the synthesis of various potential pharmacologically useful 3-mercapto-2(^{1}H)-pyridinones **172** has been reported (Scheme 54).[285] The yields and diastereoselectivities have been consistently good in favor of the *trans*-isomers, as determined by ^{1}H NMR spectroscopy. In order to extend the scope of this three-component coupling reaction, the same authors utilized the ability of $CeCl_3 \cdot 7H_2O$−NaI in promoting the formation of 3-amino-2(^{1}H)-pyridinones **176** after acid hydrolysis of the benzamido intermediates (Scheme 55).[286] The heterocycles incorporating a 2-(^{1}H)-pyridinone framework constitute an extensively studied class of compounds, owing to their diverse biological activities ranging from anti-HIV,[287] antibacterial,[288] and antifungal[289] to free-radical scavenging.[290] Consequently, the novel $CeCl_3 \cdot 7H_2O$−NaI-promoted multicomponent methodology may find application for the synthesis of various potentially pharmacologically relevant 3-substituted-2-(^{1}H)-pyridinones. The process becomes ef-

Scheme 55. Formation of 3-Amino-2(1*H*)-pyridinones

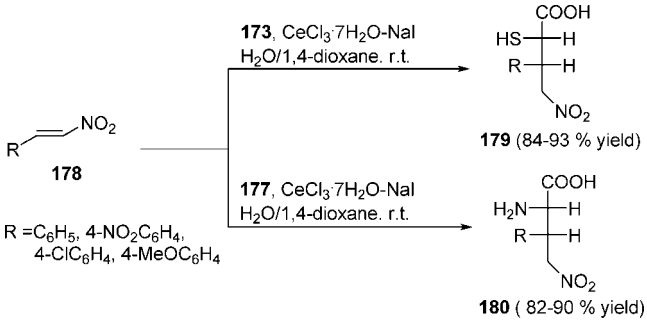


Scheme 54. $CeCl_3 \cdot 7H_2O$−NaI Catalyzed Synthesis of 3-Mercapto-2(1*H*)-pyridinones



α, β-unsaturated compound	Amine	Product	Yield (%)	*anti*/*syn*
 174a	 175a	 172a	89	94:6
 174b	 175b	 172b	81	93:7

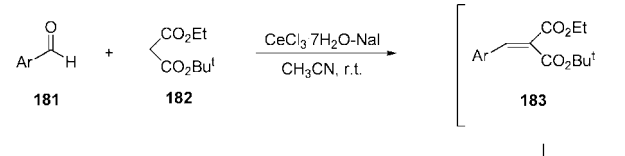
Scheme 56. Synthesis of α-Mercapto Acids 179 and α-Amino Acids 180 from Nitroalkenes

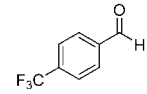
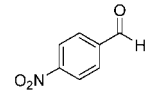
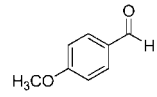
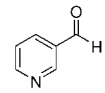


ficient if the reaction is carried out in EtOH/H_2O (5:1) as solvent system at room temperature. Unsaturated ketones give the desired adducts in high yields, while aldehydes suffer from regiochemical restrictions caused by competing 1,2- vs 1,4-addition. Mechanistically, the formation of 3-substituted-2-(^{1}H)-pyridinone requires Michael addition of the enol tautomer form of heterocycles **173** or **177** to chalcones **174** followed by condensation of the resulting Michael adduct with amines **175**. This is in conformity with the known capability of the $CeCl_3 \cdot 7H_2O$−NaI (1:1) system of promoting the addition of various nucleophiles to highly electron deficient olefins *via* a carbon−carbon bond forming Michael reaction.[22c] This observation has been exploited for direct introduction of glycine/mercapto acetic units into nitroalkenes (Scheme 56) by a synthetic protocol that involves simple operations at room temperature.[291] The products of this reaction are multifunctionalized α-amino (**180**) and α-mercapto acids (**179**), which are of significant pharmacological interest,[292] and are of considerable importance in a variety of fields, including chemistry and biology.[293] The diastereomeric ratios have been determined by ^{1}H NMR spectroscopy, and the mixtures contain a high excess of the *syn*-isomer. The *syn*-configuration has been assigned on the basis of their ^{1}H NMR coupling constant, which is smaller than that for the minor *anti*-isomer. The best solvent system in terms of the yield and diastereoselectivity is 1,4-dioxane/H_2O (2:1), and the optimum promoter loading for the $CeCl_3 \cdot 7H_2O$−NaI (1:1) system has been found to be 20 mol %. A decrease in the amount of promoter decreased both the yield and diastereoselectivity considerably.

The choice of $CeCl_3 \cdot 7H_2O$−NaI as a "friendly" promoter represents a further advance in practicability and atom economy in Michael addition. It should be noted that the Michael addition finds frequent application in organic[294] and bioorganic[295] synthesis, especially in the addition of 1,3-dicarbonyl compounds to enones and related systems. However, the classic methodology that involves base activation of the dicarbonyl reagent presents side reactions, such as condensation, bis-addition, rearrangement, and polymerization phenomena.[296] Therefore, the attention of chemists has been focused on the activation of electrophile reagents by Lewis acids able to work under neutral and mild conditions.[297] During our efforts on the synthesis of trisubstituted alkenes, we have observed that the $CeCl_3 \cdot 7H_2O$−NaI system can be utilized as a green, mild, and efficient method for the Knoevenagel condensation of ethyl *tert*-butyl malonate (ETBM) with aromatic or heteroaromatic aldehydes (Scheme 57).[298] Unlike aryl aldehydes, the methodology does not work with aliphatic aldehydes because, under these conditions, the alkylidenepropanoic half esters[299] are not stable and retro-aldol reaction takes place, allowing the

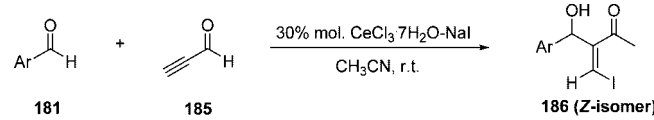
Scheme 57. Knoevenagel Condensation of Aldehydes with ETBM in the Presence of $CeCl_3 \cdot 7H_2O$−NaI in Acetonitrile

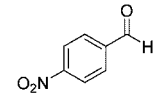
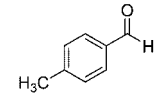
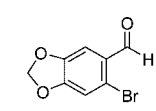


Aldehyde	Yield (%)	*E*:*Z*
	95	90:10
	97	93:7
	85	80:20
	91	60:40

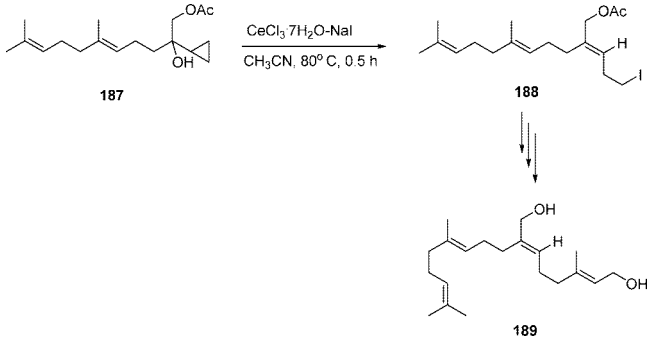
recovery of the starting aldehyde.[300] However, the method provides alkylidene malonates **184**, which appear as a suitable class of building blocks useful for the synthesis of various biologically active molecules.[301] It is noteworthy that our procedure with the $CeCl_3 \cdot 7H_2O$−NaI system has overcome two major restrictions in the broad application of the Knoevenagel reaction. That is (1) the inability to arrest the coupling of aldehydes at the monoaddition stage, since intermediates **183** show strong Michael acceptor character in their own right,[302] and (2) the spontaneous decarboxylation that occurs during the reaction with a monoester of malonic acid.[303] The (*E*)-selectivity has generally been observed in all the cases, whereas the three component coupling of aromatic aldehydes, 3-butyn-2-one (**185**), and NaI using $CeCl_3 \cdot 7H_2O$−NaI promoter has been found to be highly stereoselective, affording exclusively (*Z*)-isomers in high yields.[304] The method offers (Scheme 58) a useful and attractive strategy for the preparation of (*Z*)-β-iodovinyl ketones **186**,[305] which are versatile building blocks in organic synthesis, especially in the preparation of heterocyclic and organometallic compounds.[306] The best results for (*Z*)-β-iodo

Scheme 58. $CeCl_3 \cdot 7H_2O$−NaI Promoted Synthesis of β-Iodo Baylis−Hillman Adducts



Aldehyde	Yield (%)	Time (h)
	85	2.5
	82	3.0
	90	2.5

Scheme 59. (*E*)-Selective Olefination Promoted by the $CeCl_3 \cdot 7H_2O$−NaI Combination

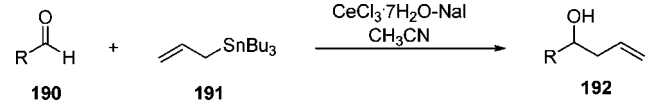


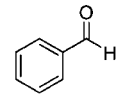
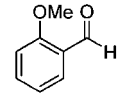
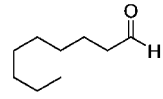
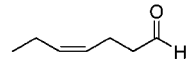
Baylis−Hillman adducts have been obtained with an equimolar ratio of $CeCl_3 \cdot 7H_2O$ and NaI. The reaction did not take place in the absence of $CeCl_3 \cdot 7H_2O$, whereas the product **186** has been observed with moderate yields when tetrabutylammonium iodide is utilized as iodide source. On the other hand, the quaternary ammonium iodide in combination with $CeCl_3 \cdot 7H_2O$ is completely ineffective in the methodology of Li and Peng.[307] They obtained a highly stereoselective synthesis of functionalized trisubstituted (*E*)-olefins[308] from cyclopropyl carbinol derivatives *via* a Julia-type olefination involving a Lewis acid promoter.[309] The alkaline metal cations seem to play a critical role, and the NaI is proven to be the best halide salt in combination with $CeCl_3 \cdot 7H_2O$ to form an effective and mild Lewis acidic system, which promotes (*E*)-selective olefination in the cyclopropyl carbinol substrates. Since these substrates are readily prepared, this facile olefination offered a practical, useful, and versatile method for the synthesis of acyclic terpenoids. As shown in Scheme 59, starting from carbinol derivative **187**, it is possible to prepare the acetoxylated homoallyl iodide **188**, and then, after several simple steps[310,311] the desired diterpene diol **189** is obtained,[312] which represents the (*E*)-isomer of Plaunotol, a naturally occurring antiulcer and antibacterial diterpenol.[313]

To demonstrate the usefulness of the $CeCl_3 \cdot 7H_2O$−NaI system in reactions that need the presence of a Lewis acid activator, we accomplished the allylation of aldehydes by addition of allyltributylstannane.[314] The procedure does not require rigorously anhydrous conditions and inert atmosphere, in comparison with known literature procedures, and it is relatively inexpensive and readily available.[315] Allylsilanes are generally more desirable than allylstannanes, particularly for environmental reasons. However, their lower reactivity[316] does not allow them to react with aldehydes under our reaction conditions, and when we examined the reaction of allyltrimethylsilane in the presence of the $CeCl_3 \cdot 7H_2O$−NaI system, no addition was observed.

The use of more reactive allyltributylstannane allowed us to circumvent this problem, and a new procedure for the preparation of homoallylic alcohols has been developed (Scheme 60). The good-to-excellent yields strongly suggest that the $CeCl_3 \cdot 7H_2O$−NaI system is an efficient Lewis acid promoter for being applied to a broad range of aldehydes. Although the mechanism remains unclear, the procedure exhibits high chemoselectivity toward aldehydes in the presence of ketones. This is due to the lower reactivity of ketones, compared to aldehydes, toward allylstannanes.[317] Among various carbonyl substrates screened, only aromatic and aliphatic aldehydes are reactive substrates, and aryl aldehydes with an electron-withdrawing substituent (NO_2, CF_3) react much faster than benzaldehyde. Hence, electron-donating substituents (CH_3, OCH_3) deactivated aryl aldehydes remarkably (Scheme 61).[318] As a consequence, the activity of the $CeCl_3 \cdot 7H_2O$−NaI system in the allylation of aldehydes is to some extent opposite to that of strong Lewis acids such as $TiCl_4$ and $Et_2O \cdot BF_3$, which selectively activate aryl aldehydes with an electron-donating substituent. We have already found opposite effects between $CeCl_3$ and $TiCl_4$, and this represents another example of how cerium(III) salts promote an organic transformation with a chemoselectivity that is reversed compared to that of the classical Lewis acid mediated reactions.[107,319]

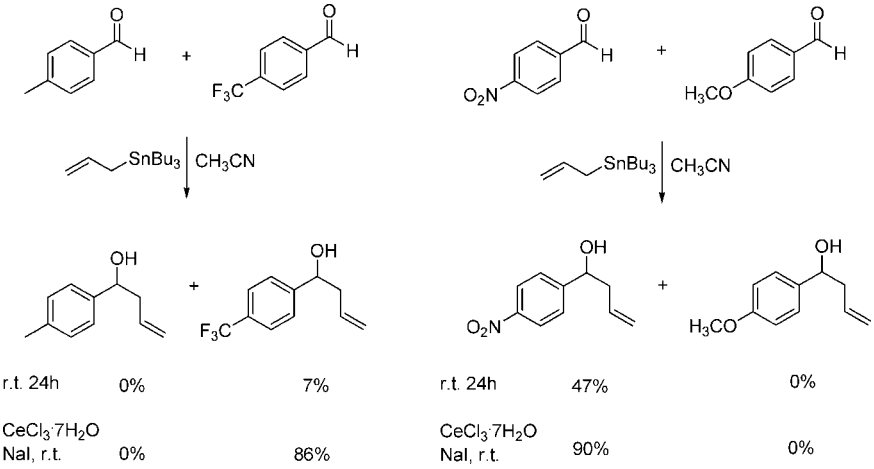
Scheme 60. Allylation of Aldehydes Promoted by the $CeCl_3 \cdot 7H_2O$−NaI System



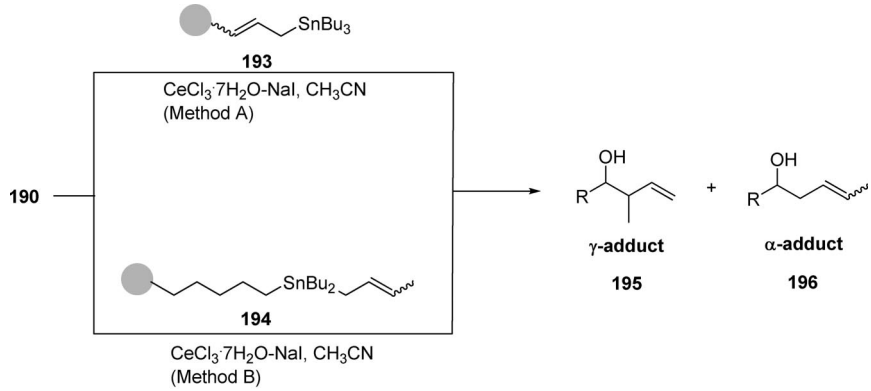
Aldehyde	Yield (%)	Time (h)
	95	27
	83	30
	91	22
	93	25.5

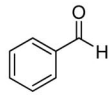
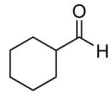
The ability of the $CeCl_3 \cdot 7H_2O$−NaI system of acting as a useful promoter in the carbon−carbon bond-forming reaction by addition of allylic metal compounds to aldehydes has received attention as well.[320] The homoallylic alcohol adducts are useful tools for the construction of complex molecules.[321] For this purpose, crotyltri-*n*-butylstannane has extensively been employed, and its condensation with aldehydes is an intriguing subject with respect to its regioselectivity (linear α-adducts/branched γ-adducts) and its stereoselectivity (*E*/*Z* ratio in α-adducts or its *syn*/*anti* ratio in γ-adducts). The $CeCl_3 \cdot 7H_2O$−NaI promoted reaction shows that the regio- and the stereochemical outcomes depend on the reaction conditions.[322] The reaction can proceed either by simple Lewis acid assistance of the metal salt on the aldehyde[323] or through a preliminary transmetalation process between allylstannane and the cerium salt.[324] Recently, Quintard and co-workers[325] marvelously described how the analysis of the diastereomeric distribution on both the branched γ-adducts (ratio *syn*/*anti*) and the linear α-adducts (ratio *Z*/*E*) can be used to achieve a primary discrimination between a transmetalation and a simple Lewis acid assistance in the crotylstannane series (Scheme 62). In agreement with that, we have observed[322] that reactions performed in the presence of $CeCl_3 \cdot 7H_2O$−NaI in acetonitrile (Method A, Scheme 62) produced the linear α-adducts as the major products with a strong preference for the Z configuration. The minor branched γ-adducts have been obtained as a mixture of *syn*/*anti* isomers, with *syn* preference

Scheme 61. Crossover Experiments with Substituted Aryl Aldehydes



Scheme 62. Crotylation of Aldehydes Promoted by the $CeCl_3 \cdot 7H_2O-NaI$ System



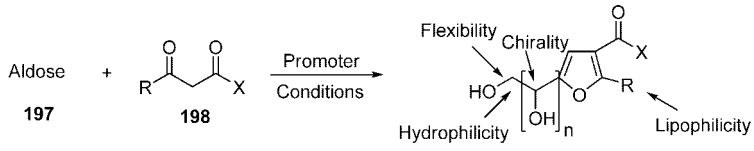
Aldehyde	Method	195 (%) (*syn*/*anti*)	196 (%) (*Z*/*E*)
	A	20 (75:25)	80 (99:1)
	B	85 (99:1)	15 (99:1)
	A	7 (21:79)	93 (95:5)
	B	88 (28:72)	12 (99:1)
$n\text{-}C_7H_{15}CHO$	A	6 (42: 58)	94 (97:3)
	B	86 (51:49)	14 (94:6)

with aromatic aldehydes and *anti* preference with both cyclic and linear aliphatic aldehydes. The methodology is very interesting because the reaction with γ-substituted allylstannanes generally proceeds with γ-regioselectivity[326] and only a few protocols for the regioselective synthesis of α-adducts have been reported. It is known that almost all allylic metal derivatives react with aldehydes to give the γ-adducts exclusively.[327] Formation of the linear Z-homoallylic alcohols as the major adducts in the reactions with $CeCl_3 \cdot 7H_2O-NaI$ in acetonitrile is consistent with Lewis acid assistance on the aldehydes. In these cases, the initial step of the sequence involves the isomerization of **193** ($Z + E$) into its unhindered isomer after a 1,3-metallotropy.[328] The occurrence of a transmetalation reaction can be ruled out in these reactions because of the high *Z*-selectivity observed, and the transmetalation of crotylstannane by $CeCl_3 \cdot 7H_2O$ has previously been excluded on the basis of spectroscopic analyses. When the same reactions have been carried out with polymer-supported crotylstannane **194**,[329] the stereochemical trends have been maintained with high *Z* selectivity for linear α-adducts and *syn* or *anti* preference for the branched γ-adducts as a function of the nature of the aldehydes, but the regioselectivity of the reaction is strongly modified with a high preference for the branched γ-adducts. This change is probably due to lower kinetics for the 1,3-metallotropy. In terms of synthetic interest, the use of polymer-supported allylstannanes in the presence of $CeCl_3 \cdot 7H_2O-NaI$ provides the desired targets in a reasonably convenient way. However, the use of this method is still relatively new, and the presence of byproducts of a polymer residue containing tin suggests that improvements are needed before this method is considered environmentally friendly.

The addition of allylstannanes to aldehydes also works well when the promoter $CeCl_3 \cdot 7H_2O-NaI$ is adsorbed on a solid support such as alumina oxide (Al_2O_3). The procedure under solvent-free conditions represents a further advance in the practical and atom economy, and a highly prevalent formation of the γ-adduct is observed. The presence of NaI and the use of the promoter supported on Al_2O_3 are essential for the efficiency of the process. In fact, in the absence of NaI or in the presence of an unsupported $CeCl_3 \cdot 7H_2O-NaI$ system under solvent-free conditions, the process becomes very sluggish and side processes largely prevail. Very likely, Al_2O_3 acts as a carrier to increase the surface area available for the heterogeneous reaction, and $CeCl_3$ interacts with oxygen atoms at the surface of the support, forming new active sites on the alumina local structure. Generally, immobilization of catalytically active species on solid materials enables not only the generation of recoverable and reusable catalysts but also remarkable catalytic performances compared with some species before the immobilization, owing to unique environments of the surfaces.[330] Many reasons have been reported for the positive effects of immobilization: for example, the increasing stability of active structure by site isolation at surfaces, the creation of new geometric and electronic structures by surfaces, and the enhancement of substrate density around active sites by high surface polarities.[331] In addition to the increasing activity of the immobilized species, cooperative catalysis of the support surfaces with the immobilized species is another advantage of the use of supports.[332] In this context, the term "cooperativity" refers to a system where at least two different catalytic entities act together to increase the rate of a reaction beyond the sum of the rates achievable from the individual entities alone. Numerous examples have been reported of inorganic cooperativity in heterogeneous catalysis by incorporating multiple different metal centers onto a support, and one of the most common supports for heterogeneous catalysis is silica gel (SiO_2).[333] The first clear result is that the use of SiO_2 support facilitates the workup of the reaction mixture with better yields of product, even though the reaction has also been observed in its absence. Solid support catalysts have attracted much interest in chemistry because of advantages they possess over homogeneous catalysts, including recyclability, more simple product isolation, and reduction of environmental pollution.[334] In fact, for practical synthesis, solvent-free processes are ideal in terms of volumetric productivities and environmental safety.[335] Although most catalytic processes are highly sensitive to the polarity of the solvent and the concentrations of substrates, a solvent-free procedure might be suitable for a reaction with a concerted mechanism because its transition state is less influenced by the features of the solvents.

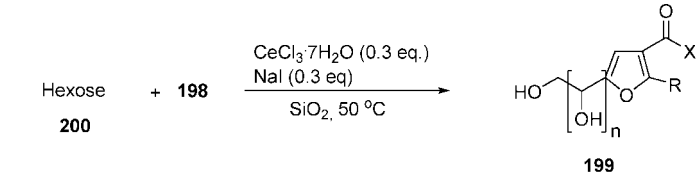
Recent advances have demonstrated that enhancing the Lewis acidity of the $CeCl_3 \cdot 7H_2O-NaI/SiO_2$ system might be a key point for achieving high efficiency in the new carbon−carbon bond-forming reactions. This solvent-free approach with the use of reagents impregnated over inorganic supports[336] offers a step forward in the direction of clean chemistry[337] even if these procedures do not exactly meet the definition of "no-solvent": the organic solvent is only eliminated at the primary reaction stage, whereas an appreciable amount of solvent is still required for the adsorption of reactants and elution of the product at the pre- and postreaction stages, respectively. However, the practical advantages of the $CeCl_3 \cdot 7H_2O-NaI/SiO_2$ Lewis acid promoter strategy—the easy preparation of the promoter system, the nearly solvent-free conditions,[338] and the high yield of the products—make this strategy attractive for the preparation of building blocks for complex molecules of biological and pharmaceutical importance.[22c] Along this line, it has become interesting to evaluate the $CeCl_3 \cdot 7H_2O-NaI/SiO_2$ in the so-called Garcia Gonzalez reaction,[339] that is the Knoevenagel condensation of a β-dicarbonyl compound with an unprotected carbohydrate to give a polyhydroxyalkyl furan (Scheme 63). Interestingly, more than 100 furans structurally similar to that of **199** have recently been isolated from plants and microorganisms,[340] albeit in low yield. This class of heterocyclic compounds[341] has a variety of useful properties,[342] which include chirality, hydrophilicity, and flexibility; consequently, polyhydroxyalkyl furans are interesting scaffolds for synthetic chemists and can be used in the preparation of polyfunctional heterocycles of interest in pharmaceutical and agrochemical practice.[343] By screening the various conditions, it has been observed that the reaction proceeds with good yields at 50 °C using our $CeCl_3 \cdot 7H_2O-NaI$ system supported on SiO_2 in solvent-free conditions, and the best results are obtained using 0.3 equiv of promoter system. This is very interesting because the use of substoichiometric promoters to minimize waste has become a demanding challenge

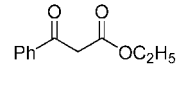
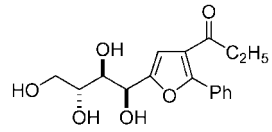
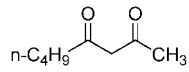
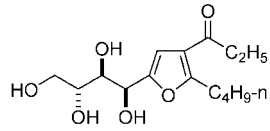
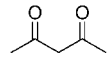
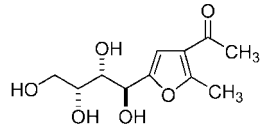
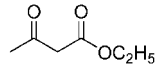
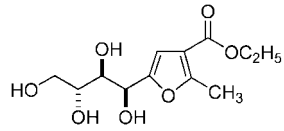
Scheme 63. Garcia Gonzalez Reaction



D-Glucose	Pentane-2,4-dione	$CeCl_3 \cdot 7H_2O$	NaI	Solvent/Time	Temp (°C)	Yield (%)
1 eq.	1 eq.	0.25 eq.	-	H_2O/ 7h	60	20
1 eq.	0.18 eq.	0.25 eq.	-	H_2O/ 7h	80	8
1 eq.	1 eq.	1 eq.	-	H_2O/ 15h	60	25
1 eq.	1.2 eq.	1.2 eq.	-	H_2O/ 15h	60	31
1 eq.	1 eq.	1 eq.	-	CH_3CN/ 15h	60	18.5
1 eq.	1 eq.	1 eq.	0.3 eq.	CH_3CN/ 15h	60	45.4
1 eq.	1 eq.	1 eq.	0.3 eq.	SiO_2/ 25h	r.t.	60
1 eq.	1.3 eq.	0.3 eq.	0.3 eq.	SiO_2/ 22h	50	95

Scheme 64. Reaction of Aldohexoses with β-Dicarbonyl Compounds Promoted by the $CeCl_3 \cdot 7H_2O$−NaI System on SiO_2 under Solvent-Free Conditions



Hexose	1,3-Dione	Product	Yield (%)
D-Glucose			90
D-Glucose			75
D-Galactose			85
D-Mannose			95

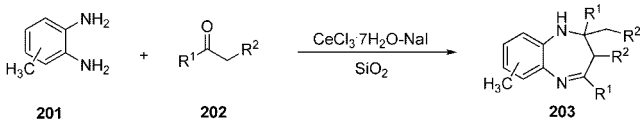
for synthetic chemists when atom economy and green chemistry are considered. Considering the physical properties of the reactants and reagents, it was found that some acetonitrile was required for this process, allowing it to stir for 0.5 h and removing the solvent afterward.

The success of the reaction is independent of the type of sugar used (Scheme 64) and aldopentose or aldohexoses react with β-dicarbonyl compounds in good yields, even though traces of unwanted hydroxytetrahydrofuranyl furans have always been observed as byproduct. In synthetic heterogeneous catalysis, mesoporous silica has often been used as solid support for creating an organic−inorganic catalyst;[344] analogously here, the SiO_2 most likely functions as an activator for the $CeCl_3 \cdot 7H_2O$−NaI system as well as a solid support. A very likely electronic interaction between a catalytically active cerium(III) species and hydroxyl or even oxide groups at the surface of SiO_2 might lead to the formation of a supported cerium(III) salt. In this complex the cerium atom is grafted to the surface *via* one covalent bond (≡SiO−Ce);[345] mass balance analysis and details of these possibilities require authentication. Consequently, this interaction may reduce the LUMO energy of cerium(III)/SiO_2, and this one is lower in energy than the LUMO of cerium(III) itself. Given that the strength of a Lewis acid is related to the energy of its LUMO in such a way that the lower the LUMO energy, the easier its interaction with a base molecule, it is possible that the Lewis acidity of $CeCl_3$ is considerably increased by incorporation of the lanthanide in the framework of SiO_2. Even the amount of SiO_2 is decisive for completion of this type of Garcia Gonzalez reaction, and 0.5 g/mmol of carbohydrate is the most appropriate ratio. The methodology is clean, and the adduct **199** has been obtained under the influence of strong acids because the solid promoter may contain simultaneously Brönsted and Lewis sites, similar to those already shown for other transition metals.[346] In fact, according to Spencer's study,[347] investigations aimed at confirming the effective catalyst do not preclude the existence of a Brönsted acid-catalyzed pathway in the procedure. The presence of the weak base 2,6-di-*tert*-butyl-4-methylpyridine, which only binds to a proton and is unable to coordinate to the metal cerium due to the bulky *tert*-butyl groups,[348] significantly retards the Garcia Gonzalez reaction.

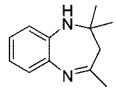
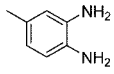
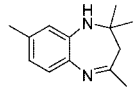
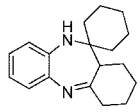
4.2. Formation of Carbon−Nitrogen Bonds

Among the lanthanide Lewis acids, we have observed how $CeCl_3 \cdot 7H_2O$ has gained much popularity, owing to its excellent properties; for example, it is water tolerant, nontoxic, easy to handle, and suitable for direct use without unnecessary extravagant preparation. Furthermore, the activity of $CeCl_3 \cdot 7H_2O$ increases dramatically in the presence of an iodide source such as NaI, resulting in shorter reaction times, diminished byproduct formation, and improved yields and purity of the products. A pertinent example is found in the work of Spinelli and co-workers on the 1,4-addition of Fischer bases to nitroenamines.[349] Although the use of the $CeCl_3 \cdot 7H_2O$−NaI system satisfies the demands of environmentally benign green chemistry,[350] in some cases the reactions are sluggish and give low yields. Therefore, $CeCl_3 \cdot 7H_2O$−NaI supported on silica gel has been developed for new carbon−nitrogen bond-forming reactions.

Scheme 65. $CeCl_3 \cdot 7H_2O$−NaI/SiO_2 Promoted Synthesis of 1,5-Benzodiazepines



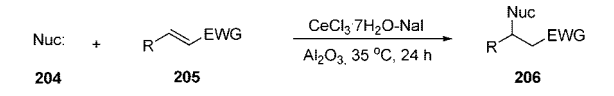
201 202 203

Diamine	Ketone	Product	Yield (%)
	CH_3COCH_3		95
	CH_3COCH_3		96
			80

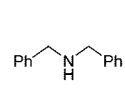
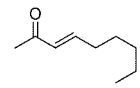
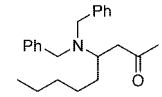
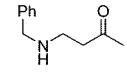
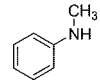
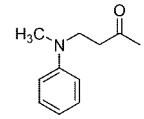
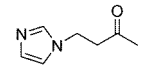
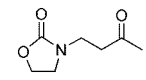
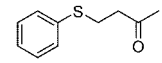
In the course of Sabitha's research on application of $CeCl_3 \cdot 7H_2O$ in various organic transformations,[247,351] the author described a new, efficient, and environmentally benign protocol for the synthesis of 1,5-benzodiazepines using $CeCl_3 \cdot 7H_2O$−NaI supported on SiO_2 under solvent-free conditions (Scheme 65).[352] Benzodiazepines are an important class of compounds that own a wide range of pharmacological activity[353] and industrial applications.[354] The present procedure is an attractive alternative to the existing methods. Methyl substituted *o*-phenylenediamines **201** well reacted with ketones **202** in the presence of 30 mol % of $CeCl_3 \cdot 7H_2O$ and 30 mol % of NaI supported on SiO_2 (05 g/mmol of diamine) without solvent at room temperature for giving the corresponding 1,5-benzodiazepines **203** in good yields. Cyclic ketones also reacted efficiently to afford the fused ring benzodiazepines. Other remarkable features of this procedure are its simplicity, together with easy and cheap preparation, air stability of the catalyst, and the use of $CeCl_3$ as environmentally friendly reagent.[355] The catalyst can be reused for 4−5 cycles with little decrease in activity after recovery by filtration.

The conjugate addition of nitrogen nucleophiles to α,β-enones (aza-Michael reaction) is noteworthy as a widely used method for carbon−nitrogen bond formation.[356] Our increase of environmental consciousness in chemical research has prompted us to extend the solventless $CeCl_3 \cdot 7H_2O$−NaI/SiO_2 methodology to aza-Michael reaction by addition of secondary amines to (*Z*)-α,β-enones.[357] The resulting β-amino ketones are versatile building blocks for the preparation of many nitrogen-containing biologically important compounds.[358] Furthermore, the use of neutral alumina (Al_2O_3) as solid support[359] permitted us to overcome some of the problems associated with the procedure of aza-Michael reactions where the inorganic support is silica gel. The instability of several β-amino carbonyl compounds on SiO_2 is well-documented,[360] so the possibility that a new $CeCl_3 \cdot 7H_2O$−NaI/Al_2O_3 promoter system circumvents this problem represents an important extension of the Michael reaction (Scheme 66). The Michael addition of amines **204** as nitrogen nucleophiles proceeds well even when the Michael acceptor (**205**) is an (*E*)-α,β-unsaturated carbonyl compound. Furthermore, although the nucleophilic addition of primary and

Scheme 66. Michael Addition Promoted by the $CeCl_3 \cdot 7H_2O$−NaI System Supported on Al_2O_3 at 35 °C for 24 h

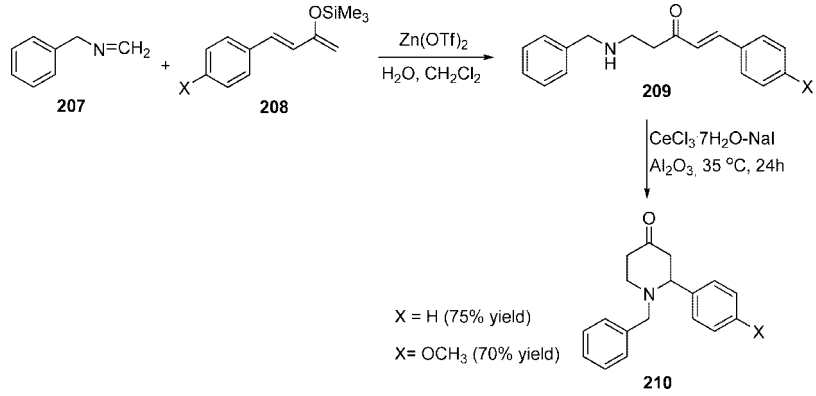


204 205 206

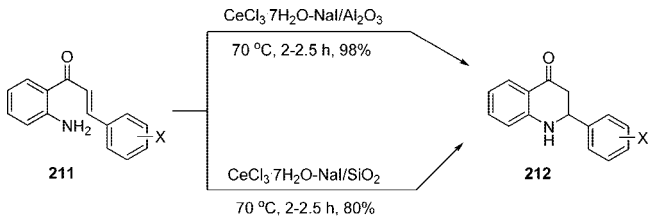
Nuc	Acceptor	Product	Yield (%)
			85
			70
			75
			93
			91
			98

secondary aryl amines generally proceeds sluggishly, owing to their reduced nucleophilicity, their addition is accomplished with good yields by this procedure. In continuing the quest to exploit the usefulness of the $CeCl_3 \cdot 7H_2O$−NaI/Al_2O_3 system, addition of weak nucleophiles such as carbamates and imidazoles has been accomplished also.[361] Also, thiols have undergone 1,4-addition to suitable Michael acceptors in the presence of a $CeCl_3 \cdot 7H_2O$−NaI/Al_2O_3 promoter system, and β-thio ketones[362] can be isolated in near quantitative yields. The promoter activity of $CeCl_3 \cdot 7H_2O$−NaI/Al_2O_3 is not weakened by adsorption of moisture from the air, and such a system can be stored for long periods without any appreciable loss of the activity. The fact that this cheap, nontoxic, and easy to handle material is optimal with regard to economic and ecological considerations has allowed useful applications in aza-Michael reactions to generate substituted six-member nitrogen-heterocycles, which are key intermediates particularly useful in the synthesis of alkaloids and pharmacological active compounds (Scheme 67).[363] The availability of precursor β-amino ketones **209**[364] focused the attention on the development of a very convenient route to substituted piperidin-4-ones,[365] which are useful building blocks because by removal of the 4-oxo group it is possible to obtain substituted piperidines, a common structural motif in many alkaloid natural products.[366] The minor differences in Al_2O_3 with respect to SiO_2 as solid support have made possible the Michael addition in high yields without any side reactions, such as polymerization and bis-addition, normally observed under the influence of strong acids. The intramolecular aza-Michael reaction without the typical disadvantage of the polymerization of enones has found useful application for cyclization of aminochalcones **211** to flavonones **212** (Scheme 68).[367] Different 2-aryl-2,3-dihydroquinolin-4(1H)-

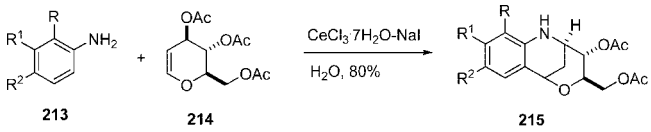
Scheme 67. $CeCl_3 \cdot 7H_2O-NaI/Al_2O_3$ as Key Promoter in the Substituted Piperidin-4-ones Synthesis



Scheme 68. Isomerization of 2′-Aminochalcone to 2-Aryl-2,3-dihydroquinolin-4(1*H*)-one



Scheme 69. $CeCl_3 \cdot 7H_2O-NaI$ Promoted Synthesis of Fused Chiral Tetrahydroquinolines



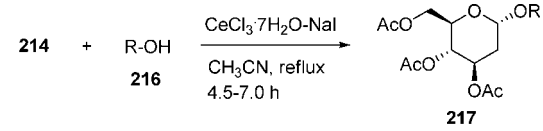
ones[368] can easily be prepared from their 2-aminochalcone precursors under solvent-free conditions, using $CeCl_3 \cdot 7H_2O-NaI/SiO_2$ as a promoter. This conversion can be further improved through the use of more economic neutral alumina supported $CeCl_3 \cdot 7H_2O-NaI$, providing high yields of up to 98% for **212**. The relatively long reaction time (2−2.5 h) likely reflects the low nucleophilicity of the aromatic amines and could not be improved upon by increasing the reaction temperature due to thermal decomposition of the substrate.[369]

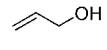
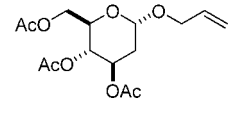
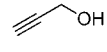
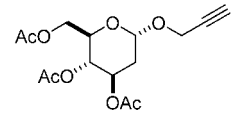
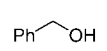
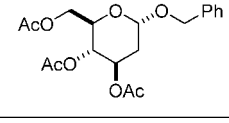
This efficacy of $CeCl_3 \cdot 7H_2O-NaI$ of being useful in alkaloid derivatives has found great attention for the synthesis of sugar derived chiral tetrahydroquinolines from D-glucal and aryl amines.[370] Given that the tetrahydroquinoline moiety is a core structure in many biologically important natural products[371] and in many active pharmaceuticals,[372] the $CeCl_3 \cdot 7H_2O-NaI$ system has been used as promoter for stereoselective synthesis of 2,4-disubstituted chiral tetrahydroquinolines (Scheme 69). Various substituted anilines **213** reacted smoothly with glucal triacetate **214** in the presence of an equimolar ratio of $CeCl_3 \cdot 7H_2O$ and NaI in water to afford the corresponding benzo-fused heterobicycles **215** in good yields. The reaction has only been successful with glucal triacetate; differently, 3,4,6-tri-*O*-methyl- or 3,4,6-tri-*O*-benzyl-D-glucal did not react with anilines under identical conditions. The method is clean and highly stereoselective only when one of the *ortho*-positions of aniline is free from substitutions because the initially formed 1,4-adduct may undergo an intramolecular cyclization, resulting in the formation of fused tetrahydroquinolines. The use of water as solvent makes this method an environmentally benign process to prepare sugar heterobicycles in a single step.

4.3. Formation Carbon−Oxygen Bonds

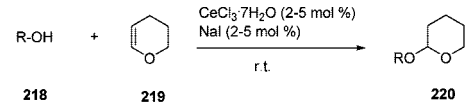
All the before mentioned studies have shown that the activity of $CeCl_3 \cdot 7H_2O$ increases dramatically in the presence of an iodide source such as NaI. Even if the low nucleophilicity of oxygen as compared to the amino nitrogen is known, Rosini and co-workers[249] reported the cyclization of 3-hydroxyalkenoic acid esters, giving 5-substituted tetrahydrofuranoacetic or 6-substituted tetrahydropyranacetic esters in good yield and with complete retention of the absolute configuration of the starting 3-hydroxy esters. The methodology involves the $CeCl_3 \cdot 7H_2O-NaI$ system to facilitate the carbon−oxygen bond formation. In the same year, Yadav and co-workers[373] showed that glucal triacetate **214** reacts with a variety of alcohols **216** in the presence of the $CeCl_3 \cdot 7H_2O-NaI$ system in refluxing acetonitrile, affording the corresponding 2-deoxy-α-glycopyranosides **217**[374] in high yields (Scheme 70). The method avoids the use of strongly acidic or basic conditions, and it does not require the use of expensive or corrosive reagents and no precautions need to be taken to exclude moisture from the reaction medium. Interestingly, in the absence of NaI, the glycols underwent Ferrier rearrangement under the influence of $CeCl_3 \cdot 7H_2O$ to afford the corresponding 2,3-unsaturated hexopyranoside in good yields.

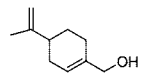
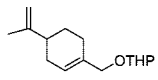
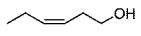
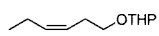
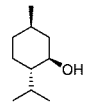
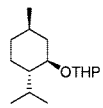
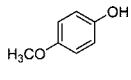
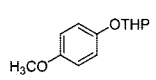
Scheme 70. $CeCl_3 \cdot 7H_2O-NaI$ Promoted Synthesis of 2-Deoxyglycopyranosides 217



ROH	Product	Yield (%)
		87
		85
		87

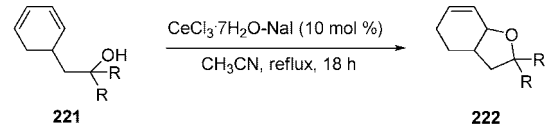
Scheme 71. Tetrahydropyranylation of Hydroxy Compounds in the Presence of 2−5 mol % of a $CeCl_3 \cdot 7H_2O$−NaI System under Solvent-Free Conditions

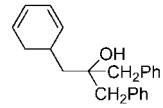
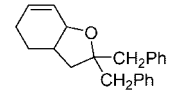
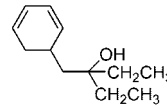
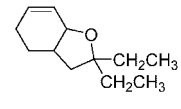
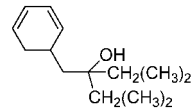
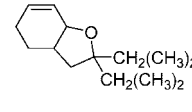


Hydroxy compound	Product	Time	Yield (%)
		48	99
		6	96
		24	76
		26	99

The high levels of stereoselectivity in $CeCl_3 \cdot 7H_2O$−NaI Lewis acid promoted procedures combined with a simple operation indicated that new reactions for carbon−oxygen bond formation can be further developed. In fact, as a part of our ongoing research program to develop new methodologies involving $CeCl_3$, we investigated the protection of hydroxyl groups by tetrahydropyranylation (Scheme 71).[375] Given that the protection of alcohols and phenols plays a key role in the synthesis of polyfunctional organic molecules,[376] we have established an efficient and inexpensive method for introducing the tetrahydropyranyl protecting group (THP) by addition of free hydroxyl compounds **218** to 3,4-dihydro-2H-pyran (DHP, **219**) in the presence of the $CeCl_3 \cdot 7H_2O$−NaI system under solvent-free conditions. An equimolar ratio of $CeCl_3 \cdot 7H_2O$ and NaI is found to give THP ethers **220** in good yields, and the amount of the $CeCl_3 \cdot 7H_2O$−NaI system can be reduced to a practical limit of catalysis without an appreciable loss of activity. This is in agreement to waste minimization in fine chemicals syntheses,[377] and a very simple workup procedure for the recovery of the tetrahydropyranyl ether **220** has been adopted. The reaction mixture has been treated with an organic solvent (Et_2O) capable of dissolving the organic material but not the promoter system, which can easily be removed by filtration. The procedure has been repeated five times without noting any appreciable decrease in activity. Particularly interestingly, for hydroxyl compound substrates which include a stereogenic center, the tetrahydropyranylation generates adducts with a new stereogenic center. However, low diastereoselectivity is observed, and the corresponding THP ethers are isolated as diastereomeric mixtures in an about 1:1 ratio. Furthermore, the efficiency of this tetrahydropyranylation is shown from the capacity of promoting the hydroxyl compounds protection in the presence of other protective groups. Not only is the tetrahydropyranyl ether obtained in the presence of *N*-*tert*-butoxycarbonyl and acetate groups, but also free hydroxyl groups can be selectively protected in the presence of *p*-methoxybenzyl and trialkylsilyl ethers, which have been reported to be cleaved by stoichiometric amounts of the $CeCl_3 \cdot 7H_2O$−NaI system.

Scheme 72. Intramolecular Addition Promoted by 10 mol % of the $CeCl_3 \cdot 7H_2O$−NaI System



Substrate	Product	Yield (%)
		58
		56
		22

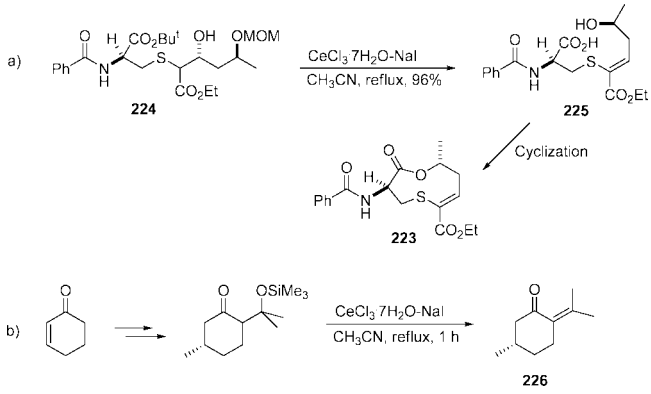
Another example of cyclization to furan derivatives has been reported by Yeh and co-workers.[378] The methodology outlined that $CeCl_3 \cdot 7H_2O$−NaI (10 mol %) catalyzed intramolecular cyclization of 7-hydroxy-1,3-diene (**221**) under mild conditions to afford hexahydrobenzofurans (**222**) (Scheme 72). Due to the fact that the $CeCl_3 \cdot 7H_2O$−NaI system is an efficient reagent for the conversion of tertiary alcohols into alkyl iodides, only fair yields are observed.[379] This $CeCl_3 \cdot 7H_2O$−NaI promoted diastereoselective intramolecular cyclization[222] represents a useful reply to the challenge for synthetic chemists to find safer and milder conditions for the preparation of a tetrahydrofuran skeleton.[380,381] It should be noted that the six-member ring of tetrahydropyran cannot be formed because of unfavorable formation of a *cis*-decaline intermediate.

4.4. Application in Organic Synthesis

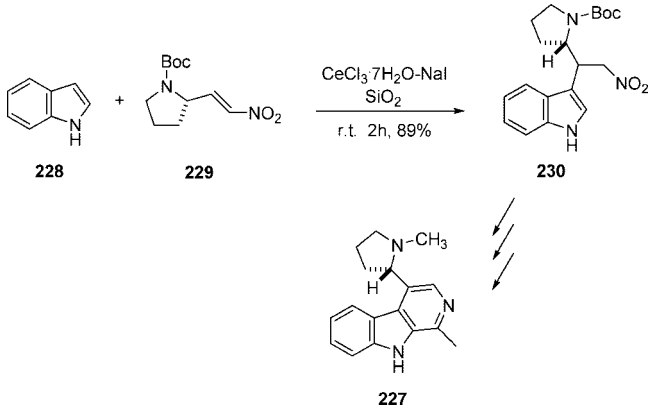
The development of promoters for the carbon−carbon and carbon−heteroatom bond-forming reactions is a fundamental topic in organic synthesis. However, many currently accessible methods are impractical, for example, in terms of environmental considerations. For this reason, $CeCl_3 \cdot 7H_2O$−NaI Lewis acid promoter has found wide application in solving specific problems of selectivity, and its use is now a method of choice in organic synthesis. Two typical examples are the $CeCl_3 \cdot 7H_2O$−NaI protocol that we have successfully applied to accomplish both deprotection and the elimination in a one-pot procedure for the stereospecific synthesis of the *N*-protected nine-membered macrocyclic **223**,[382] a component of Griseoviridin,[383] as well as the $CeCl_3 \cdot 7H_2O$−NaI promoted construction of the carbon−carbon double bond[384] in the first synthesis of (*S*)-(−)-Pulegone (**226**)[385] (Scheme 73).

The fact that the $CeCl_3 \cdot 7H_2O$−NaI system is optimal with regard to suppressing side reactions in multifunctional molecules allows us to believe that our system Lewis acid promoter can find other useful applications in new bond-forming procedures starting from molecules with high

Scheme 73. Applications of $CeCl_3 \cdot 7H_2O$−NaI Promoted New Bond-Forming Reactions in Synthesis



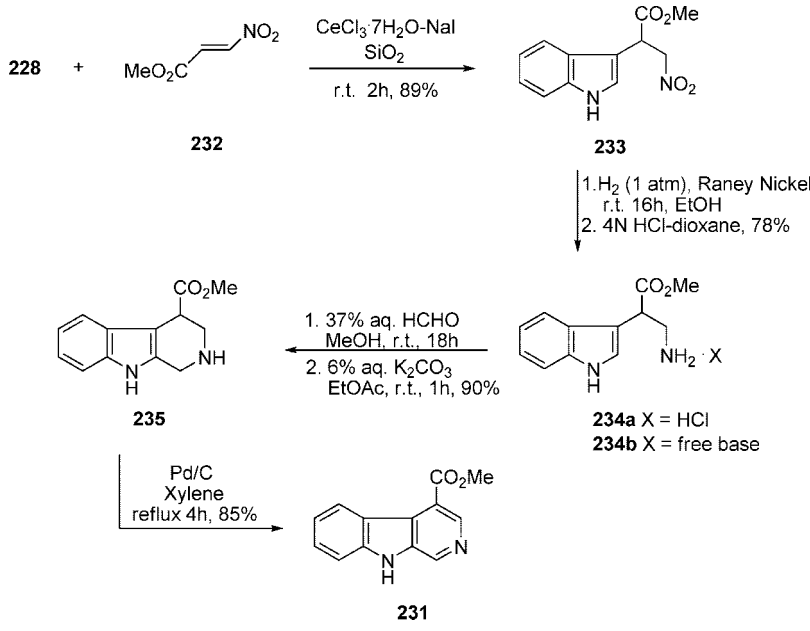
Scheme 74. Synthetic Application of $CeCl_3 \cdot 7H_2O$−NaI/SiO_2 in the Synthesis of (*S*)-(−)-Brevicolline



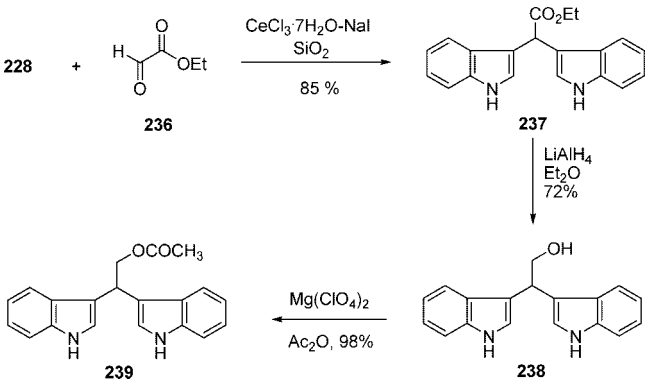
tendency to polymerize under acid-catalyzed conditions. In fact, the treatment of indole derivatives with α,β-disubstituted nitroalkenes in the presence of a $CeCl_3 \cdot 7H_2O$−NaI system gave the corresponding β-indolylnitroalkanes without traces of polymerization phenomena of the acid-sensitive substrates.[22c] It is known that nitroalkenes are one of the strongest Michael acceptors,[386] providing a common pathway to nitroalkanes,[387] which could serve as stock compounds for corresponding amino compounds.[388] The reaction proceeds with good yields even in the case of poorly reactive indoles,[389] and the corresponding adduct is in satisfactory yield obtained in the case of an indole derivative containing a hydroxyl group. Direct reaction of hydroxylindoles is generally problematic, often resulting in low Michael adduct yields due to interaction of the indolyl interaction of the indolyl hydroxy group with the Lewis acid catalyst.[246] The synthetic potentialities of this $CeCl_3 \cdot 7H_2O$−NaI procedure have been applied to promote the synthesis of (*S*)-(−)-Brevicolline (**227**), the major alkaloid of the plant *Carex Brevicollis*, which exhibits a phototoxic effect against bacteria and fungi.[390] The synthesis (Scheme 74) began using Michael addition of indole (**228**) to the chiral nitroalkene **229**, affording the nitro compound **230**. This is converted to the β-carboline ring of the Brevicolline target by several steps. The chiral nitroalkene synthon **229** has been obtained starting from the natural amino acid (*S*)-proline.[391]

The straightforwardness of this synthetic strategy and the use of solvent-free conditions that reduce the harmful effects of organic solvents on the environment suggest a facile access to the synthesis of 4-substituted β-carbolines. In this manner, tryptamine derivatives are obtained by Friedel−Crafts-type conjugate addition of indoles to nitroalkenes. As an example, the methyl 9*H*-β-carboline-4-carboxylate (**233**) belongs to heterocycles of interest to the pharmaceutical industry, as witnessed by many reported biological activities,[392−394] and our approach[395] involves introduction of the 4-substituent without *N*-protection[396] of the indolyl nucleus (Scheme 75). Product **233** obtained by the reaction of indole **228** with the readily available *trans*-β-nitroacrylate (**232**) promoted by $CeCl_3 \cdot 7H_2O$−NaI/SiO_2 under solvent-free conditions has been converted into the tryptamine[397] derivative **234** by hydrogenation in the presence of Raney nickel in ethanol. Compound **234** is not stable as a free base, so it has been isolated as its stable hydrochloride by treating with aqueous 4 N HCl in dioxane. The free base **234b** has directly been used without purification, but its treatment with formaldehyde under protic conditions followed by Pictet−Spengler cyclization of the imine[398] afforded a modest yield of the 4-substituted 1,2,3,4-tetrahydro-β-carboline **235**. On the other hand, synthesis of compound **235** proceeded in good yield

Scheme 75. Synthesis of Methyl 9*H*-β-Carboline-4-carboxylate (231)



Scheme 76. Synthesis of Streptindole (239) Starting from Addition of Indole to Ethyl Glyoxylate



when a 37% formalin solution has been added to the hydrochloride of **234a** in methanol, followed by conversion into the free base. Finally, aromatization with palladium-on-carbon[399] afforded the fully aromatic β-carboline **231** with substitution at the 4-position.

The application has shown that the substitution on the indole nucleus occurs exclusively at the 3-position, and *N*-alkylation products have not been observed. With regard to Michael acceptors, besides the nitroalkenes, α- or β-substituted enones also afforded the corresponding 3-oxoalkylindole product in good yields. The procedure did not work for α,β-unsaturated sulphones and nitriles, and the corresponding esters showed modest reactivity.[22c] In the case of α,β-unsaturated aldehydes, the reaction suffers from regiochemical restriction caused by competing 1,2- or 1,4-addition. Hence, this has suggested the usage of the $CeCl_3 \cdot 7H_2O$−NaI system in the addition of indoles to saturated carbonyl compounds on a silica gel surface under solvent-free conditions.[400] The reaction with aliphatic aldehydes proceeded well, giving the bis-indole derivatives in good yields without the presence of some indole dimer. For better evaluating the synthetic usefulness of the present methodology, we focused our attention on the synthesis of a biological active *bis*-indole, such as Streptindole (**239**), for its broad range of pharmacological activity (Scheme 76).[401] It has been isolated from intestinal bacteria *Streptococcus faecium* IB37 and causes DNA lesions in *Bacillus subtilis* cells. Previous syntheses of this genotoxic metabolite have been carried out by several groups; however, these routes are either laborious, comprised of steps of low yield, or require harsh reagents that may lead to degradation of the indole nucleus.[402,403] As a consequence, we have exploited and identifed an alternative route to Streptindole by utilizing relatively eco-friendly reaction conditions. The strategy has proceeded through known intermediates, but with a new method, and provided the highest overall yield from indole to date. The corresponding ethyl bis(1*H*-indol-3-yl) acetate (**237**) adduct is reduced to the alcohol **238** by the action of $LiAlH_4$. Finally, the alcohol **238** has been *O*-acetylated in the presence of Lewis acid catalyst to afford the Streptindole target (**239**). This acylation reaction has been facilitated by the action of dried $Mg(ClO_4)_2$[300,404] as a useful alternative to metal triflate promoters,[405] which are rather expensive, and their uses, especially for large-scale synthetic operation, may not be economical. Recently, it has been reported that, by replacing acetonitrile with glycerin, it is possible to use $CeCl_3 \cdot 7H_2O$ alone as recyclable catalyst for the synthesis of bis(indolyl)-methanes.[406]

5. Conclusions

The results summarized in this review clearly indicate that there has been and continues to be substantial interest in the organic reactions promoted by $CeCl_3$. The advent of effective methods for selective functional group transformations and for new bond-forming reactions that circumvent common difficulties, including low yields, insufficient stereoselectivities, and the formation of product mixtures, is an important endeavor. The usefulness of $CeCl_3$ in this regard could help fellow researchers to find more efficient procedures in organic chemistry, and it would represent an environmentally benign alternative to current chemical processes.

Tremendous progress and major breakthroughs have been realized over the last decades in carbon−carbon bond-forming reactions using organolithium reagents or Grignard reagents in the presence of dry $CeCl_3$. With a wide range of substrates, the addition reactions usually occur much more smoothly, and high selectivities are now reached routinely. As a consequence, these procedures can be added, conveniently, to the toolbox of any practitioner of organic synthesis. This fundamental role that $CeCl_3$ plays in developing new stereoselective additions of nucleophile moieties to functionalized carbonyl compounds has extensively been utilized as one of the most known ways to obtain an alcoholic unit.

Particularly noteworthy are the reductions of organic compounds where small amounts of $CeCl_3$ give rise to changes in conversion rate, yield, stereoselectivity, and reaction pathway. The presence of $CeCl_3$ not only improves the reactivity and stereoselectivity in the transition metal catalyzed hydrogenation but also dramatically improves chemo- and regioselectivities in the reductions of multiple bonds by metal hydrides. Consequently, after the pioneering works of Luche appeared around 1980, numerous reductions employing $CeCl_3$ as key component have been developed. The level of stereoselectivity is particularly high when "hard" donors groups such as nitrogen or oxygen atoms are present in the substrate. These results have commonly been explained in terms of chelate-controlled processes. However, this interpretation has recently been challenged by various authors, who argue that in many cases an open chain mechanism can better account for the observed results. Many of the reported $CeCl_3$ mediated reductions show a stereochemical outcome fully consistent with an open chain controlled pathway.

In facing the strong Lewis character of the complex formed from the interaction between $CeCl_3 \cdot 7H_2O$ and NaI, it has been particularly rewarding to be able to utilize the $CeCl_3 \cdot 7H_2O$−NaI system in many synthetic methodologies. The broad utility of this system offers tremendous opportunities in complex natural product synthesis under solvent-free conditions. In addition, in some cases, the promoter system can be supported on inorganic support scaffolds. The adopted experimental conditions allowed in all cases the recovery of the catalyst, which can be reused without loss of activity. Thus, the $CeCl_3 \cdot 7H_2O$−NaI system-based heterogeneous promoted reaction offers attractive opportunities in green chemistry. Aside from features commonly highlighted in this regard, including simplicity of workup, recyclability, and minimization of metallic waste,[407] this combination promotes multiple types of bond constructions.

Taking into account that $CeCl_3$ is cheap, nontoxic, stable to water, oxygen, and moisture, and easy to handle, all these

protocols represent an optimal development with regard to economic and ecological consideration. We think that the $CeCl_3$ will find in the future many other interesting applications owing to its peculiar properties, especially when its structure and the origin of its high activity are disclosed.

6. Acknowledgments

We would like to express our heartfelt gratitude to our young co-workers whose intelligence, hard work, and creativity produced most of the results described here, and their names appear in the appropriate references cited herein. Much of this work results from ongoing and enjoyable collaborations with Prof. Roberto Ballini, Marcella Bosco, Renato Dalpozzo, Marino Petrini, and Gabriele Renzi, to whom we are grateful. E.M. gratefully thanks the friend Dr. Riccardo Giovannini of the Boehringer Ingelheim Italia S.p.A., Milan (Italy), for essential discussion. We also thank the MIUR, Rome, and University of Camerino for providing financial assistance during production of this review, and M.M. gratefully acknowledges the Pfizer Ascoli Piceno Plant for a graduate fellowship.

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CR100084G