Application of Lanthanide Reagents in Organic Synthesis

GARY A. MOLANDER

Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado 80309-0215

Received July 15, 1991 (Revised Manuscript Received October 29, 1991)

Contents

Gary A. Molander received his B.S. degree in 1975 from Iowa State University and his Ph.D. degree in 1979 under the direction of Herbert C. Brown at Purdue University. He spent a year and a half at the University of Wisconsin as an NIH postdoctoral fellow with Barry M. Trost. He subsequently joined the faculty at the University of Colorado in 1981, becoming full professor in 1990. He currently holds an Alfred P. Sloan Foundation Fellowship and was an American Cyanamid Academic Awardee in 1989.

I. Introduction

Few areas of synthetic chemistry have witnessed growth as explosive as that brought about by the application of lanthanide reagents to organic synthesis. Long ignored in the arena of selective organic synthesis, this class of reagents now boasts many protocols that have become the standards to which all analogous procedures are compared. As testimony to the dramatic surge in research activity, several excellent reviews on various aspects of lanthanide chemistry applied to organic synthesis have appeared.[1] The current review is intended to focus on those transformations of greatest utility to synthetic organic chemists and covers published material through mid-1991.

The organization of this review is along traditional lines in synthetic organic chemistry. Utilization of lanthanide reagents for simple functional group transformations (for example oxidation and reduction processes) is first outlined, followed by a more comprehensive delineation of the application of lanthanides in selective carbon–carbon bond forming reactions. Synthetic transformations are emphasized to the near exclusion of kinetic and mechanistic studies. Even with this limitation a truly comprehensive exposition is impossible. Consequently, the concentration is on those processes transpiring in a highly selective manner or that cannot be carried out efficiently utilizing other currently available technologies.

II. Functional Group Transformations

A. Oxidation Reactions

1. Cerium(IV)-Promoted Oxidations

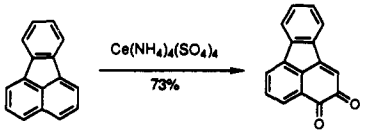
Cerium(IV) compounds represent the most notable oxidants among lanthanide reagents. In particular, ceric ammonium nitrate [$(NH_4)_2Ce(NO_3)_6$, CAN] has been utilized extensively for a variety of oxidative transformations.[2] As might be expected for very powerful one-electron oxidants, the chemistry of Ce(IV) oxidations of organic molecules is dominated by radical and radical cation chemistry. The fate of these reactive intermediates determines the nature of the organic oxidation products isolated. These intermediates may undergo fragmentation, rearrangement, C–H bond cleavage, hydrogen atom transfer, or C–C bond cleavage, depending on the structure of the starting material.

Although much of the early work on Ce(IV)-promoted oxidations was carried out in strongly acidic media using stoichiometric CAN, recent studies have focused on development of much milder and more convenient procedures. The synthesis of new cerium salts has permitted oxidation under less vigorous conditions, and procedures employing catalytic amounts of various Ce(IV) salts have emerged as well. Further developments making Ce(IV)-promoted oxidative transformations even more convenient, selective, and efficient are expected. A complete description of the chemistry of the various Ce(IV) oxidants is beyond the scope of this review; however, some important and useful highlights

0009-2665/92/0792-0029$10.00/0

of their reactivity are outlined below.

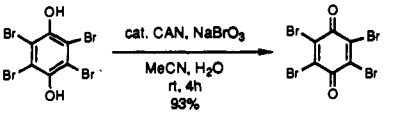
a. Aromatic Systems. Although polynuclear aromatic systems are oxidized by Ce(IV) oxidants, in general the reaction is limited to simple symmetrical molecules such as naphthalene or anthracene. Oxidation of these substrates provides high yields of quinones (eq 1).[2,3] Substituted, unsymmetrical substrates rarely provide a single oxidation product, but rather produce complicated mixtures.[2,4]



(1)

Electrolytic oxidation of aromatics in the presence of cerium(III) methanesulfonate [$Ce(OMs)_3$] provides the advantage of a recyclable oxidation system, and further development along these lines could lead to useful catalytic procedures.[5]

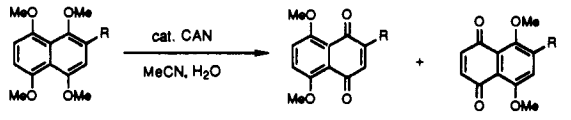
b. Hydroquinones, Catechols, and Derivatives. Hydroquinones are very readily oxidized to quinones by Ce(IV) reagents. Use of silica-supported reagents aids in the efficiency of the process.[6] Systems employing catalytic Ce(IV) oxidants with sodium bromate as the stoichiometric oxidant have also been developed, alleviating the need to use large quantities of cerium salts for the reactions (eq 2).[7] Reagents other than



(2)

CAN have been developed for oxidation of hydroxylated aromatics,[8] and in at least one case these reagents demonstrate the ability to be regenerated under specific oxidation conditions.[8b]

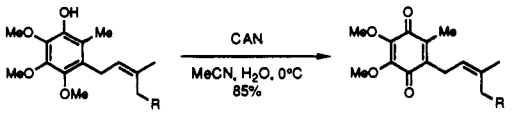
Oxidative demethylations of hydroquinone monomethyl or dimethyl ethers are also achieved readily with Ce(IV) oxidants.[2,9] As expected, in polynuclear aromatic systems the most electron-rich ring system is preferentially oxidized (eq 3).[10] Related procedures



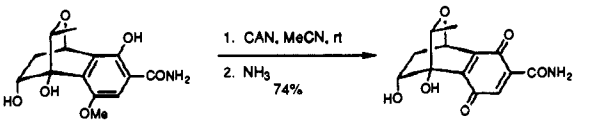
(3)

R	% isolated yield	
H	70	0
CH_2OH	75	13
COMe	7	77
CHO	0	65

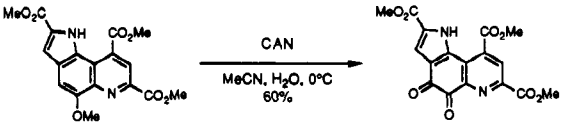
have been utilized in key steps leading to total syntheses of the ubiquinones (eq 4),[11] the antibiotic (±)-sarubicin A (eq 5),[12] and the quinonoid alcohol dehydrogenase coenzyme methoxatin (eq 6).[13] These examples demonstrate the chemoselectivity achievable by Ce(IV) oxidations in diverse systems.



(4)

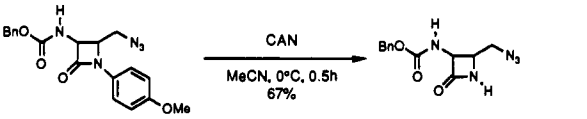


(5)



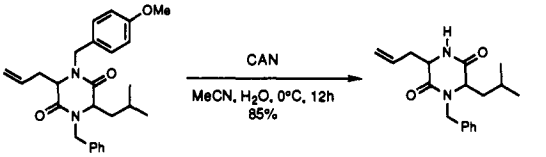
(6)

A variant of the oxidative demethylation has proven useful in another context. When appropriately functionalized *N*-aryl 2-azetidinones were treated with CAN, N-dearylated β-lactams were isolated in quite good yields (eq 7).[14] Again in these instances, diverse functionality (esters, azides, olefins and acetals) was tolerated.



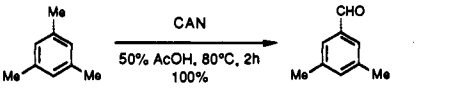
(7)

A further example of the chemoselective nature of CAN is demonstrated in oxidative removal of the 4-methoxybenzyl protecting group from functionalized 2,5-piperazinediones (eq 8).[15] This deprotection can be effected in the presence of functional groups possessing very similar oxidation profiles to that of the protecting group.

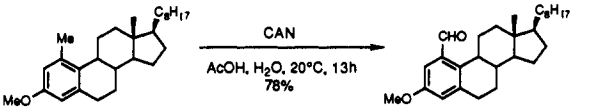


(8)

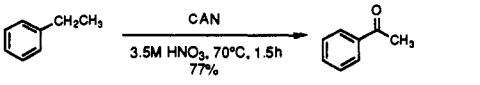
c. Arenes. Cerium(IV) salts are generally excellent reagents for selective side-chain oxidation of arenes. Methyl-substituted aromatic systems can usually be oxidized cleanly to a single aldehyde with CAN (eqs 9 and 10), but homologous alkyl-substituted derivatives result in generation of corresponding ketones (eq 11).[16] As might be expected, electron-withdrawing groups on the aromatic ring tend to diminish the yield of desired oxidation products.



(9)

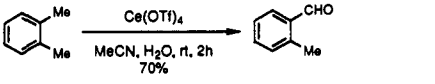


(10)



(11)

Cerium(IV) triflate [$Ce(OTf)_4$] has been touted as a useful alternative to CAN for oxidation of arenes.[17] Oxidations with $Ce(OTf)_4$ proceed under exceedingly mild conditions (eq 12). Reactions with $Ce(OTf)_4$ are



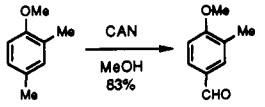
(12)

claimed to be less prone to side reactions than those with CAN, but it should be pointed out that a very

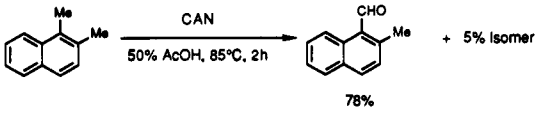
limited sampling of substrates has been evaluated to date.

Electrolytic oxidation of arenes in the presence of $Ce(OMs)_3$ provides another protocol for selective side-chain oxidation to aromatic aldehydes or ketones.[5] This and related methods utilizing CAN[18] take advantage of the ability to reoxidize Ce(III) byproduct salts. Although the cycle can be repeated more than 10 times, truly efficient catalytic processes for these conversions have yet to be developed.

With certain substitution patterns, enhanced chemoselectivity is achieved in side-chain oxidation reactions (eqs 13 and 14).[5,18,19] Frontier molecular orbital theory has been invoked to explain the observed results.[19]

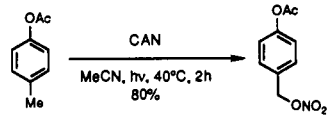


(13)



(14)

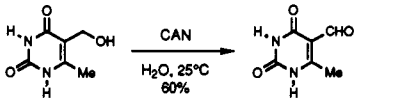
Depending upon the solvent system employed, derivatives other than aldehydes or ketones may be generated by the Ce(IV) oxidation of arenes. For example, acetates are generated in synthetically useful yields if reactions are performed in glacial acetic acid,[20] ethers result if reactions are run in alcohol,[21] and nitrates can be prepared in very good yields when CAN and the substrates are photolyzed in acetonitrile solvent (eq 15).[22]



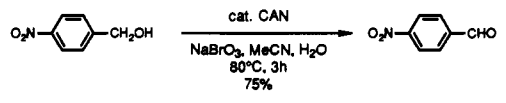
(15)

d. Alcohols. The Ce(IV) oxidation chemistry of alcohols is exceedingly dependent on substrate structure. Although in some cases straightforward oxidation to the corresponding carbonyl compound is achieved, it is also possible to observe C–C bond cleavage and tetrahydrofuran generation.

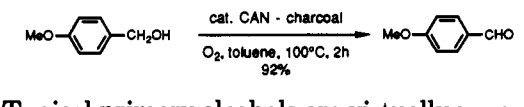
Benzylic and related alcohols are very readily oxidized to aldehydes and ketones utilizing a variety of Ce(IV) reagents (eq 16).[8,23] Of particular interest is development of procedures in which catalytic cerium salts are utilized. Sodium bromate[24] and even oxygen[25] have been utilized as stoichiometric oxidants to achieve desired transformations (eqs 17 and 18).



(16)

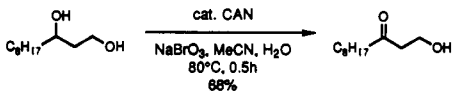


(17)

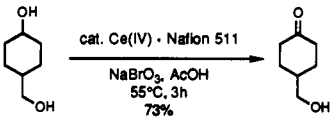


(18)

Typical primary alcohols are virtually unreactive in the presence of Ce(IV) oxidants. Consequently, cerium reagents exhibit exceptional selectivity in oxidation of secondary alcohols in the presence of primary alcohols.[25,26] Both sodium bromate[26c] and *tert*-butyl hydroperoxide[26b] have been utilized as stoichiometric oxidants for reactions in which Ce(IV) salts serve as catalysts, and a polymer-supported catalyst prepared by treatment of Nafion 511 with CAN provides another useful extension of the method (eqs 19 and 20).[26b]

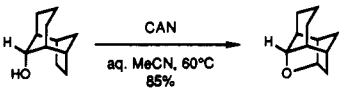


(19)

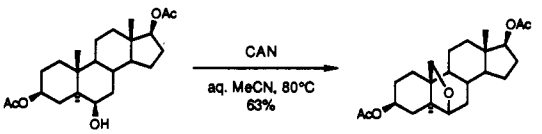


(20)

Although not normally a significant problem, in particularly favorable cases tetrahydrofuran formation (via alkoxy radical δ-hydrogen abstraction and subsequent ring closure) can be the predominant pathway in Ce(IV)-promoted oxidation of alcohols (eqs 21 and 22).[27]

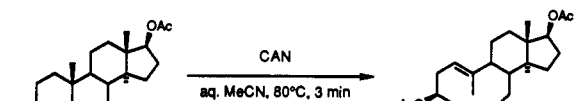


(21)

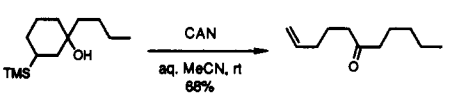


(22)

Oxidative cleavage of tertiary alcohols can provide exceptional yields of fragmented products (eq 23).[27c] As expected, cleavage occurs in the direction providing the most stable free radical fragment. The presence of a β-trimethylsilyl group makes this type of fragmentation more facile and provides a synthetically useful route to unsaturated aldehydes and ketones (eq 24).[28] Homoallylic alcohols, cyclobutanols, and strained bicycloalkanols in which the hydroxyl group is α to the bridgehead also undergo ready fragmentation in Ce(IV)-promoted oxidation reactions.[2b]

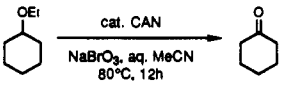


(23)

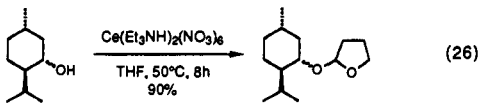


(24)

e. Ethers. Simple ethers are converted directly to aldehydes or ketones utilizing catalytic CAN in the presence of $NaBrO_3$ (eq 25).[29] Additionally, the oxidation of tetrahydrofuran in the presence of valuable alcohol intermediates has been promoted as a convenient means to provide protection of the alcohol functional group as the THF acetal (eq 26).[30] Unfortunately, neither of these procedures has been extensively explored with more complicated systems. Consequently the full scope of these particular processes remains unknown.

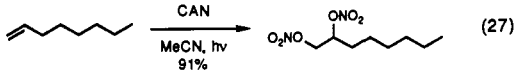


(25)



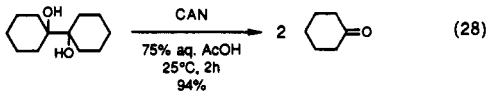
(26)

f. Olefins. Products obtained in the oxidation of olefins are generally quite solvent dependent, and mixtures are often obtained.[2b] However, selective synthesis of vicinal dinitrates can be accomplished when a Ce(IV) photolytic oxidation is carried out in acetonitrile (eq 27).[31]



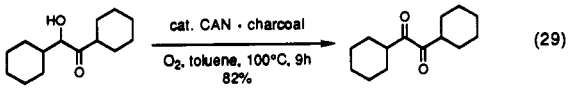
(27)

g. Vicinal Diols and α-Hydroxy Ketones. Cerium(IV) oxidants are extremely effective reagents for oxidative cleavage of vicinal diols.[2b] Both *cis*- and *trans*-cycloalkane-1,2-diols are transformed to corresponding acyclic dialdehydes, and vicinal tertiary alcohols react efficiently as well (eq 28).



(28)

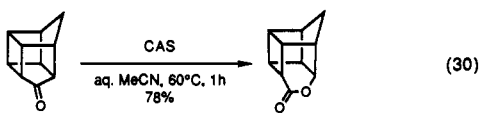
Interestingly, a variety of reagents and protocols have been developed in which α-hydroxy ketones are oxidized to vicinal dicarbonyl products without cleavage.[8,23c,25] This provides one route to biacetyls and related compounds (eq 29).



(29)

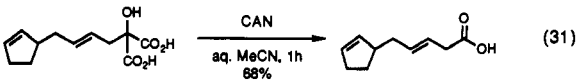
h. Ketones and Aldehydes. Limited studies have been performed on selective oxidation of aldehydes and ketones with Ce(IV) oxidants.[2b] Although the oxidation of a small sampling of aldehydes indicates that conversion to carboxylic acids is possible, it does not appear that there are significant advantages to utilizing this technique over the many others that are available.

Similarly, oxidation of ketones has not been thoroughly explored.[2b] Although in limited cases (strained polycyclic ketones) a Baeyer–Villiger oxidation product can be isolated in good yields (eq 30), usually a rather unselective conversion of cyclic ketones to ring-cleaved acyclic nitrato carboxylic acids is observed. The example in eq 30 is of particular interest because oxidation of the same substrate with *m*-chloroperbenzoic acid provides a mixture of lactones in which the opposite regioisomer predominates to the extent of 5:1.



(30)

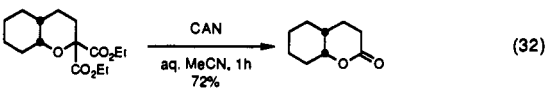
i. Carboxylic Acids. Isolated carboxylic acids are generally inert toward oxidation by Ce(IV) reagents. However, decarboxylation can be accomplished when stable radical fragments are generated by the action of cerium oxidants.[2b] For example, diphenylacetic acid is converted to benzophenone in 90% yield in the presence of $[Ce(NO_3)]CrO_4 \cdot 2H_2O$,[8c] and α-hydroxy carboxylic acids are readily decarboxylated to provide carboxylic acids possessing two fewer carbon atoms (eq 31).[32] For the substrate chosen as an example in eq



(31)

31, the analogous process utilizing $NaIO_4$ as the oxidant provided the desired compound in less than 5% yield.

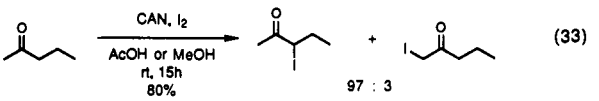
Oxidative bisdecarboxylations provide a unique entry to lactones (eq 32).[33] Substrates for this conversion can be conveniently generated in several ways by one- or two-step processes from readily available starting materials.



(32)

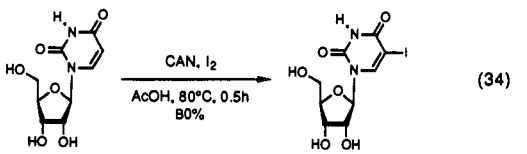
j. Oxidative Halogenation. Oxidation of para-substituted toluenes with CAN in aqueous solutions of trifluoroacetic acid/NaBr provides a route to corresponding benzyl bromides.[34] Electron-withdrawing substituents on the aromatic ring facilitate the desired conversion. Oxidative halogenation of the aromatic ring and production of aromatic aldehydes are competing processes.

Oxidative halogenation of ketones can be accomplished by utilizing CAN in the presence of iodine (eq 33).[35] The procedure is regioselective, providing the more highly substituted α-halo ketones in very good yields.



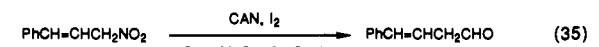
(33)

Asakura and Robins have reported a mild procedure for selective preparation of 5-halouracil nucleosides utilizing CAN in the presence of I_2 or metal halogenides (eq 34).[36] The method provides significant advantages over other reported procedures in terms of generality, selectivity, and ease of performance. Uracil and 1,3-dimethyl uracil can also be selectively halogenated under similar reaction conditions.

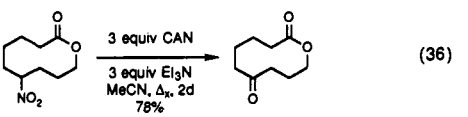


(34)

k. Nitroalkanes. Ceric ammonium nitrate oxidation of nitroalkanes in the presence of triethylamine provides an extremely useful alternative to the Nef reaction and related procedures for generation of ketones and aldehydes (eq 35).[37] The procedure has been applied to macrolactone syntheses, where alternative procedures failed because of competitive ring-opening and other non-productive reaction pathways (eq 36).[38]



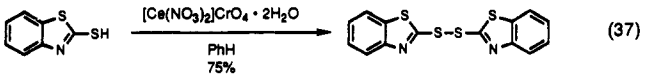
(35)



(36)

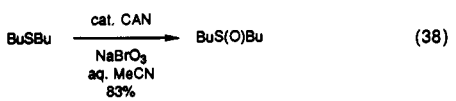
l. Organosulfur Compounds. Thiols are selectively oxidized to disulfides utilizing modified Ce(IV) oxidants

(eq 37).[8b,c] The reaction appears to be general for a variety of substitutionally differentiated thiols.



(37)

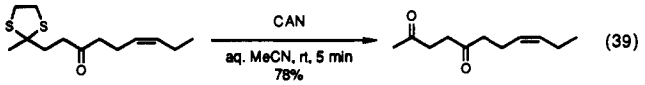
Cerium(IV) reagents are also exceptional for chemoselective oxidation of sulfides to sulfoxides. Sulfones are typically not observed in these reactions, even when excess oxidant is present. Although early versions of the oxidation were restricted to diaryl sulfides (presumably because aliphatic sulfoxide products were prone to Pummerer rearrangements), more recent protocols have been applied to selective oxidation of dialkyl sulfides as well. Procedures employing catalytic CAN have been developed, with $NaBrO_3$[7] or O_2[39] serving as the stoichiometric oxidant (eq 38). Phase-



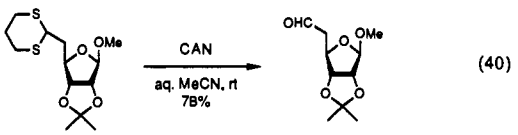
(38)

transfer conditions utilizing stoichiometric CAN have also been reported, providing nearly quantitative yields of sulfoxides in virtually all cases.[40]

Cerium(IV) salts can be utilized to effect deprotection of ketones which have been protected as 1,3-dithiolanes or 1,3-dithianes.[41] The method has demonstrable utility in chemoselective deprotection of ketones in the presence of keto olefins (eq 39)[42] and sensitive acetals (eq 40).[43]



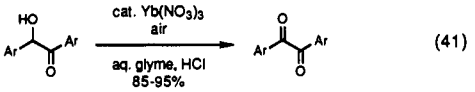
(39)



(40)

2. Oxidative Processes Promoted by Other Lanthanides

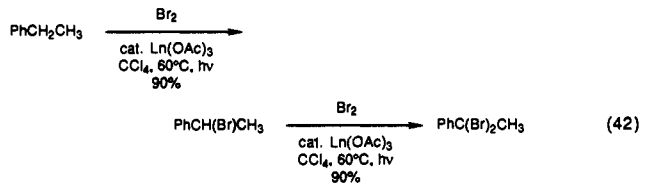
Other lanthanide reagents have been utilized as catalysts for a variety of different oxidative processes in organic synthesis. For example, $Yb(NO_3)_3$ has been utilized in oxidation of benzoins to benzils (eq 41).[44]



(41)

Nitrate is believed to be the primary oxidant in this process. The nitrite produced in the reaction was postulated to be reoxidized to nitrate by O_2 in the presence of the $Yb(NO_3)_3$ catalyst.

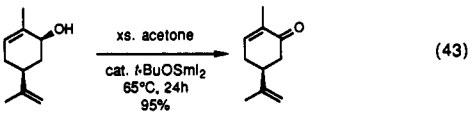
Lanthanum(III) acetate has been utilized as an effective catalyst for side-chain halogenative oxidation of arenes (eq 42).[45] Other lanthanide complexes can also



(42)

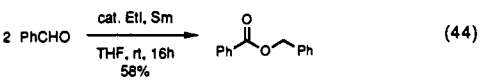
be utilized as catalysts for the reaction, however several main-group and transition-metal salts fail to promote the reaction. No reaction occurs in the dark or without the lanthanide catalyst. A limitation of the reaction is that one cannot utilize electron-rich aromatic systems owing to competitive ring halogenation.

Samarium(III) alkoxides serve as highly effective catalysts for the Oppenauer-type oxidation of alcohols to aldehydes and ketones (eq 43).[1f,46] Procedures conducive to oxidation of primary, secondary, allylic, aliphatic, and aromatic carbonyl substrates have been developed. A curious limitation of the process is that unhindered terminal double bonds completely inhibit the oxidation reaction.[46b]



(43)

Samarium alkoxides derived from samarium(II) iodide were also found to induce Tischenko-type oxidoreductions of aldehydes to corresponding esters.[46b] The latter process has been more fully developed by Fujiwara and co-workers, who utilized "ethylsamarium iodide" complexes as catalyst precursors for the desired redox reaction (eq 44).[47]



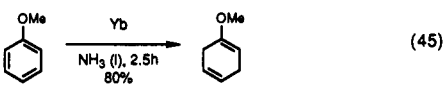
(44)

B. Reduction Reactions

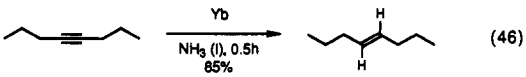
1. Reduction of Unsaturated Systems

a. Alkenes, Alkynes, and Aromatic Systems. Lanthanide metals and various organometallic complexes have been utilized for selective reduction of alkenes, alkynes, and aromatic systems. Although in its infancy, development of catalytic procedures employing lanthanide reagents has a very promising future.

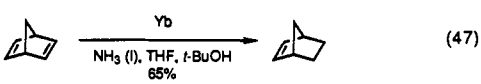
One of the first practical uses of lanthanide reductants was in dissolving metal reductions.[48] Thus ytterbium metal in liquid ammonia provides a useful alternative to the more traditional use of alkali metals in Birch-type reductions (eqs 45–47). Ease of handling and avoidance of strongly basic hydroxides in the workup of reaction mixtures were viewed as distinct advantages in these processes.



(45)



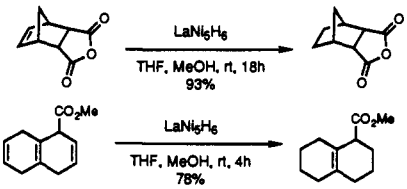
(46)



(47)

Lanthanide intermetallics such as $LaNi_5$ are able to react with up to 3 equiv of hydrogen very rapidly, generating pyrophoric materials capable of delivering hydrogen to a variety of organic substrates.[49] Alkenes and alkynes are efficiently reduced with these stoichiometric reductants, but carboxylic acids, acid chlorides, esters, amides, anhydrides, sulfoxides, sulfones and 1,3-dithianes are unreactive (eqs 48 and 49). Neither amines nor alkyl halides poison the reducing

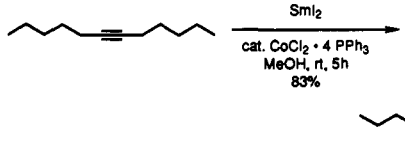
reagents, and the alloys can be repeatedly utilized without decreasing their activity.



(48)

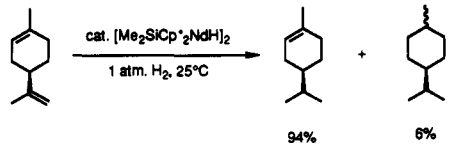
(49)

Samarium(II) iodide (SmI_2) has been developed as a mild, ether-soluble one electron reducing agent with applications in diverse synthetic organic transformations (vide infra).[1] The reagent itself is most conveniently prepared by reaction of samarium metal with CH_2I_2 in THF at ambient temperatures, and under these conditions deep blue solutions of SmI_2 in THF are produced. The limiting solubility of SmI_2 in THF is about 0.1 M. Samarium(II) iodide serves as an effective reductant of alkynes when utilized in the presence of catalytic cobalt complexes (eq 50).[50] Although relatively few examples have been reported, the procedure exhibits promise for selective syntheses of functionalized (*Z*)-alkenes owing to the chemoselective nature of SmI_2.



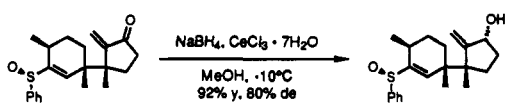
(50)

Application of organometallic lanthanide hydrides to organic synthesis has yet to be fully exploited, but promising procedures for catalytic hydrogenation of alkenes and alkynes have already been reported (eq 51).[51] The ability to "tune" both the metal and the ligands of various lanthanide complexes makes these especially attractive catalysts for hydrogenation of alkenes and alkynes.

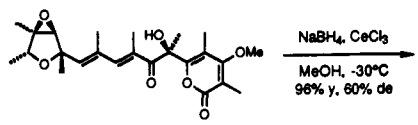


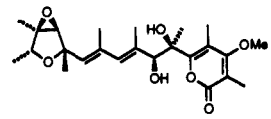
(51)

b. Carbonyl Substrates. Perhaps no procedure involving lanthanide reagents has been so thoroughly embraced by the synthetic organic chemistry community as the Luche protocol for selective reduction of conjugated aldehydes and ketones to allylic alcohols.[52] Literally hundreds of citations to the original work, where the combination of $NaBH_4$ and $CeCl_3$ were first described, attest to the broad generality of this procedure and its value in selective organic chemistry. It would be impossible to describe in detail all of the individual examples employing this reduction system. The following examples serve to demonstrate the general attributes of this protocol, and the superiority of the Luche procedure for 1,2-reduction of enones where other reagents [e.g., DIBAL, LAH, $Zn(BH_4)_2$, or $NaBH_4$ alone] failed to provide the desired products or provided vastly inferior results (eqs 52–55).[53]

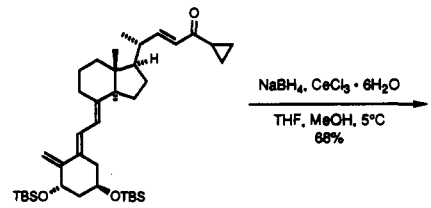


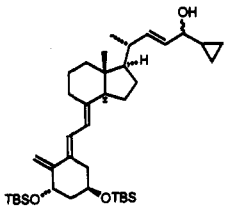
(52)



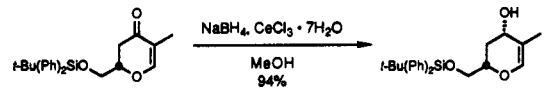


(53)



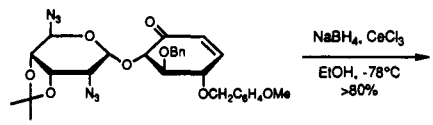


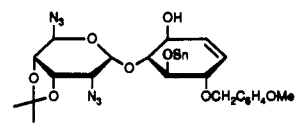
(54)



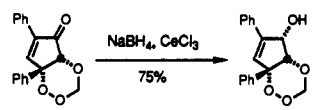
(55)

In addition to providing excellent selectivity for 1,2-carbonyl addition, the Luche procedure exhibits high chemoselectivity for substrates possessing a variety of sensitive functional groups (eqs 56–59).[54]

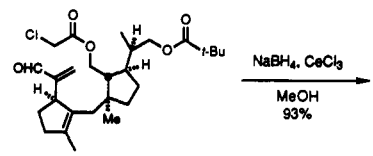


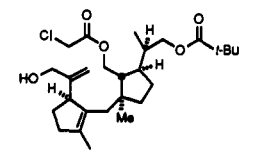


(56)

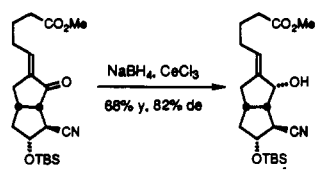


(57)





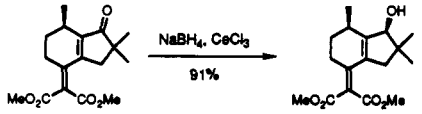
(58)



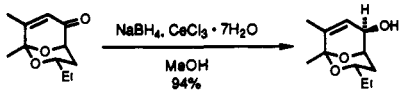
(59)

Diastereoselectivity in reduction of chiral ketones is not a particular strength of the Luche protocol. Nevertheless, in rigid bicyclic systems high stereochemical

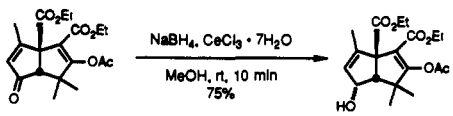
induction can be anticipated, with hydride attack occurring from the less hindered carbonyl face (eqs 60–64).[55] In more flexible six-membered ring systems axial hydride attack, generating the equatorial alcohol, is generally observed (eqs 65–70).[56] Chiral acyclic ketones generally provide little in the way of relative asymmetric induction,[57] although some exceptions have been reported (eq 71).[58]



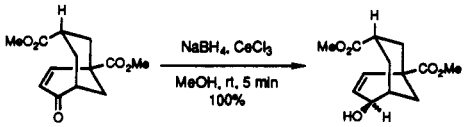
(60)



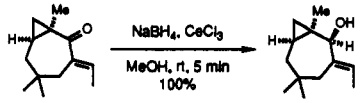
(61)



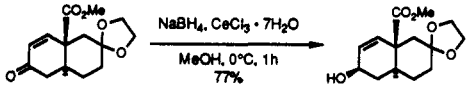
(62)



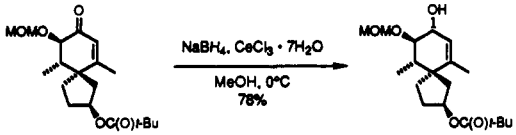
(63)



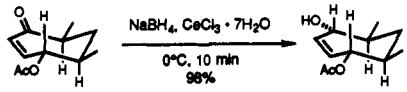
(64)



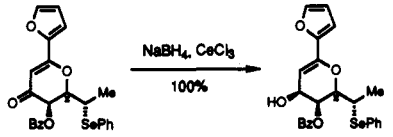
(65)



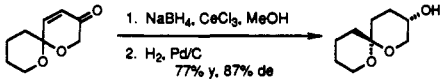
(66)



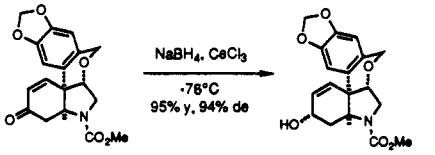
(67)



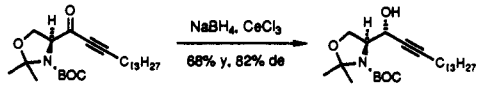
(68)



(69)

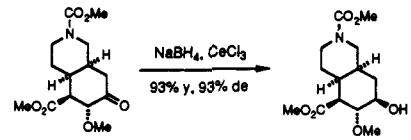


(70)

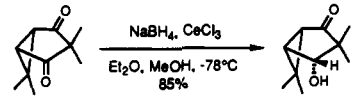


(71)

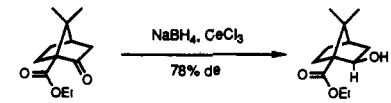
Even with saturated ketones the Luche procedure often provides advantages over other reduction protocols in terms of overall yields and/or diastereoselectivities (eqs 72–75).[59] Use of $NaBH_4/CeCl_3$ has found particularly extensive utility in reduction of α,β-epoxy cyclohexanones, in all reported cases of which >96% diastereoselectivities have been achieved (eq 76).[60]



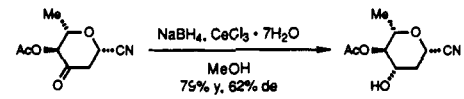
(72)



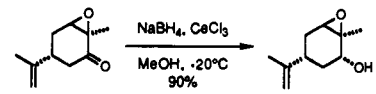
(73)



(74)

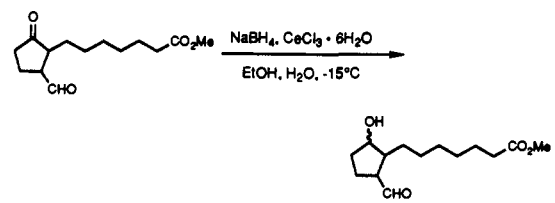


(75)

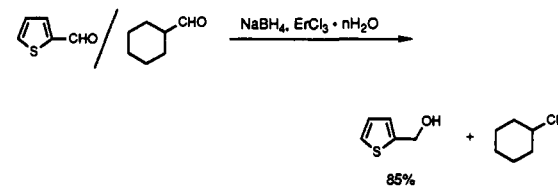


(76)

Lanthanide salts are known to serve as effective Lewis acids for acetalization and related reactions of aldehydes and ketones (vide infra). Consequently, isolated alkanals undergo in situ transformation to acetals under Luche conditions, preventing their reduction to alcohols. On the other hand, ketones and conjugated aldehydes are less readily acetalized and are therefore reduced under Luche conditions.[61] This leads to considerable chemoselectivity in reduction of bifunctional molecules. For example, reduction of ketones can be accomplished in the presence of aldehydes, and conjugated or aromatic aldehydes can be reduced in preference to isolated alkanals (eqs 77 and 78).

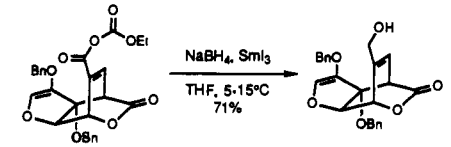


(77)

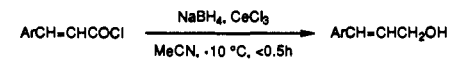


(78)

Under appropriate reaction conditions, the combination of lanthanide salts and hydride reducing agents is useful for selective reduction of other carbonyl functional groups, including anhydrides (eq 79)[62] and carboxylic acid chlorides (eq 80).[63]

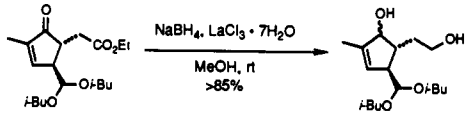


(79)

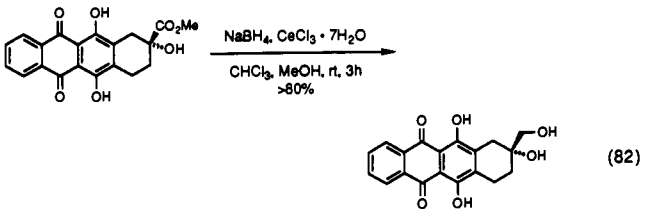


(80)

Sodium borohydride reduction of carboxylic acid esters is normally an extremely slow process. However, addition of $CeCl_3$ or other lanthanide salts has proven effective for dramatically facilitating this transformation (eqs 81 and 82).[64] In eq 82, the substrate is un-



(81)

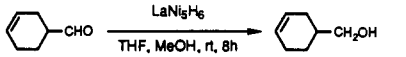


(82)

doubtedly exhaustively reduced, with reoxidation to the anthraquinone subunit occurring by simple air oxidation upon workup.

Lithium aluminum hydride has also been utilized in conjunction with various lanthanide salts for selective 1,2-reduction of a variety of conjugated carbonyl substrates.[65] Although in general its properties mimic those of $NaBH_4/CeCl_3$, it appears to be somewhat less selective for 1,2-addition to unsaturated ketones than the original Luche procedure. For example, 2-cyclopenten-1-one provides a 64:36 mixture of allylic alcohol to saturated alcohol with $LiAlH_4/CeCl_3$, but the Luche protocol provides >98% of the allylic alcohol. Unsaturated carboxylic acids and esters are reduced to allylic alcohols by $LiAlH_4/CeCl_3$, although again chemoselectivity is low. In most instances saturated alcohols appear as significant byproducts of the reactions. Perhaps the best substrates for the $LiAlH_4/CeCl_3$ protocol are unsaturated aldehydes. In a limited study (cinnamaldehyde and citral), exclusive formation of the allylic alcohol was observed.

Still other lanthanide reagents have been employed in selective reduction reactions. For example, the lanthanide intermetallic hydrides mentioned above effectively reduce isolated aldehydes and ketones to alcohols (eq 83).[49] Isolated olefins can be reduced by these

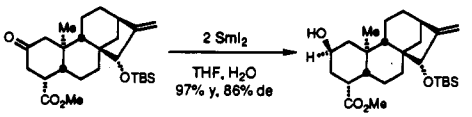


(83)

reagents, however as illustrated selective reduction of aldehydes in the presence of such functional groups is quite feasible. Although some efforts have been made to develop enantioselective processes based on related chemistry, to date these efforts have not been enormously successful.[66]

Samarium(II) iodide also provides considerable chemoselectivity in reactions with various carbonyl substrates. Carboxylic acids and esters are not reduced by SmI_2, but aldehydes react very rapidly and efficiently to provide primary alcohols. Because ketones react much more slowly, selective reduction of aldehydes in the presence of ketones is readily achieved.[67]

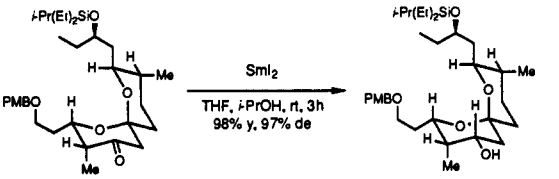
Stereochemical control in the reaction of SmI_2 with chiral aldehydes and ketones has been studied to some degree, although diastereoselectivities achieved to date in simple systems are not particularly high.[50,68] A stereoselective carbonyl reduction by SmI_2 was utilized in Corey's synthesis of (±)-atractyligenin (eq 84).[69]



(84)

Asymmetric versions of the SmI_2 reduction reaction have been reported, but at this point these are somewhat limited in scope.[70] Asymmetric induction is derived from optically active proton sources (e.g., quinidine) utilized in the reaction.

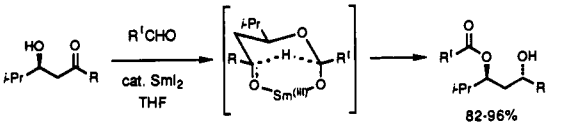
Various lanthanide alkoxides possess demonstrable catalytic activities in Meerwein–Ponndorf–Verley-type reduction reactions.[46,71] These methods are tolerant of a variety of functional groups, including esters and nitro groups. Although requisite alkoxides can be generated in a variety of ways, one of the more convenient is to add a catalytic amount of SmI_2 to the reaction mixture. The requisite samarium alkoxide is thus generated in situ. The latter procedure has been utilized in one step of the synthesis of the macrolide antibiotic cytovaricin (eq 85).[72] The samarium-catalyzed version of the



(85)

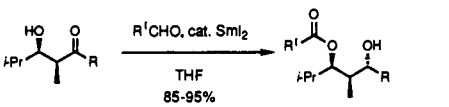
Meerwein–Ponndorf–Verley reduction succeeded where many other reductants failed, thus solving a significant problem in the synthesis of this complex molecule.

As mentioned previously, lanthanides are also effective catalysts for Tischenko-type redox reactions of aldehydes.[46b,47] An ingenious, very elegant application of this process in selective organic synthesis has been reported by Evans and Hoveyda.[73] Thus, an intramolecular version of the reaction allows stereoselective generation of anti 1,3-diol monoesters from β-hydroxy ketones (eq 86). The intramolecularity of the reaction

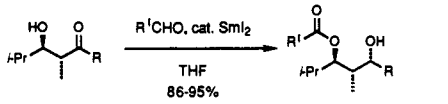


(86)

facilitates the derivation of asymmetric induction from the distal hydroxy stereocenter, and thus both syn and anti α-methyl β-hydroxy ketones provide the same sense of relative asymmetric induction from this remote center (eqs 87 and 88).

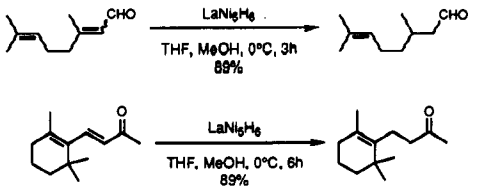


(87)

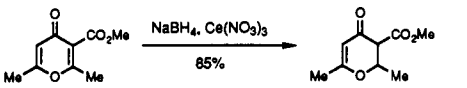


(88)

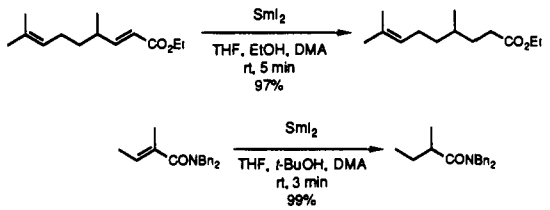
c. Conjugate Reduction. Lanthanide intermetallic hydrides are highly selective reagents for conjugate reduction of α,β-unsaturated aldehydes and ketones.[49] Both isolated olefins and isolated aldehydes and ketones can also be effectively reduced by these reagents (vide supra); however, simple conjugate reduction is clearly the most rapid process among these (eqs 89 and 90).



Although known more for its ability to reduce enones to allylic alcohols, in selected instances the combination of $NaBH_4$ with cerium(III) salts provides the conjugate addition product as well.[74] This protocol has been utilized for substrates where complex metal hydrides alone fail to provide the desired product (eq 91), but appears limited to highly electron deficient enones.

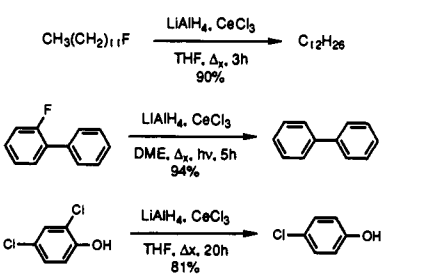


α,β-Unsaturated carboxylic acids, esters, and amides undergo efficient reduction to saturated derivatives upon treatment with SmI_2 in the presence of a proton source (usually methanol, ethanol, or *tert*-butyl alcohol).[67] An optimized protocol for this conversion involves use of *N,N*-dimethylacetamide (DMA) or *N,N*-dimethylformamide (DMF) as a cosolvent with THF.[50] Under these conditions reduction is extremely rapid, and products are isolated in virtually quantitative yields (eqs 92 and 93). Conjugated ketones provide mixtures of 1,2- and 1,4-reduction under these conditions, and conjugated aldehydes are polymerized by SmI_2.[67]



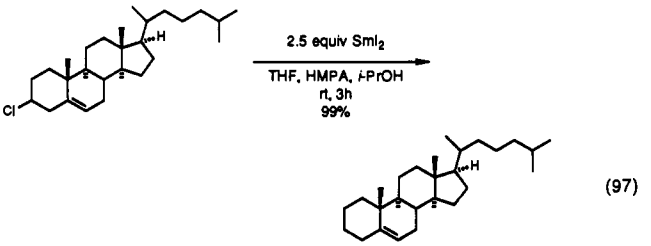
2. Organic Halides and Related Substrates

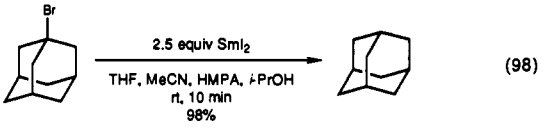
Several different lanthanide-based systems have been developed for reduction of organic halides and related substrates. For example, activated cerium (prepared by treatment of cerium metal with $HgCl_2$ or I_2) is a very powerful reducing agent, capable of reducing even alkyl fluorides.[49c] Yields in these processes are somewhat low, however, because of competitive reductive dimerization. Utilization of $LiAlH_4$ in the presence of $CeCl_3$ appears to solve this problem.[49c,75] Alkyl and aryl halides, including fluorides, are readily reduced by $LiAlH_4/CeCl_3$, providing corresponding hydrocarbons in high yields (eqs 94–96). The reaction appears to proceed via

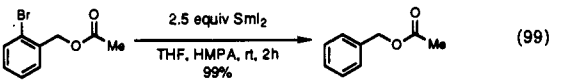


radical intermediates, because use of $LiAlD_4$ does not result in the incorporation of deuterium in the final product.

Alkyl halides are readily reduced to hydrocarbons by SmI_2 in the presence of a proton source such as water, methanol, *tert*-butyl alcohol, or 2-propanol.[50,67,76] In terms of the halide, ease of reduction follows the expected order (I > Br > Cl). The effectiveness of reduction is highly solvent dependent. When performed in THF–HMPA solvent, the method can be utilized to reduce primary, secondary, and tertiary alkyl halides (eqs 97 and 98), as well as aryl and alkenyl halides (eq 99).[50,76] In THF alone, only primary alkyl iodides and bromides are effectively reduced.[67] Primary organic

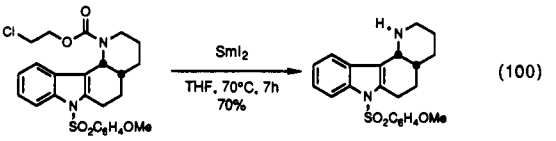




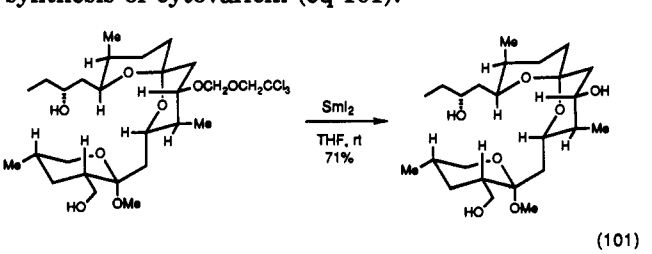


tosylates are reduced to hydrocarbons under the same reaction conditions. Presumably, tosylates are converted to corresponding iodides by SmI_2 under the reaction conditions, and the iodides are subsequently reduced to the observed products.[67,77] Reduction of allylic and benzylic halides results in high yields of Wurtz coupled dimeric products.

Magnus and co-workers have utilized a SmI_2-promoted halide reduction to initiate deprotection of a 2-chloroethyl carbamate to the corresponding amine (eq 100).[78] Several other attempted reduction procedures ($Zn/AcOH$, $CrCl_2/HCl$, $Bu_3SnH/AIBN$) failed to provide more than a few percent of the desired product.

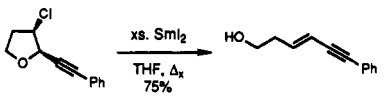


Other deprotection schemes initiated by SmI_2-promoted reduction of halides have been reported as well. For example, reductive cleavage of a (2,2,2-trichloroethoxy)methoxy ether by SmI_2 has been used by Evans and co-workers to release a protected alcohol in the total synthesis of cytovaricin (eq 101).[72]



Some of the difficulties incurred when sodium is utilized as reductant for the ring scission of 3-halotetrahydrofurans have been solved by use of SmI_2.[79]

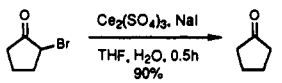
Sodium often provides mixtures of stereoisomeric olefins in this transformation, and overreduction is also a problem in many cases. Reactions employing SmI_2 have proven to be much cleaner (eq 102). Isomer purities are typically >97%, and there is <3% overreduction. Curiously, 3-halotetrahydropyrans are best reduced by sodium, as SmI_2 provides mixtures of stereoisomers.



(102)

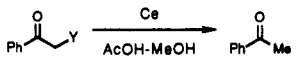
3. α-Heterosubstituted Carbonyl and Related Substrates

α-Haloketones are readily reduced to unsubstituted ketones by treatment with cerium(III) sulfate in the presence of NaI. The reaction is performed in aqueous media and is noted as a convenient method for selective dehalogenation.[60] Presumably, a cerium enolate is generated and rapidly protonated under these reaction conditions (eq 103).



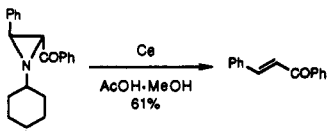
(103)

Cerium metal in acetic acid/methanol has also been utilized for reduction of α-heterosubstituted ketones (eq 104).[49c] Curiously, in one case an aziridinyl ketone leads not to the expected β-amino ketone, but rather to an α,β-unsaturated carbonyl product (eq 105). Clearly further synthetic and mechanistic work is required to outline the full scope and ramifications of this chemistry.



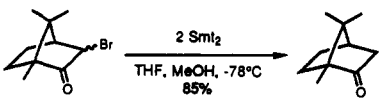
(104)

Y	% yield
Br	98
$S(O)CH_3$	85
SO_2CH_3	70

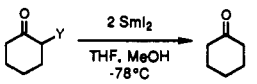


(105)

A wide range of α-heterosubstituted ketones is rapidly reduced under extremely mild conditions by SmI_2, providing unsubstituted ketones (eqs 106 and 107).[81]



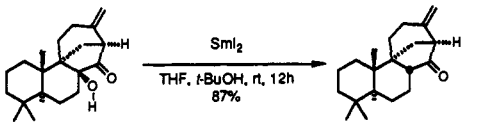
(106)



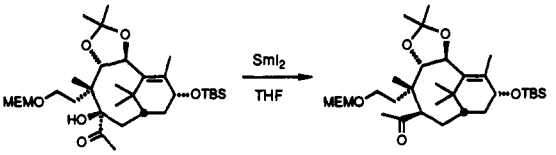
(107)

Y	% isolated yield
Cl	100
SPh	76
S(O)Ph	64
SO_2Ph	88

The reaction is highly selective and can be performed in the presence of isolated iodides as well as isolated ketones.[81] Even hydroxyl groups are reductively cleaved with SmI_2 under these conditions, providing a useful entry to unsubstituted ketones (eqs 108 and 109).[82]

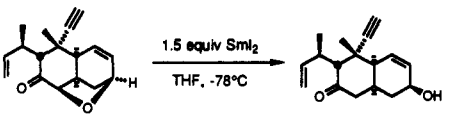


(108)



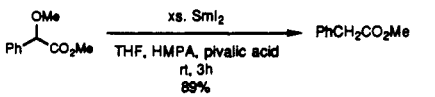
(109)

Hopkins and Pratt have utilized the protocol for α-alkoxy cleavage in synthetic studies en route to betaenone B (eq 110).[83]



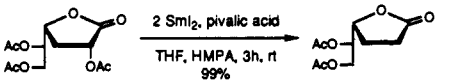
(110)

α-Halo esters are reduced under the same reaction conditions utilized for α-heterosubstituted ketones.[81a] However, α-oxygenated esters are virtually inert to the reaction conditions outlined for the ketone counterparts mentioned above. Fortunately, when HMPA is added as a cosolvent to the reaction mixture clean reduction of these systems is accomplished (eq 111).[50,84] The

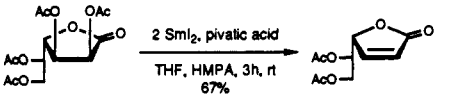


(111)

reaction has been utilized for the preparation of deoxy sugars and chiral butenolides derived from carbohydrate precursors (eqs 112 and 113).[50]

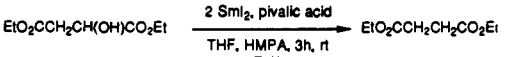


(112)

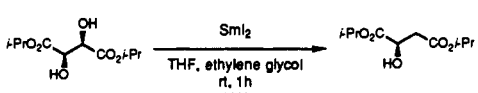


(113)

Even α-hydroxy esters are reduced to unsubstituted esters via a modified procedure (eq 114).[50,84] A minor adjustment in the protocol (utilizing ethylene glycol instead of HMPA) permits selective mono dehydroxylation of (*R,R*)-diisopropyl tartrate, with generation of (*R*)-isopropyl malate (eq 115).[50,84]



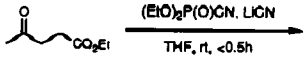
(114)

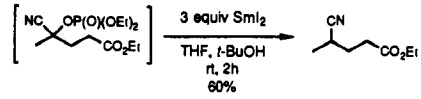


(115)

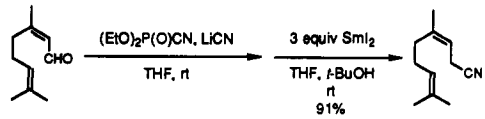
A useful reaction sequence for transformation of carbonyl compounds to one carbon homologated nitriles has evolved from the ability of SmI_2 to deoxygenate cyanohydrin *O,O'*-diethyl phosphates.[85] A variety of cyanophosphate substrates (generated by reaction of diethyl phosphorocyanidate with ketones or aldehydes) are readily reduced by SmI_2 in THF, providing deoxy-

genated nitriles (eqs 116 and 117). The procedure is





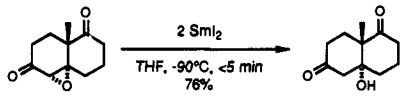
(116)



(117)

tolerant of a number of functional groups, including alcohols, esters, amides, sulfonamides, acetals, alkenes, alkynes, and amines. Furthermore, it provides distinct advantages over other previously developed procedures for similar one-carbon homologations.

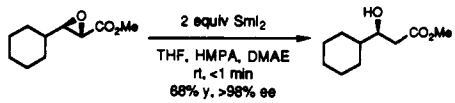
Reduction of α,β-epoxy ketones and α,β-epoxy esters has been utilized as a convenient route to β-hydroxy carbonyl compounds.[50,86] Reduction of epoxy ketone substrates proceeds in a straightforward fashion in THF/MeOH at −90 °C (eq 118).[86a] Many such sub-



(118)

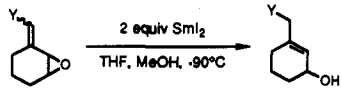
strates can be derived from enantiomerically enriched epoxy alcohols synthesized by Sharpless asymmetric epoxidation reactions. The procedure thus provides direct access to a variety of chiral, nonracemic α-unsubstituted β-hydroxy ketones difficult to acquire by more traditional procedures (e.g., aldol condensations). In particular, tertiary alcohol aldol products should be accessible in high enantiomeric excess by the reductive epoxide ring opening process.

α,β-Epoxy esters require more vigorous conditions for efficient reduction. Reactions on a variety of these substrates have been carried out at room temperature in THF/HMPA utilizing (*N,N*-dimethylamino)ethanol (DMAE) as a proton source (eq 119).[50,86b]



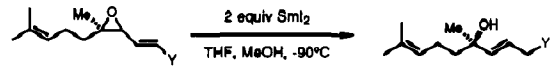
(119)

Functionalized vinyloxiranes undergo facile reductive epoxide ring opening with SmI_2 in THF in the presence of a proton source, providing (*E*)-allylic alcohols.[50,86b,87] These reactions are extremely fast, taking place within minutes at −90 °C. Ketones, esters, nitriles, and other functional groups survive the reaction conditions intact, and the Sharpless asymmetric epoxidation reaction can again be utilized to gain entry to chiral, nonracemic substrates for the reactions (eqs 120 and 121). Higher



(120)

Y	% isolated yield
$-CO_2Et$	68
$-CH{=}CHCO_2Et$	65
-CN	71
-COMe	69



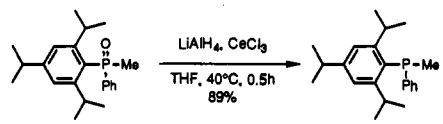
(121)

Y	% isolated yield
COSEt	80
SO_2Ph	82
$P(O)(OEt)_2$	84
H	69
Me	42
SPh	54

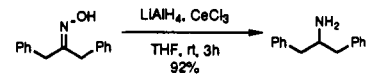
temperatures (room temperature) are required for electron-rich vinyloxiranes (Y = H, Me, SPh in eq 121), and byproducts resulting from simple deoxygenation (i.e., conjugated dienes) are detected in substantial quantities (9–32%) in these cases. Significantly, a single regioisomeric and diastereomeric allylic alcohol is generated in nearly every example studied to date. Nearly neutral conditions are maintained during the reaction, inhibiting equilibration to more stable (conjugated) olefinic isomers. The method thus provides a useful entry to highly functionalized, enantiomerically pure allylic alcohols.

4. Deoxygenation Reactions

The combination of $LiAlH_4$ and $CeCl_3$ has been mentioned previously as a powerful reducing system for organic halides (vide supra). This tandem set of reagents has also been utilized for deoxygenation of phosphine oxides (the process is unfortunately not stereospecific at phosphorus), and for reductive deoxygenation of oximes to provide the corresponding amines (eqs 122 and 123).[49c,88]

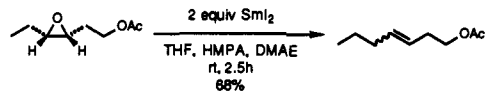


(122)



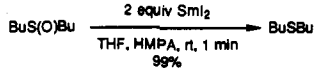
(123)

Samarium(II) iodide possesses a broad reduction spectrum, and it too has been utilized for deoxygenation of diverse functional groups. For example, epoxides are readily converted to olefins by this reductive process (eq 124).[67,89] Unfortunately, the reaction is not stereospecific, and a mixture of diastereomeric olefins is therefore isolated.



(124)

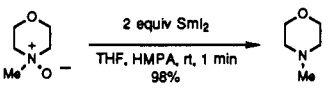
Sulfoxides are also readily reduced to sulfides by SmI_2 (eq 125).[50,67,90] This process is rapid enough to be carried out efficiently in the presence of isolated ketones, with no reduction of the latter. Sulfones can also be reduced to the corresponding sulfides by SmI_2, although only aryl sulfones provide synthetically useful yields (eq 126).[50,90]



(125)

$$PhSO_2Ph \xrightarrow[\text{THF, HMPA, rt, 10 min}]{\text{2 equiv } SmI_2} PhSPh \quad (126)$$
99%

Samarium(II) iodide has also proven to be an effective reagent for conversion of aliphatic and aromatic amine *N*-oxides to corresponding amines (eq 127).[50,90,91] Along the same lines, hydroxylamines are also deoxygenated by SmI_2, although little is known of the scope of this latter process.[92]



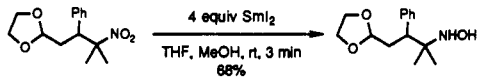
(127)

Although phosphine oxides are essentially inert to SmI_2 in THF alone,[67] addition of HMPA facilitates their reduction to phosphines (eq 128).[50,90] Interestingly, triaryl arsine oxides are reduced to triaryl arsines without addition of HMPA.[91]

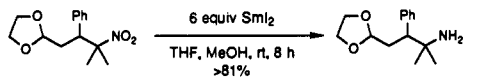
$$Ph_3PO \xrightarrow[\text{THF, HMPA, 65°C, 16h}]{\text{2 equiv } SmI_2} Ph_3P \quad (128)$$
75%

5. Reduction of Nitrogen-Based Functional Groups

Deoxygenation of amine oxides and reductive deoxygenation of oximes by various lanthanide reagents have been described previously (vide supra). Lanthanide reagents have also been utilized extensively in other reductions of nitrogen-based functional groups. For example, nitro compounds are selectively reduced by SmI_2 to either hydroxylamines or amines, depending upon the reaction conditions employed.[91,93] Thus, treatment of nitroalkanes with 4 equiv of SmI_2 for short periods of time leads to isolation of hydroxylamines, whereas use of 6 equiv of SmI_2 for longer reaction times results in the generation of corresponding amines (eqs 129 and 130). Because nitriles are not readily reduced



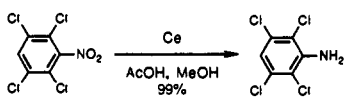
(129)



(130)

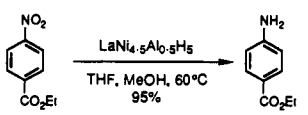
by SmI_2, the reaction is quite selective for reduction of nitro groups in the presence of cyano groups.[93a]

Nitro groups are readily reduced to amines by cerium metal in AcOH/MeOH.[49c] The scope of this particular reaction has yet to be delineated, but the initial report appears promising (eq 131).



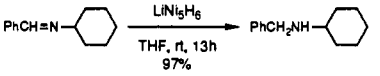
(131)

Use of lanthanide intermetallic reagents represents yet another means to reduce nitro groups to the corresponding amines.[49a,b] Although little is known of the chemoselectivity of this process, esters are tolerated in such transformations (eq 132).



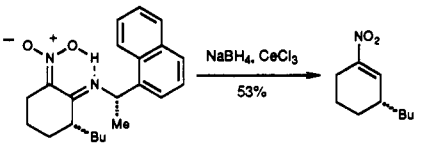
(132)

Lanthanide intermetallics have also been utilized for the reduction of imines to amines.[49a,b] Reaction conditions are very mild, and yields of isolated products are virtually quantitative in all cases examined to date (eq 133).



(133)

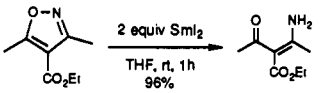
The Luche protocol ($NaBH_4/CeCl_3$) has been developed as a mild and general method for one-pot conversion of α-nitro imines to nitroalkenes.[94] Yields typically exceed 75% for this process, which can be utilized to generate chiral, nonracemic products from enantiomerically enriched substrates with no loss of stereochemistry (eq 134).



(134)

6. Miscellaneous Reductions

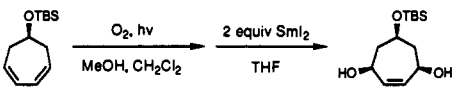
The relatively weak nitrogen–oxygen bond in isoxazoles renders them susceptible to reduction by SmI_2. Products resulting from this reduction are the corresponding enamino ketones (eq 135).[95] In competitive



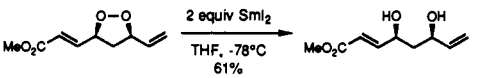
(135)

reactions, reduction of aldehydes is accomplished in the presence of isoxazoles, whereas halides are probably reduced somewhat more slowly than these heterocycles.

Samarium(II) iodide has been utilized for the selective reduction of cyclic peroxy compounds to corresponding diols.[96] Substrates are generally prepared by singlet oxygen addition to conjugated dienes, and the overall process represents an efficient, stereoselective route to diols (eqs 136 and 137).

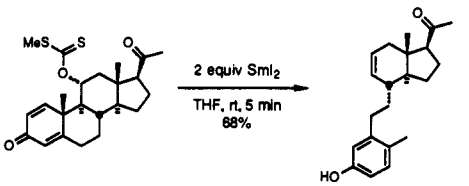


(136)



(137)

Samarium diiodide has also been employed in one case to effect a reductive cleavage reaction (eq 138).[78]

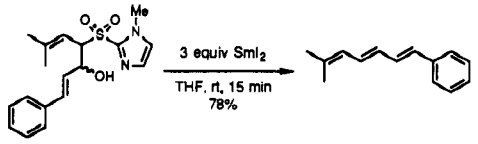


(138)

This particular reaction could not be achieved in satisfactory yields with Bu_3SnH/AIBN nor with Li/NH_3. The reaction was originally proposed to be initiated by reduction of the xanthate ester functional group. Isolated xanthate esters were later shown to be virtually inert to SmI_2.[97] Consequently, initial electron transfer must occur to the conjugated dienone system, with subsequent reductive cleavage from the radical anion generated therein.

Reductive elimination of β-hydroxy imidazolyl sulfones has been developed by Kende and Mendoza,

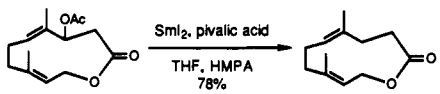
providing an improved variation of the Julia olefin synthesis (eq 139).[98] Although in most cases mixtures



(139)

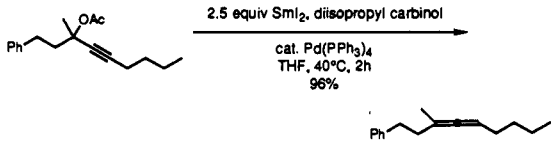
of diastereomeric olefins are generated in this process, in a head-to-head comparison with Na(Hg) as a reducing reagent SmI_2 proved to be the superior reagent in terms of overall conversion to product.

In a rather special type of reduction process, allylic acetates are reduced to alkenes by SmI_2.[50] Procedures with and without Pd(0) catalysis have been reported.[99] Reactions catalyzed by Pd(0) presumably occur via a π-allylpalladium intermediate, which is reductively transmetalated to an allylsamarium species. The latter is protonated to provide the alkene. Generally, mixtures of olefinic regio- and stereoisomers are generated in this process. Curiously, in the total synthesis of ferrulactone I utilizing the SmI_2 promoted reduction of an allylic acetate as the key step, no olefinic regio- or stereoisomers were observed (eq 140). This particular conversion was carried out in the absence of Pd(0).



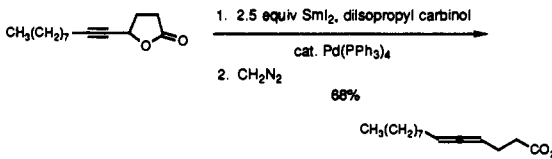
(140)

Propargyl acetates undergo the same type of conversion, providing a mild and convenient entry to allenes.[100] Tertiary propargylic acetates lead exclusively to allenes (eq 141).



(141)

The ratio of allene to alkyne product derived from secondary propargylic acetates is very dependent on steric bulk of the protonating agent, with highly hindered alcohols required for selective generation of allenes (eq 142). Primary propargylic acetates provide mixtures of allene and alkyne in which the alkyne predominates, even when sterically encumbered alcohols are employed as proton sources.



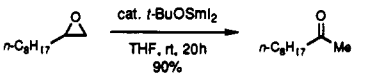
(142)

C. Lewis Acid Catalyzed Functional Group Transformations

Lanthanide ions are considered "hard" Lewis acids and form complexes with substantial ionic character because of poor overlap of the contracted 4f orbitals. Consequently, lanthanides preferentially complex to hard bases such as fluoride ion and oxygen donor ligands. The Lewis acidity of lanthanide complexes has been exploited extensively in their use as shift reagents for nuclear magnetic resonance studies and in promotion of Lewis acid catalyzed functional group transformations outlined below.

1. Rearrangements

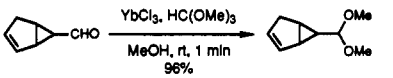
Acid-catalyzed rearrangements of terminal epoxides can provide either aldehyde or ketone products, with the former typically predominating. Mildly Lewis acidic lanthanide catalysts have been utilized to provide the complementary ketone products of such rearrangements.[101] Thus, treatment of a variety of terminal epoxides with t-$BuOSmI_2$ results in a highly selective net rearrangement process from which the desired ketones are isolated in excellent yields (eq 143). The process is somewhat limited in scope, as 2,2-disubstituted epoxides do not react, and branched monosubstituted olefins react slowly under the reaction conditions developed. Although they react very slowly, symmetrical 1,2-disubstituted epoxides also rearrange to the desired ketones.



(143)

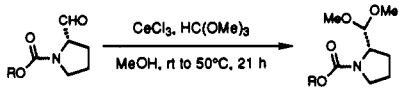
2. Acetalizations and Deacetalizations

Acetalization remains one of the most effective means for protecting aldehydes against undesired reactions with nucleophiles. Because acetalization is usually utilized only as a means to protect a carbonyl, the demand for high yields and high chemoselectivity is at a premium. Lanthanide salts have proven to be extraordinarily effective Lewis acids in acetalization reactions, providing essentially quantitative yields of desired acetals. Processes are generally carried out with minimal side reactions.[102] As one example, conversion of bicyclo[3.1.0]hex-2-ene-6-carbaldehyde to its dimethyl acetal was accomplished in virtually quantitative yield when $YbCl_3$ was utilized as the Lewis acid, whereas rearrangement products were obtained when H_2SO_4 or TsOH were utilized (eq 144).



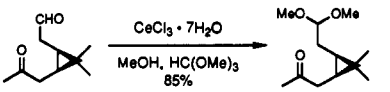
(144)

Use of lanthanide Lewis acids is also beneficial in the case of chiral aldehyde substrates which are easily enolized and therefore epimerized. In such instances, no racemization is seen (eq 145).[103]

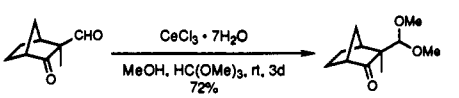


(145)

Numerous examples attest to the ability of lanthanide Lewis acids to chemoselectively acetalize aldehydes in the presence of ketones (eqs 146 and 147).[104] Again,



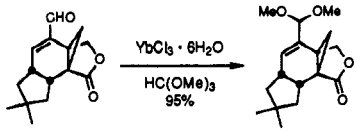
(146)



(147)

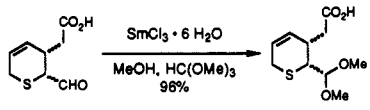
no Lewis acid promoted rearrangements are seen in these systems, and even very highly hindered aldehydes are protected reasonably efficiently. These reactions are also applicable to substrates possessing *tert*-bu-

tyldimethylsilyl protecting groups and esters (eq 148).[105]



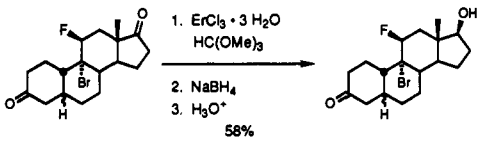
(148)

Carboxylic acids may also be present in substrates without undergoing esterification under the reaction conditions (eq 149).[106]

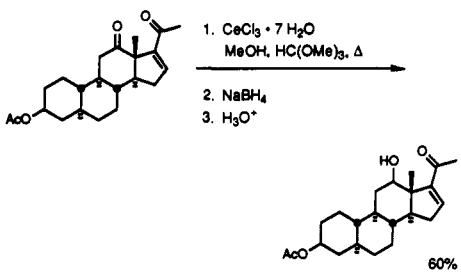


(149)

In some instances, selective protection of one ketone can be accomplished in the presence of another. For example, the well-known trend of rapid ketal protection of 3-ketosteroids in the presence of a 17-keto functional group is observed (eq 150),[107] and an acyclic enone carbonyl can also be protected to some degree in the presence of a hindered cyclohexanone carbonyl (eq 151).[108]

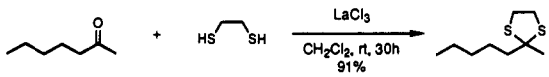


(150)



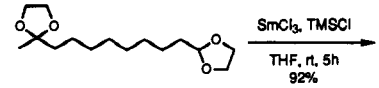
(151)

Thioacetals are also readily generated through the agency of lanthanide salt catalysis.[109] Although the procedure works well for simple alkyl aldehydes and ketones, more highly hindered systems (e.g., camphor) and aryl ketones are resistant to attack by dithiols (eq 152).

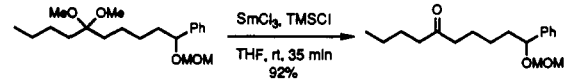


(152)

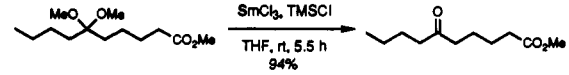
Lanthanide salts have been utilized in conjunction with chlorotrimethylsilane (TMSCl), for selective cleavage of ketone acetals.[110] This protocol provides an alternative to other nonaqueous procedures (e.g., TMSI, Me_2BBr, PI_3, etc.) for mild deprotection of acetals, with certain advantages inherent to the procedure. For example dimethyl acetals, diethyl acetals, 1,3-dioxanes, and 1,3-dioxolanes are all readily cleaved by the lanthanide-promoted procedure, but cyclic acetals are often only difficultly removed by other protocols. Because ketone acetals are more efficiently deprotected under the reaction conditions than aldehyde acetals, chemoselective reactions in the presence of aldehyde acetals is possible (eq 153). Other acid labile protecting groups (e.g., *tert*-butyldimethylsilyl ethers and methoxymethyl ethers) are not affected by reaction conditions required for removal of acetals (eq 154), and benzyl ethers and esters (which are known to be cleaved by TMSI and Me_2BBr) are also stable (eq 155).



(153)



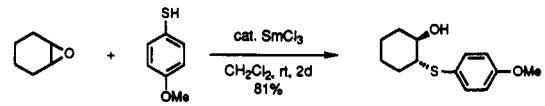
(154)



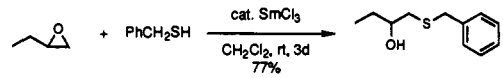
(155)

3. *Miscellaneous Lewis Acid Promoted Functional Group Transformations*

Anhydrous lanthanide salts catalyze the regio- and stereoselective ring opening of cyclohexene oxide (eq 156) and terminal alkyl epoxides (eq 157) by thiol nucleophiles.[111] The procedure has advantages over those employing other Lewis acids [e.g., $AlCl_3$, $AlEt_3$, $ZnCl_2$, $Ti(O\text{-}i\text{-}Pr)_4$] in that the latter generally require longer reaction times. Aryl-substituted terminal epoxides provide high yields of thiol-substituted products; however, regioselectivity is much lower than that observed with the alkyl-substituted counterparts.



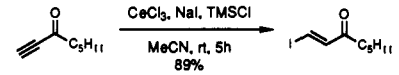
(156)



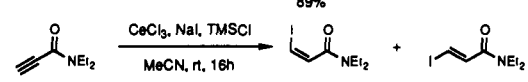
(157)

D. Miscellaneous Functional Group Transformations

A net conjugate addition of HX to alkynyl ketones and alkynylamides has been reported which relies on the combination of $CeCl_3$ and TMSCl to promote the process.[112] Alkynyl ketones provide (*E*) isomers exclusively (eq 158), whereas alkynyl amides provide mixtures of diastereomers in which the (*Z*) isomer predominates to the extent of 11:1 (eq 159). No rationale has been offered to explain these interesting results.

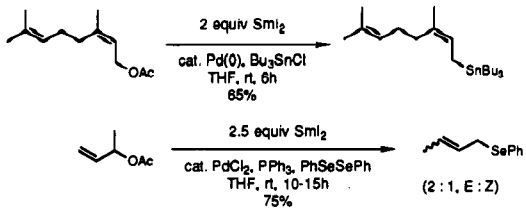


(158)

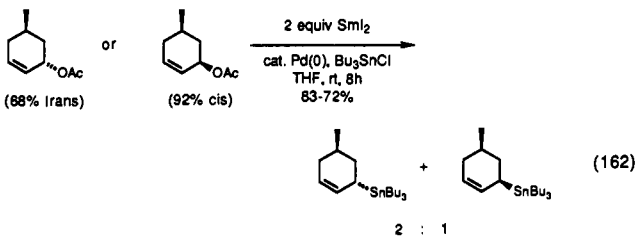


(159)

Allylic acetates are converted to allylstannanes or allyl phenyl selenides through a reductive coupling process promoted by SmI_2 and catalyzed by Pd(0).[113] Reaction of allylic acetates with SmI_2/Pd(0) in the presence of trialkyltin chlorides produces allylstannanes under quite mild conditions (eq 160). Similarly, with diphenyl diselenide as the electrophile in an analogous process, allyl phenyl selenides are generated (eq 161). These electrophiles react at the least substituted terminus of the presumed allylsamarium species, and stereospecific substitution results when trisubstituted allylic acetates are utilized as substrates for the reaction. Unfortu-

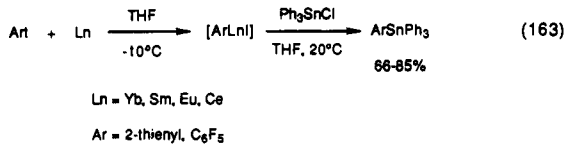


nately, these reactions are apparently not stereospecific with regard to facial addition to the allylic system. Stereodefined *cis*- and *trans*-5-methylcyclohexenyl acetates thus react via a common anionic intermediate, providing the same stereoisomeric mixture of products within experimental error (eq 162).[113a] Isolated esters

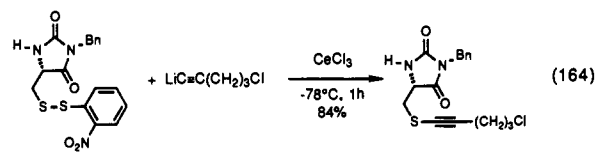


and organic halides are tolerated in allylic acetate substrates, permitting construction of functionalized allylic derivatives.

Direct coupling of various aryllanthanides with chlorotriphenylstannane has also been reported as a convenient route to arylstannanes (eq 163).[114]



Organocerium reagents have proven effective in substitution reactions on disulfides. Corey and Mehrotra utilized an alkynylcerium reagent to cleave a chiral, nonracemic disulfide substrate en route to (+)-biotin (eq 164).[115]



III. Carbon–Carbon Bond Forming Reactions

A. Substitution Reactions

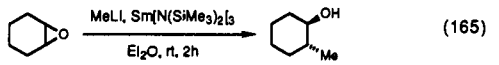
1. Wurtz Coupling, Organic Halide Substitution, and Related Processes

Cross-coupling of organolanthanides with organic halides has not been developed into a particularly useful process. Although several reports of such transformations catalyzed by cobalt, nickel, palladium, and copper reagents have been reported,[116] by and large these do not compete effectively with other currently available methods. Use of benzyldicyclopentadienylsamarium in cross-coupling reactions with benzylic halides has also been reported, but at present the scope of this transformation is rather narrow.[117]

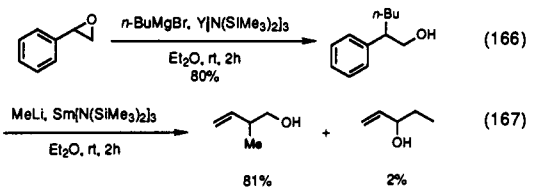
Samarium(II) iodide promoted Wurtz-type coupling reactions of allylic and benzylic halides can be carried out effectively, but again these processes appear to have limited synthetic utility.[1d,h,67,77] Although yields are generally high in these cases, regioselectivity in the allylic coupling reaction is low. Alkyl halides, alkenyl halides, and aryl halides undergo simple reduction under conditions where allylic and benzylic halides Wurtz couple (vide supra).

2. Oxiranes

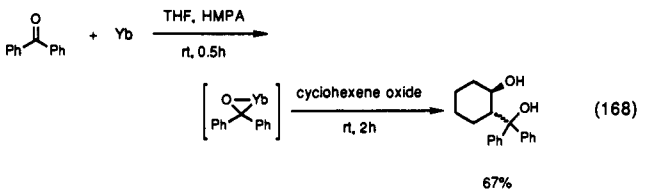
Lanthanide "ate" complexes react very efficiently with a wide range of epoxides, providing excellent yields of resultant alcohols.[118] Essentially quantitative yields of *trans*-2-methylcyclohexanol are obtained upon addition of cyclohexene oxide to a reagent derived from methyllithium and $Sm[N(SiMe_3)_2]_3$ or $Y[N(SiMe_3)_2]_3$ (eq 165). 1,2-Epoxybutane reacts with nucleophilic ring



opening at the least hindered position, providing 3-pentanol in 74% yield. Styrene oxide and butadiene monoepoxide are also alkylated in S_N2 processes. In the latter case the lanthanide "ate" complexes complement the S_N2' reactivity patterns generally observed in reactions of unsaturated epoxides with organocopper reagents (eqs 166 and 167).



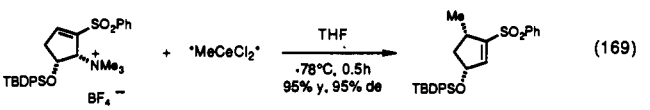
Organoytterbium diaryl ketone dianions react with epoxides, providing 1,3-diols.[119] The reactive organometallics are prepared by treatment of diaryl ketones with activated ytterbium. Addition of epoxides to the reaction mixture leads directly to the observed diols (eq 168). Diaryl carbinols and regioisomeric 1,3-diols are



significant side products of the reaction, detracting from the value of the method. In addition, the process is limited in scope because only diaryl ketones can be utilized as ultimate precursors to the nucleophilic intermediates in these transformations.

3. Miscellaneous Electrophiles

Fuchs and Hutchinson have utilized organocerium reagents for the S_N2' methylation of an allylic ammonium ion.[120] The reaction is competitive with analogous organocuprate reactions in terms of both yield and diastereoselectivity, and superior to methyllithium in the only substrate examined (eq 169). The syn stereochemistry resulting from the nucleophilic substitution is notable in these reactions. Organocuprates provide



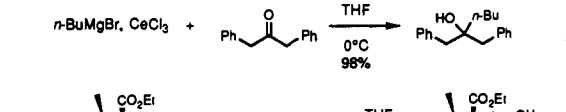
the anti diastereomer in conjugate addition reactions to unsaturated amino sulfones, but also lead to the syn diastereomer in substitution reactions of allylic ammonium salts.

B. Carbonyl Addition Reactions

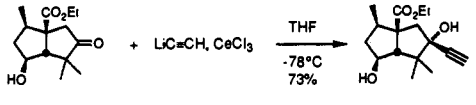
1. Discrete Organometallic Reagents

One of the more important applications of lanthanide reagents to synthetic organic chemistry is the use of organocerium reagents in carbonyl addition reactions. Imamoto and co-workers were the first to recognize that the attenuated basicity and high oxophilicity of organocerium reagents could be utilized to advantage within the context of selective synthetic organic transformations. Organocerium reagents are generated in situ by transmetalation reactions from organolithiums or organomagnesiums.[49c,121] Alkyl (primary, secondary, and tertiary), alkenyl, alkynyl, allyl, and aryl organocerium compounds can all be prepared by this simple procedure. Little is known of the structure of these organoceriums, or the exact nature of the reactive species. Although they have been denoted as σ-alkyl species ("$RCeX_2$"), other compositions (e.g., $RM{\cdot}CeCl_3$, "ate" complexes or species resulting from Schlenk-type equilibria)[122] cannot be ruled out. Regardless of the true nature of the reactive nucleophiles, these reagents react efficiently with aldehydes and ketones, providing alcohols in yields that are often superior to those reported utilizing Grignard or organolithium reagents. Organoceriums are not unique among the lanthanide organometallics in serving as suitable alternatives to Grignard reagents and organolithiums for certain carbonyl addition reactions. However, the low cost of cerium compounds and proven success of organocerium reagents makes thorough investigations into analogous organolanthanides less compelling.

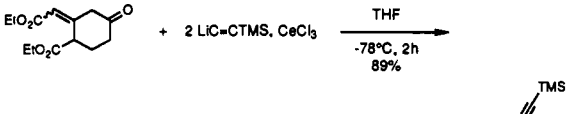
There are several reactivity profiles of organoceriums which make them attractive reagents for selective organic synthesis. Particularly impressive is the ability of organocerium reagents to effect carbonyl addition to highly enolizable substrates. This has been amply demonstrated by Imamoto,[121e] and many others have reported similarly successful examples (eqs 170–173).[123]



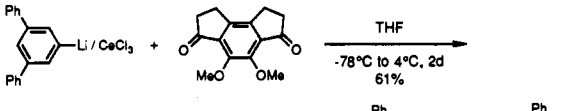
(170)



(171)



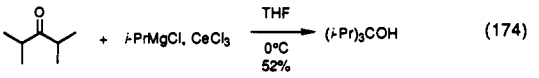
(172)



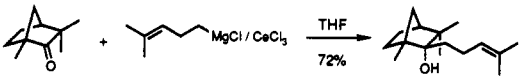
(173)

More often than not, organolithium or organomagnesium reagents have been utilized with these substrates without success.

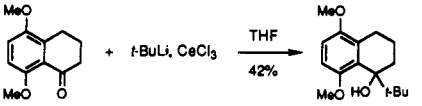
Highly hindered systems (where either the nucleophilic component, the carbonyl component, or perhaps both components are sterically encumbered) are notable for their inability to undergo carbonyl addition. Enolization and/or reduction processes often compete with the desired transformation. Conversion of organolithiums or organomagnesiums to organocerium counterparts often eliminates these problems, providing enhanced yields of desired alcohols in all but the most difficult cases (eqs 174–176).[121e,124]



(174)

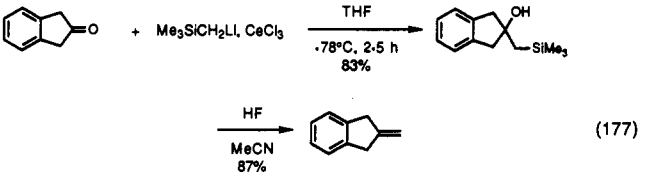


(175)



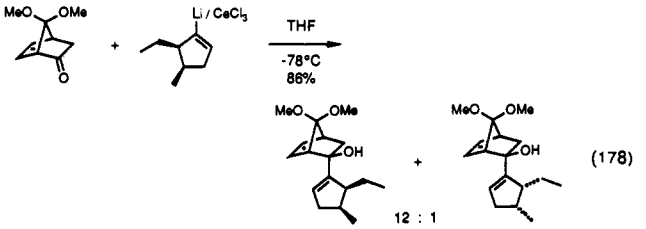
(176)

The ability of organocerium reagents to undergo carbonyl addition without enolizing the aldehyde or ketone substrate has been utilized by Johnson and Tait to develop a useful alternative to the Wittig reaction for carbonyl methylenation.[125] Treatment of a variety of aldehydes and ketones with $Me_3SiCH_2Li/CeCl_3$ provides 2-hydroxy silanes, which can be regioselectively converted under standard reaction conditions to the desired alkenes (eq 177).

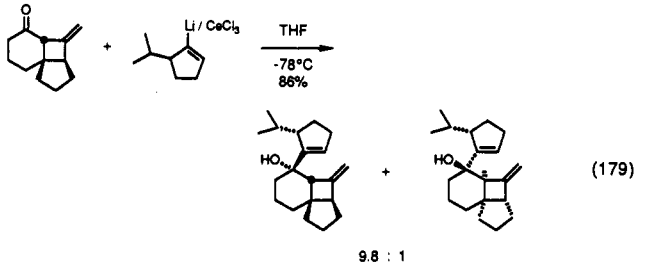


(177)

In an important series of papers, Paquette and coworkers have utilized organocerium reagents to assess intermolecular recognition of chiral cycloalkenyl cerium reagents with a variety of conformationally rigid ketones.[126] Double stereodifferentiation is very impressive in many of these cases even though directing stereocenters are remote from the reaction center (eqs 178 and



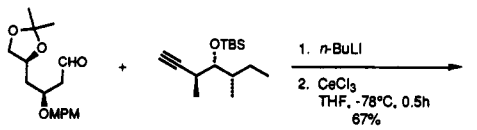
(178)



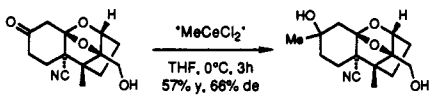
(179)

179). Products from such reactions have been utilized as key components in several natural product syntheses.

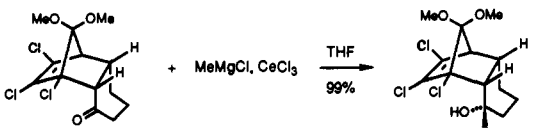
The chemoselectivity of organocerium reagents has been illustrated in instances in which organomagnesium and/or organolithium reagents initially failed to provide the desired carbonyl addition reactions (eqs 180–182).[127] Halides, esters, epoxides, amines, acetals, amides, and nitriles are all compatible functional groups in such processes. In fact, it is rare to find functionalized ketones or aldehydes for which organoceriums do not provide higher yields of carbonyl addition, regardless of the nature of the substrate.



(180)

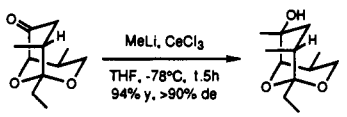


(181)

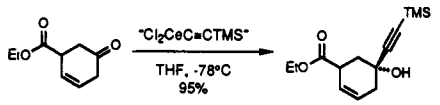


(182)

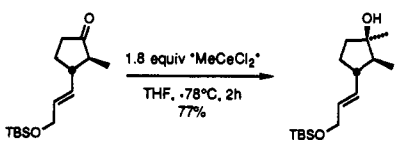
The sense and magnitude of diastereoselectivity achievable in the addition of organocerium reagents to chiral carbonyl substrates has not been investigated in a systematic fashion. In cyclohexanone substrates axial attack appears to predominate with unencumbered nucleophilic species (eqs 183 and 184).[128] In cyclopentanone substrates, nucleophilic attack occurs trans to substituents α to the carbonyl (eq 185).[129]



(183)

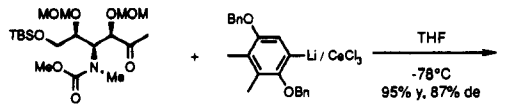


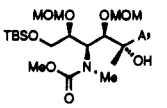
(184)



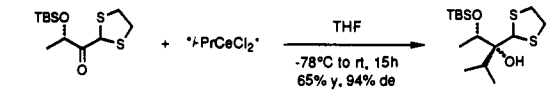
(185)

In terms of acyclic diastereoselection, the lack of a rigorous systematic investigation makes assessment of organocerium carbonyl addition reactions particularly difficult. Both chelation control and Felkin–Anh reactivity patterns have been observed, and thus both the sense and magnitude of acyclic stereocontrol appear to be highly substrate dependent (eqs 186–189).[130] In many of these cases, the sense of asymmetric induction provided by organocerium reagents is complementary to that observed for the corresponding organolithiums or organomagnesiums.

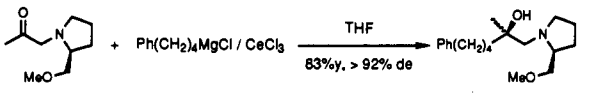




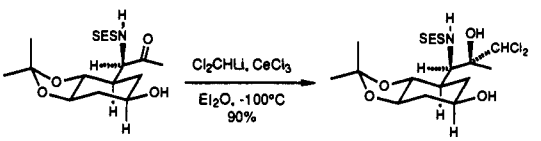
(186)



(187)

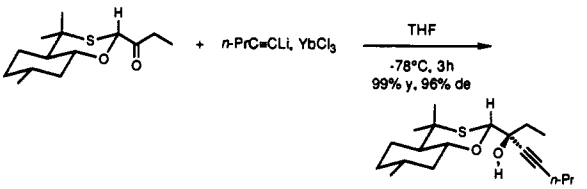


(188)



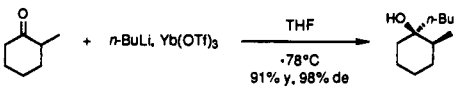
(189)

Reagents derived by addition of $YbCl_3$ to alkynyllithiums provide surprising results in carbonyl addition reactions to chiral 2-acyl-1,3-oxathianes (eq 190).[122b] Not only are diastereoselectivities exceedingly high (>94:6), but there is also a reversal in the sense of asymmetric induction from that of the corresponding alkynyllithiums and alkynylmagnesium halides. Although postulates based on chelated models have been proposed, a definitive rationale awaits further studies on the nature of the reactive nucleophilic species involved.

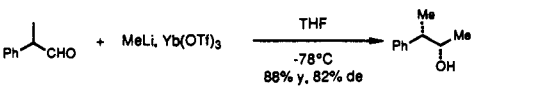


(190)

Organoytterbium triflates also display enhanced diastereoselectivities in carbonyl addition to chiral aldehydes and ketones.[131] In fact, diastereoselectivities are among the highest reported for addition of any organometallic reagent to the standard substrates chosen as examples (eqs 191 and 192). Alkyl (primary, secondary, and tertiary), alkenyl, and aryl organometallics can all be employed, providing a distinct advantage over nucleophilic reagents such as organotitaniums which afford lower yields in many of these cases owing to decomposition of the nucleophilic species. The precise nature of the organoytterbium reagents involved is not known, although there are indications that it may in fact be a complex mixture of reactive intermediates.[122a]



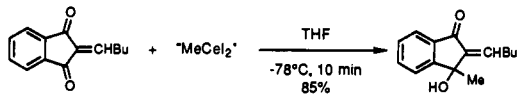
(191)



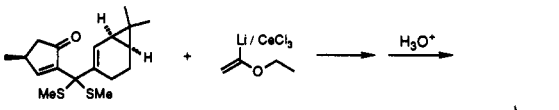
(192)

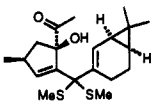
Organoceriums generally provide higher yields of 1,2-carbonyl addition products in reactions with conjugated aldehydes and ketones than their organolithium or organomagnesium counterparts.[132] This has been demonstrated in highly enolizable substrates, as well

as in examples where the alternative conjugate addition competes effectively using more traditional reagents (eqs 193–195).



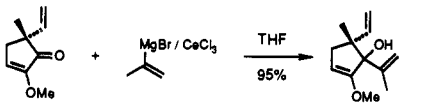
(193)





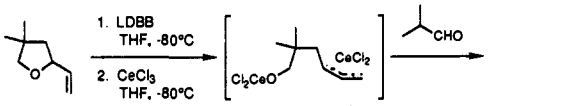
(194)

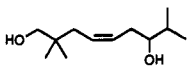
71%



(195)

Allylcerium reagents prepared by transmetalation from corresponding allyllithium reagents also undergo selective 1,2-addition to unsaturated aldehydes and ketones.[133] Furthermore, allylceriums exhibit reactivity patterns unique from those of many other allylmetallic reagents. Most allylmetallic nucleophiles add to aldehydes and ketones predominantly at the most substituted terminus of the allyl unit. By contrast, allylcerium reagents react with a variety of carbonyl substrates to provide products resulting from predominant reaction at the least substituted end of the allylmetallic system, regardless of the substitution pattern about the allylcerium starting material. Allyl anions (prepared by reaction of allylic ethers or thiophenoxides with lithium *p,p'*-di-*tert*-butylbiphenylide, LDBB) are kinetically generated in the cis configuration. By maintaining this geometry in the transmetalation reaction, one can take advantage of the unique regiochemical outcome of the allylcerium carbonyl addition reactions to construct cis homoallylic alcohols (eq 196). Equil-

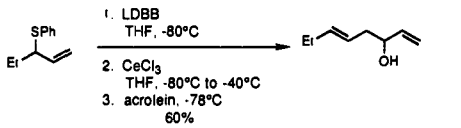




(196)

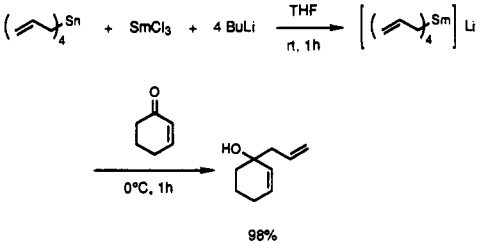
63%

ibration of the allylcerium π-complex to the thermodynamically more stable trans isomer permits generation of the corresponding diastereomer (eq 197). Al-



(197)

lyllanthanide "ate" complexes also provide a high degree of 1,2-regioselectivity in carbonyl addition to a variety of conjugated aldehydes and ketones.[134] The "ate" complexes are readily prepared by reaction of allylstannanes with *n*-butyllithium in the presence of lanthanide(III) chlorides, and subsequent addition of unsaturated carbonyl compounds leads to high yields of product in which the homoallylic alcohol predominates to an impressive extent (eq 198). Allyllithiums alone provide no better than an 85:15 ratio of 1,2- to 1,4-addition product.

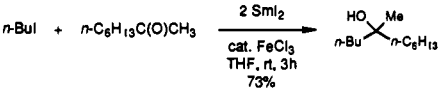


(198)

98%

2. Barbier-Type Reactions

Samarium(II) complexes have proven highly effective for promoting Barbier-type reactions between aldehydes or ketones and a variety of organic halides.[1] The efficiency of the SmI_2 promoted Barbier-type coupling process is highly dependent upon the substrates utilized, as well as the precise reaction conditions employed. For example, primary organic iodides and even organic tosylates undergo Barbier-type coupling with ketone substrates, but require heating for 8–12 h in boiling THF. A Finkelstein-type reaction presumably converts tosylates to the corresponding iodides, which subsequently are involved in the coupling process. Alkyl bromides are less reactive, and alkyl chlorides are virtually inert. Much milder reaction conditions can be utilized by adding catalytic quantities of Fe(III) salts to the reactions. Thus, when 2 mol % $FeCl_3$ is added to SmI_2, the Barbier reaction between a primary organic iodide and a ketone is complete within hours at room temperature (eq 199).



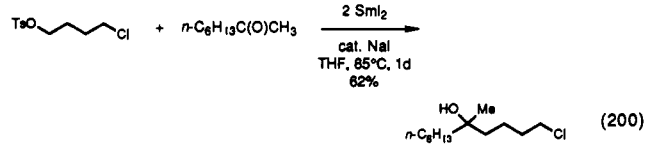
(199)

A further facilitation of the reaction can be realized by utilizing HMPA as a cosolvent with THF for the reaction.[135] Even in the absence of a catalyst, both *n*-BuBr and *sec*-BuBr are cleanly coupled to 2-octanone within 1 min at room temperature in this solvent system, providing greater than 90% yields of the desired tertiary alcohols.

Some restrictions apply in the nature of carbonyl substrates that may be utilized in reactions with SmI_2. Aldehydes cannot be coupled to marginally reactive organic halides. A mixture of products results in these cases as a consequence of a Meerwein–Ponndorf process, initiated by reaction of secondary samarium alkoxide intermediates with the aldehyde.[93a,136] These problems are solved by utilizing dicyclopentadienylsamarium (Cp_2Sm) as the reducing agent. This reagent is prepared from SmI_2 by reaction with dicyclopentadienyl sodium. Dicyclopentadienylsamarium shows enhanced reactivity in many reductive coupling reactions promoted by Sm(II) species.[137] For example, experimental conditions in intermolecular Barbier reactions are much milder with Cp_2Sm (room temperature) than with SmI_2 (THF heated at reflux). Secondary alkyl iodides, reluctant to react with SmI_2 in THF, are efficiently coupled with Cp_2Sm under mild conditions. Dicyclopentadienylsamarium also permits efficient Barbier coupling of organic halides (even secondary bromides) with aldehydes, providing the desired

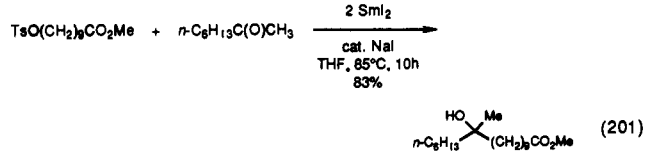
alcohols in reasonable yields.

Highly selective synthetic transformations are accomplished by taking advantage of the unique reactivity patterns of SmI_2. As mentioned, there is a tremendous reactivity difference in Barbier-type reactions of primary organic iodides or tosylates versus that of organic chlorides. As expected, selective alkylation of ketones can be accomplished by utilizing appropriately functionalized dihalides or chloro-substituted sulfonate esters (eq 200).[67] Alkenyl halides and, presumably, aryl halides are also tolerated under these reaction conditions.



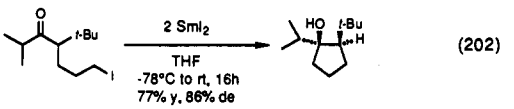
(200)

Nitriles and esters are less reactive under normal SmI_2-promoted reaction conditions than ketones. Consequently, it is possible to perform a Barbier-type coupling reaction in the presence of these functional groups and isolate the desired product in reasonable overall yield (eq 201).[67]



(201)

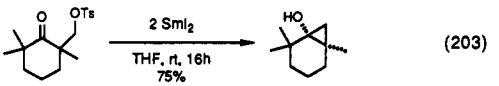
Although numerous reductants have been employed in attempts to promote intramolecular Barbier-type reactions, SmI_2 is by far the most general reductive coupling agent in terms of its utility and its scope of application. It has therefore become the reagent of choice for such processes. Isolated cyclopentanols can be synthesized with considerable diastereoselectivity when appropriately substituted ω-iodoalkyl ketones are treated with SmI_2 in THF at −78 °C and allowed to warm to room temperature (eq 202).[138] Reactions are



(202)

not sterically inhibited, and the procedure thus provides a useful alternative to intermolecular carbonyl addition reactions for synthesis of hindered cyclic tertiary alcohols.

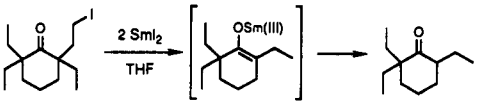
Perhaps most valuable are applications of the SmI_2 reductive coupling technology to syntheses of bicyclic alcohols. The SmI_2-mediated Barbier reaction can be utilized to generate three-membered rings starting from α-(tosyloxy)methyl cycloalkanones (eq 203).[139] An



(203)

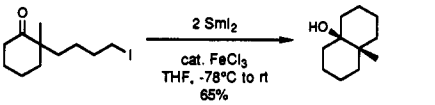
advantage of SmI_2 over reductants like magnesium is that one is not restricted to organic halides in these reactions. As in this example, tosylates appear perfectly well-suited to the Barbier process as well.

Syntheses of cyclobutanols by this protocol has yet to be thoroughly explored, but in one reported attempt the desired cyclization could not be realized. Rather, a reductive elimination took place, generating a samarium enolate (eq 204).[138] Because of the special nature of this highly hindered substrate, it would not seem appropriate to extrapolate this reactivity pattern to all related cyclizations.

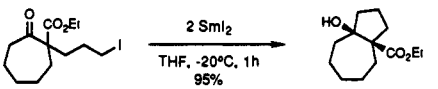


(204)

Samarium diiodide can be utilized in annulation of five- and six-membered rings via an intramolecular Barbier process.[140] Development of this approach to six-membered rings in fused bicyclic systems is particularly important, because prior to this discovery there existed no reliable and convenient method to achieve this simple annulation process. Reactions proceed with considerable diastereoselectivity when cyclopentanone substrates are utilized, or when substituents are placed at the α position of the cycloalkanone (eqs 205 and 206).



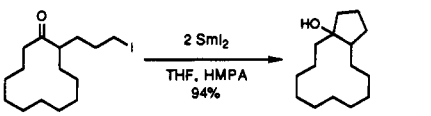
(205)



(206)

Unfortunately, the sense and magnitude of stereoselectivity achievable by employing SmI_2 as a reductant with other substrates is fairly unpredictable, and must be determined for each individual class of substrates under specific reaction conditions.

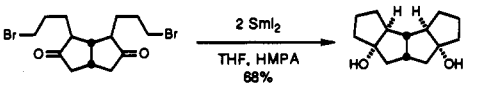
The SmI_2-mediated intramolecular Barbier procedure has been applied to diverse systems, and in virtually every case has been determined to be superior to other protocols. Suginome and Yamada have applied the technique to syntheses of exaltone and (±)-muscone (eq 207).[141] Yields employing the SmI_2 protocol in the



(207)

cyclization were appreciably better than those utilizing $Mg/HgCl_2$ or n-butyllithium as the reductants.

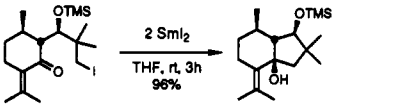
In an elegant approach to polyquinenes, Cook and Lannoye developed a bis-annulation process based upon the SmI_2-mediated cyclization process (eq 208).[142]



(208)

Remarkably, each of the carbon–carbon bond forming reactions in this process proceeds in over 80% yield, and in other analogous substrates they exceed 90%, providing an efficient entry to complex molecules.

Very little work has been reported on the Barbier-type cyclization reactions utilizing conjugated enone substrates. Preliminary studies indicate that these, too, cyclize with extraordinary efficiency, providing desired allylic alcohols in high yields (eq 209).[143] High diast-

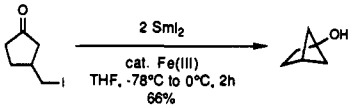


(209)

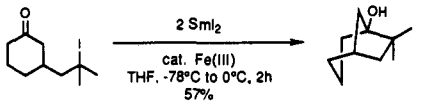
ereoselectivity is achieved in this reaction as well, and

under the mild conditions required for cyclization the trimethylsilyl ether protecting group remains intact. Somewhat surprisingly, even a neopentyl halide is quite effective in the cyclization.

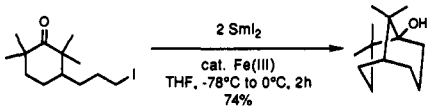
The SmI_2-mediated intramolecular Barbier synthesis can be applied to the synthesis of bridged bicyclic alcohols as well as the fused bicyclic systems described above.[144] The generality of this procedure is particularly impressive: even highly strained bicyclo[2.1.1]hexan-1-ols are generated in acceptable yield (eq 210). Ketones possessing primary, secondary, tertiary, and neopentyl iodides can all be utilized as precursors for the reaction (eq 211), and again steric encumbrance about the ketone provides little impedence to the cyclization process (eq 212). None of these cyclizations can be carried out with magnesium metal or organolithiums as reductants. Consequently, application of SmI_2 as a reductive coupling agent to this process represents a significant synthetic advance because it represents perhaps the only general route to this class of bridgehead bicyclic alcohols. Although this approach



(210)



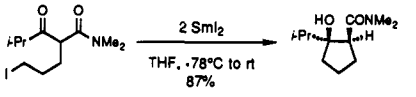
(211)



(212)

to bicyclo[*m.n.*1]alkan-1-ols is quite general, it has not been possible to extend the method to construction of bicyclo[*m.n.*2]alkan-1-ols. Furthermore, allylic halides exhibit capricious reactivity in related reactions.

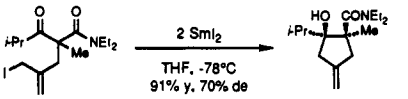
The Sm(III) ion generated after electron transfer in Barbier-type processes can be utilized as an effective Lewis acid template to control stereochemistry via chelation in suitably functionalized substrates. In fact, a number of systems have been designed with this idea in mind. In pertinent β-ketoamide substrates, Sm(III) ions participate in a rigid, chelated intermediate which serves to control stereochemistry in the cyclization process (eq 213).[145] These particular cyclization reac-



(213)

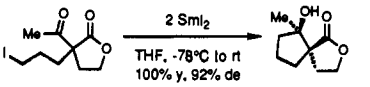
tions are apparently under kinetic control; there is no evidence to suggest that any equilibration takes place under the reaction conditions, and a single diastereomer is generated in each example. Six-membered rings can also be constructed by this process, although yields are somewhat lower. Approximately 30% of reaction mixture byproducts derived from simple reduction of the ketone to an alcohol are isolated in these cases.

Allylic halide precursors also provide exceptional yields of cyclic products. In these instances, both five- and six-membered rings comprising several different substitution patterns can be accessed by the same technology (eq 214).[144] Some erosion of yield and diastereoselectivity is noted on applying the chemistry to synthesis of six-membered rings. However, the method still provides unique access to highly functionalized, stereodefined carbocycles.



(214)

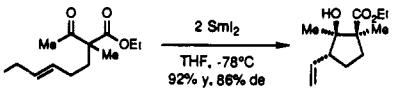
A number of analogous substituted β-keto esters have also been explored as substrates for intramolecular Barbier cyclization.[144] In the alkyl halide series, a convenient route to hydroxycyclopentanecarboxylates results. However, six-membered rings are inaccessible when this procedure is utilized (eq 215). In contrast



(215)

to β-keto amide substrates, β-keto esters provide products which are under thermodynamic control. The observed diastereoselectivity is apparently a result of a retro-aldol–aldol process which serves to equilibrate initially formed samarium aldolates. In most cases, diastereoselectivity is actually quite good. However, it is highly dependent on substituent and solvent effects. In particular, use of coordinating solvents or additives (such as tetraglyme, 18-crown-6, or *N,N*-dimethylacetoacetamide) which serve to strip the Sm(III) ion away from the chelating center radically diminish diastereoselectivity observed in these reactions.

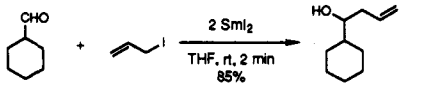
Allylic halide substrates in the β-keto ester series cyclize quite nicely, and convenient routes to five-, six-, and even seven-membered rings have been described (eq 216).[144] Unfortunately, diastereoselectivities in



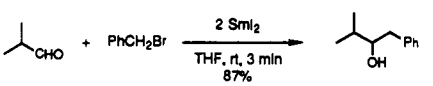
(216)

these examples again are highly dependent upon the substitution patterns about the dicarbonyl substrate.

Because of the difficulties in synthesizing discrete allylic and benzylic organolithiums and -magnesiums, Barbier coupling processes employing allylic halides and benzylic halides are often employed in lieu of the two step (organometallic synthesis, carbonyl addition) process. Samarium(II) iodide is particularly effective in promoting intermolecular coupling between these reactive halides and aldehydes, because these partners react quickly enough to suppress the undesired side reactions normally seen in Barbier-type processes between organic halides and aldehydes (eqs 217 and 218).[67,136a] Unfortunately, unsymmetrical allylic halides provide mixtures of regio- and stereoisomers in these instances, and progargyl halides lead to both allenic and alkynyl substituted alcohols.



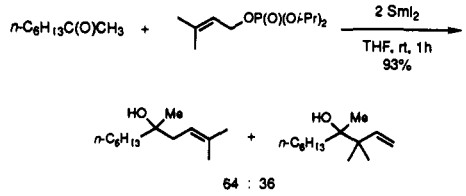
(217)



(218)

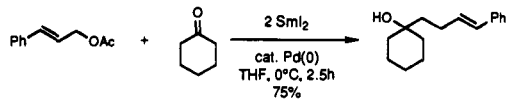
Even allylic phosphates can be utilized as precursors for Barbier-type coupling processes, although the procedure is impractical for aldehydes and more easily reducible ketones (e.g., acetophenone and benzophenone) because of competitive pinocol formation (eq 219).[146] Generation of regio- and stereoisomeric hom-

oallylic alcohols from unsymmetrical precursors again detracts somewhat from the value of the method.

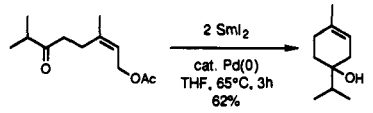


(219)

Allylsamarium species generated by the Pd(0)-catalyzed reductive transmetalation of allylic acetates provide another facile route to homoallylic alcohols via coupling with aldehydes and ketones (eq 220).[147] In most cases, carbon–carbon bond formation occurs at the least substituted terminus of the allylic unit, in accord with the allylcerium chemistry described above. A wide range of aldehydes and ketones can be utilized in the reaction, and one cyclization process has been reported (eq 221). Aromatic and α,β-unsaturated substrates



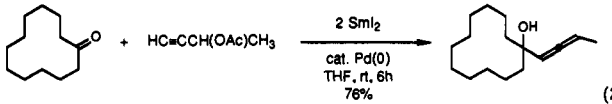
(220)



(221)

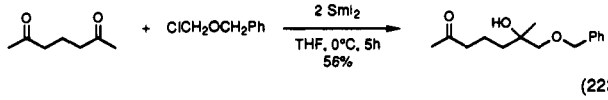
cannot be used owing to competitive pinacolic coupling reactions.

Progargylic acetates undergo an analogous reaction with ketones.[148] Aldehydes can only be utilized with highly reactive propargylic acetates because of competitive pinacolic coupling. Primary propargylic acetates produce mixtures of allenic and homopropargylic alcohols, whereas most secondary and all tertiary propargylic carboxylates provide exclusively the allenic alcohols (eq 222).



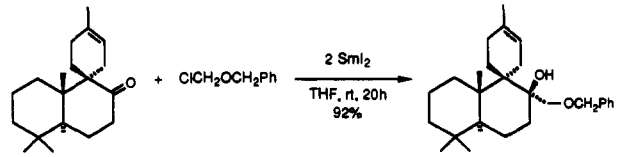
(222)

A number of modified Barbier-type reactions have been developed which further expand the scope of these SmI_2 promoted processes. For example, a convenient hydroxymethylation process has been developed based on the SmI_2-mediated Barbier-type reaction.[149] Treatment of aldehydes or ketones with benzyl chloromethyl ether in the presence of SmI_2 provides alkoxymethylated products. Subsequent reductive cleavage of the benzyl ether affords hydroxymethylated products (eq 223). Even ketones with a high propensity for enolization are alkylated by this process in reasonable yields. The method has been utilized by White and Somers as a key step in the synthesis of (±)-desoxystemodinone (eq 224).[82a] This particular substrate resisted carbonyl addition by many other nucleophilic reagents (such as methyllithium), with enolate formation constituting the primary mode of reaction.



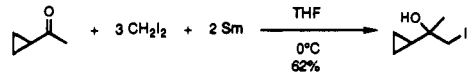
(223)

Halomethylation of aldehydes and ketones is difficult to achieve by utilizing α-halo organolithium species

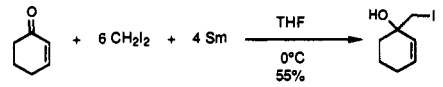


(224)

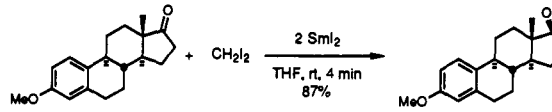
because of the extreme thermal instability of these organometallics. Either SmI_2 or samarium metal can be utilized as the reductant in conjunction with diiodomethane to accomplish an alternative iodomethylation process.[49c,150] A wide range of aldehydes and ketones are efficiently alkylated at room temperature under these conditions (eq 225). Even enolizable substrates (such as β-tetralone) react reasonably well, providing moderate yields of iodohydrin. Conjugated aldehydes and ketones react to provide only 1,2-addition products, although yields are somewhat modest (eq 226). Excellent diastereoselectivity is achieved in reactions with both cyclic and acylic ketones (eqs 227 and 228), and the method is tolerant of other functional groups such as esters.



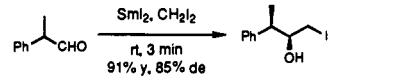
(225)



(226)

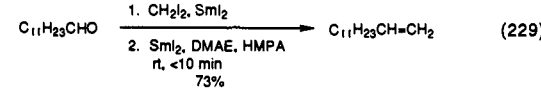


(227)



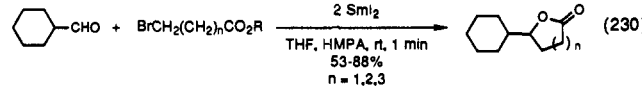
(228)

A one-pot carbonyl methylenation reaction has been developed based upon this iodomethylenation reaction.[89] Treatment of an (iodomethyl)samarium alkoxide (generated in situ by reaction of aldehydes or ketones with SmI_2/CH_2I_2) with SmI_2/HMPA and (*N,N*-dimethylamino)ethanol (DMAE) induces a reductive elimination process, resulting in generation of the corresponding methylenated material (eq 229).



(229)

Lanthanide mediated coupling reactions performed under Barbier-type conditions are tolerant of ester functional groups. Useful procedures for lactone synthesis have been developed making use of this fact. For example, treatment of γ-bromobutyrates or δ-bromovalerates with SmI_2 in THF/HMPA in the presence of aldehydes or ketones results in generation of lactones (eq 230).[135] This procedure provides a convenient

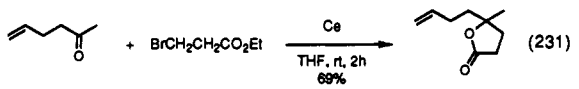


(230)

means to generate γ-carbanionic ester equivalents and δ-carbanionic ester equivalents.

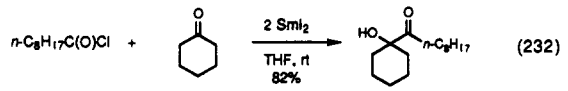
A comparable route to butyrolactones derives from reaction of lanthanide metals with β-bromopropionates in the presence of ketones (eq 231).[151] Lanthanum,

samarium, neodymium, and cerium metals all promote this coupling, although the latter is generally utilized. This protocol is limited to ketone substrates because aldehydes undergo preferential pinacol formation under the reaction conditions.



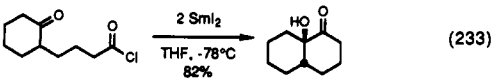
(231)

Samarium acyl anions react with aldehydes or ketones, providing a rapid synthesis of α-hydroxy ketones. The procedure may either be carried out under Barbier-type conditions (eq 232),[152] or via generation of discrete acylsamariums. The latter are generated either by reaction of SmI_2 or Cp_2Sm with acyl halides,[152b] or by carbonylation of Cp_2SmR species.[153] Intramolecular



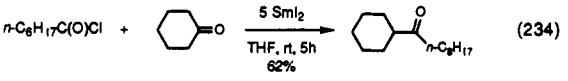
(232)

versions of this Barbier-type reaction have been performed, although the scope of the process is somewhat limited because of the difficulty of obtaining suitable substrates for the reaction (eq 233).[154]



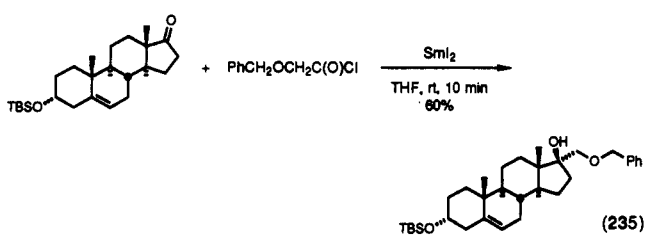
(233)

Acyl anion coupling/reduction sequences can be accomplished when an excess of SmI_2 is utilized for the initial Barbier process.[155] Under the conditions of the reaction, an α-alkoxy ketone is presumably generated first, and this is then reduced by SmI_2 to an α-keto radical. The latter abstracts a hydrogen from THF to complete the process (eq 234). No deuterium is incorporated when these reactions are quenched with D_2O, indicating that enolates are apparently not involved.



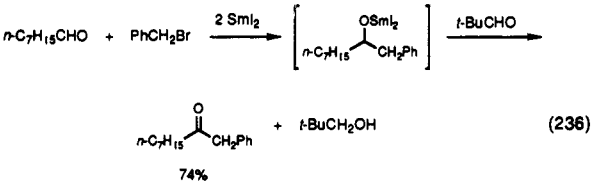
(234)

Certain acyl radicals generated by SmI_2 reduction of carboxylic acid halides rapidly decarbonylate before transfer of a second electron, thereby providing a stabilized radical instead of an acylsamarium species. α-Alkoxyacetyl chlorides are among these classes of substrates. Kagan and co-workers have developed this observation into procedures for alkoxyalkylation of ketones.[156] Thus, treatment of ketones with α-(benzyloxy)acetyl chloride in the presence of SmI_2 provides corresponding (benzyloxy)methyl-substituted alcohols in modest to good yields (eq 235). The procedure provides an alternative to the alkoxy methylation reactions described above, in which α-chloromethyl ethers were required as (benzyloxy)methyl anion equivalents.



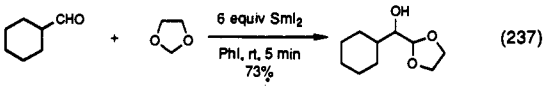
(235)

Another efficient sequential process promoted by an initial SmI_2-mediated Barbier reaction is a reductive coupling/Oppenauer oxidation.[46] Although only a single example of this one-pot synthesis of ketones has been reported (eq 236), the concept appears useful enough to merit further consideration.



(236)

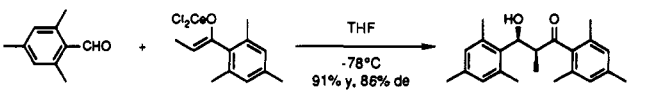
A new method for masked formylation of aldehydes and ketones has been developed which relies upon a rather complex series of reactions. Aryl halides do not undergo Barbier-type coupling reactions with ketones in the presence of SmI_2. Instead, aryl radicals generated abstract a hydrogen from THF, and THF adducts of the carbonyl compounds are observed.[76] An adaptation of this process (replacing THF with 1,3-dioxolane) has been utilized to perform the aforementioned formylation. Thus, when aldehydes or ketones are treated with iodobenzene in 1,3-dioxolane as solvent, the initially formed phenyl radical abstracts a hydrogen from dioxolane. The resulting dioxolanyl radical can couple with the carbonyl, generating the desired carbonyl addition product (eq 237).[157] Yields in these processes range from 73–77% for five different substrates. The reaction is limited because the dioxolane must be utilized as solvent for the reaction. Consequently, more highly functionalized (i.e., less readily accessible) dioxolane substrates would not be suitable partners in analogous reactions.



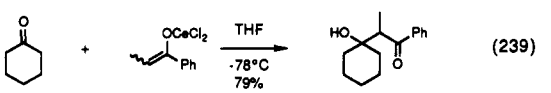
(237)

3. Aldol and Reformatsky Reactions

Lanthanides play a key role in several different aldol and Reformatsky-type protocols. In one of the earliest reported methods, cerium enolates derived from lithium enolates and $CeCl_3$ were found to undergo aldol condensations with sterically encumbered aldehydes and even ketones (eqs 238 and 239).[158] Presumably, retro-aldol and cross-enolization processes are inhibited in these reactions owing to formation of a tightly chelated cerium aldolate intermediate. Stereoselectivity in the cerium enolate aldol reactions was nearly identical to that of the corresponding lithium enolates, implying that transmetalation occurred with retention of enolate geometry, and that the aldol reaction itself proceeded through the familiar six-membered ring transition state.



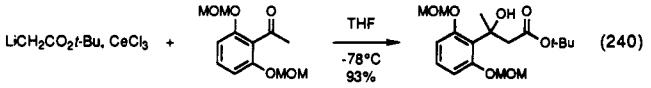
(238)



(239)

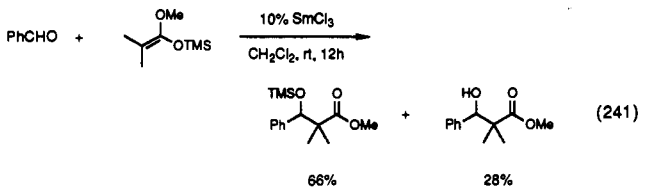
Ester enolates also appear to benefit by incorporation of a cerium counterion in aldol-type reactions. Ketone electrophiles incapable of undergoing aldol reactions with lithium ester enolates produce the desired products

in nearly quantitative yields when a cerium enolate is employed (eq 240).[159]



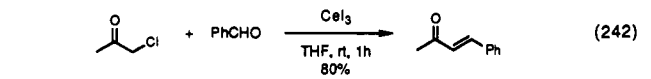
(240)

Lanthanide complexes can serve as Lewis acids to promote the reaction of silyl enol ethers with aldehydes.[160] Various lanthanide chlorides provide inexpensive and convenient catalysts for the reaction, but long reaction times are required and diastereoselectivity has not been examined in these cases. Mixtures of aldol and silylated aldol are generally isolated from the reaction mixtures (eq 241).



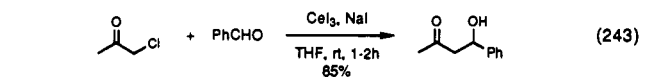
(241)

Methods involving reductive coupling dominate aldol and Reformatsky-type reactions promoted by lanthanide reagents. For example, cerium enolates derived from α-halo ketones can be trapped by a variety of aldehyde electrophiles.[161] Resulting products are either α,β-unsaturated ketones or β-hydroxy ketones, depending on the nature of the salts utilized. Cerium triiodide provides unsaturated enones directly in high yields (eq 242). Similar procedures leading to unsaturated carbonyl products can be carried out with SmI_2 as the reductant.[162] Treatment of an isolated β-hydroxy ketone with CeI_3 also provides α,β-unsaturated ketones in quantitative yield. This suggests that elimination of the cerium aldolate occurs in the presence of a Ce(III) Lewis acid. Ketones are unreactive as enolate electrophiles in these processes.



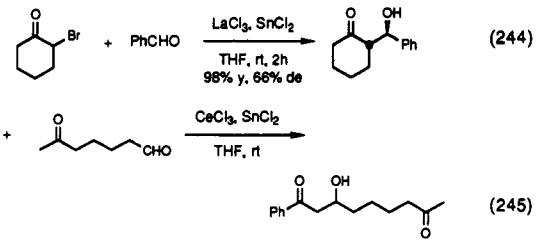
(242)

The combination of $CeCl_3$–NaI in conjunction with α-halo carbonyl substrates and carbonyl electrophiles provides aldol products upon aqueous workup, with little or no elimination to unsaturated ketones (eq 243).[161] Reactions are regioselective; i.e., no aldol products resulting from retro-aldol or cross-enolization processes are detected. Only low levels of stereochemical control is achieved in those instances where diastereomers are possible. Ketone electrophiles provide low yields of desired aldol products (30–50%), and treatment of ethyl bromoacetate and benzaldehyde with $CeCl_3$–NaI provides no Reformatsky-type coupled product.



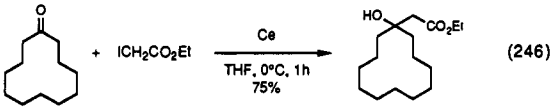
(243)

Crossed aldol condensations utilizing lanthanide salts ($LnCl_3$) in conjunction with $SnCl_2$ as a reductive coupling agent provide yet another level of selective reactivity.[161] Improved diastereoselectivity is observed over previously mentioned methods (eq 244), and a chemoselective aldol condensation to 6-oxoheptanal is readily achieved by utilizing α-bromo ketone precursors (eq 245). Again, Reformatsky-type reactions cannot be carried out utilizing this combination of reagents, and α-chloro ketones are also unreactive as cerium enolate precursors under these conditions. A cerium enolate is implicated by these results because $SnCl_2$ alone affords none of the coupled products, and reaction of 2-bromocyclohexanone with benzaldehyde in the presence of low-valent tin ($SnCl_2$/$LiAlH_4$) affords erythro aldol product in low yields.[163]



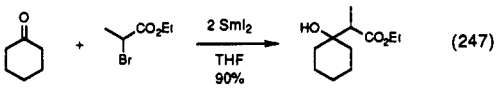
(244)
(245)

Reaction of α-halo esters with ketones or aldehydes in the presence of cerium metal or cerium amalgam generally proceeds at low temperatures, providing good to excellent yields of β-hydroxy esters (eq 246).[121b] Halides, nitriles, esters, and nitro groups are tolerated within the ketone or aldehyde electrophiles. Diastereoselectivities in intermolecular Reformatsky-type reactions promoted by cerium are poor. In pertinent examples examined, the ratio of erythro:threo diastereomers is no greater than 57:43.



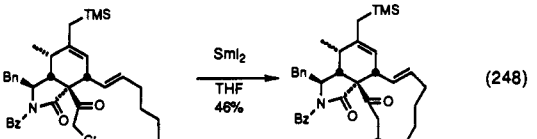
(246)

Reformatsky-type coupling reactions can be carried out between α-halo esters and ketone electrophiles when mediated by SmI_2 (eq 247).[67,77] Although a systematic survey has not been conducted, this reaction appears to provide another useful alternative to normal Zn-promoted Reformatsky reactions. The latter often perform well only when an activated form of Zn is utilized, and thus the homogeneous conditions afforded by SmI_2 may provide some advantages.

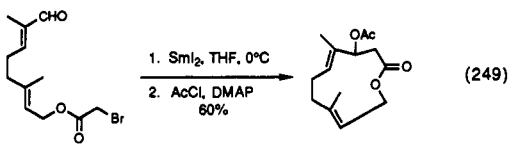


(247)

The procedure has been adapted to construction of medium- and large-ring molecules through an intramolecular process.[164] Both α-halo esters and α-halo ketones can be utilized as substrates for the reaction, and eight- through fourteen-membered ring compounds can be synthesized in this fashion in reasonable yields (eqs 248 and 249). Diastereoselectivities in these SmI_2-mediated cyclizations is quite variable.



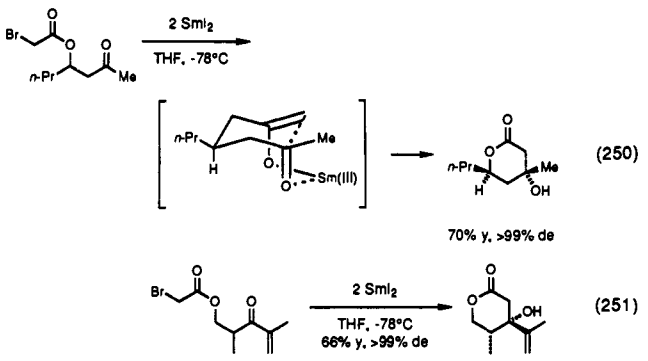
(248)



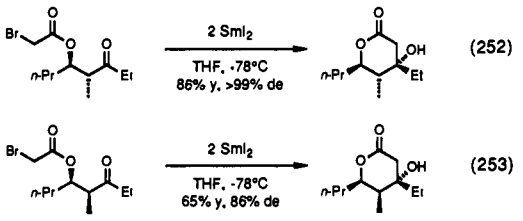
(249)

Reductive cyclizations of β-bromoacetoxy aldehydes and β-bromoacetoxy ketones promoted by SmI_2 afford

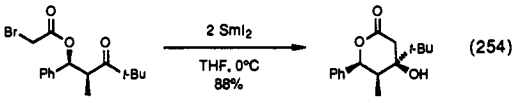
β-hydroxy valerolactones with unprecedented degrees of 1,3-asymmetric induction (eq 250).[165] High 1,2-asymmetric induction is achieved only in substrates possessing a relatively large group on the ketone (eq 251). Reactions of SmI_2 with β-bromoacetoxy carbonyl substrates are proposed to generate a Sm(III) ester enolate, with cyclization taking place through a rigid cyclic transition structure enforced by chelation (eq 250).



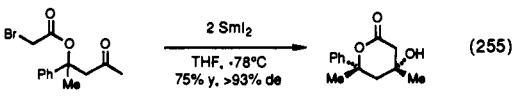
In contrast to other reported methods of 1,3-asymmetric induction, the SmI_2-mediated intramolecular Reformatsky procedure permits strict control of stereochemistry even in diastereomeric pairs of substrates bearing α substituents (eqs 252 and 253).[165] Although



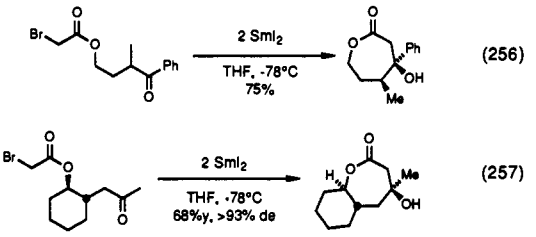
diastereoselectivity is somewhat lower for syn diastereomeric substrates, where one substituent must be axially disposed in the proposed transition structure leading to product, 1,3-asymmetric induction is still predominant, overwhelming the effect of a stereocenter α to the carbonyl to an impressive degree. Diastereoselectivity further erodes in syn diastereomeric substrates as substituents become more and more highly hindered, to the point where the sense of asymmetric induction is opposite to that predicted by the simple six-membered transition structure above (eq 254). For such substrates, reactions presumably transpire through alternative transition structures.



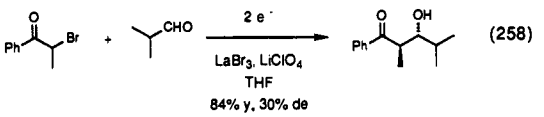
Perhaps most impressive is the induction of 1,3-asymmetry from a tertiary stereocenter (eq 255).[166] Consideration of the chelated six-membered transition structure implies that the phenyl group in this example occupies the axial orientation. This orientation is expected on the basis of conformational analyses of 1-methyl-1-phenylcyclohexane derivatives.



High levels of 1,2-asymmetric induction are also achieved in intramolecular Reformatsky-type reactions forming seven-membered lactones (eqs 256 and 257).[167] However, 1,3-asymmetric induction for appropriate substrates is low (about 3:1) and 1,4-asymmetric induction is virtually nonexistent.

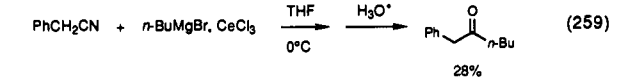


Finally, lanthanide ion assisted electrochemical aldol reactions between α-halo ketones and aldehyde electrophiles have been outlined.[168] The $LaBr_3$ employed in these reactions serves to activate the aldehyde by forming a Lewis acid–Lewis base complex. This complex suffers nucleophilic attack by a free lithio enolate, forming the aldolate product. Unfortunately, although the process is kinetically selective for the erythro diastereomer, the reaction is reversible and thus an equilibrium mixture of aldols is eventually isolated (eq 258).

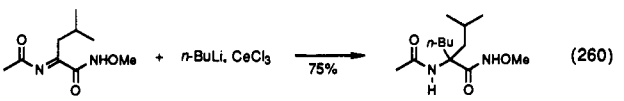


C. Addition to Carbon–Nitrogen Multiply Bonded Functional Groups

Organocerium reagents provide a useful alternative to organolithiums and organomagnesiums in nucleophilic addition reactions to carbon–nitrogen multiply bonded electrophiles. As one example, addition of organoceriums to phenylacetonitrile provides enhanced yields of desired ketones by minimizing the amount of metalation normally observed with analogous organomagnesium reagents.[121e] Absolute yields are still modest, however (eq 259).

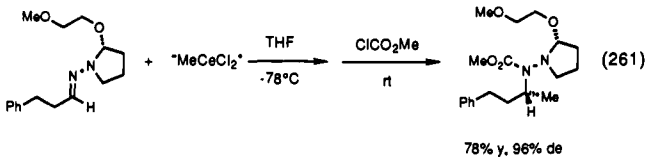


Acyl amines react with organocerium reagents to furnish α,α-disubstituted amino acid bisamides in good yields.[169] Although this procedure has not been generalized for organocerium reagents, it appears to be highly competitive with those employing organolithiums, organomagnesiums, or organocuprates (eq 260).



Organocerium reagents have found more extensive use in diastereoselective addition to chiral imines and related derivatives. For example, Denmark and coworkers have reported a general synthesis of chiral, nonracemic amines utilizing addition of organoceriums to chiral hydrazones as a key step.[170] Good yields and high diastereoselectivities are achieved in these addition reactions (eq 261) which failed when other organometallics (e.g., RLi, RMgX, or R_2CuLi) were utilized. Competitive enolization was a major problem with these

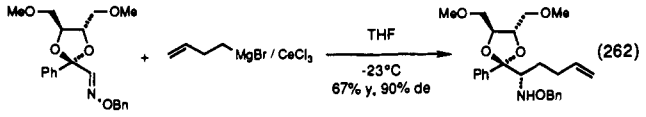
other nucleophilic reagents. Subsequent conversions



(261)

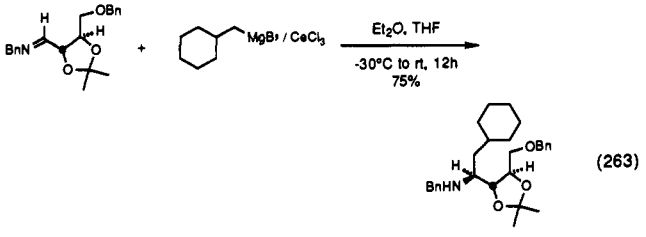
lead to the desired amines. A variety of organoceriums (alkyl, alkenyl, and aryl) ultimately derived from both organomagnesium and organolithium reagents are suitable for the reaction. Of the nucleophiles examined, only an alkynyllithium-derived reagent failed to add to the hydrazone. Precomplexation of one of the hydrazones with $CeCl_3$ followed by addition of MeLi resulted in poor yields (28%) of the desired product, suggesting involvement of organoceriums.

Another potentially useful route to chiral amines employs chiral α-aldoxime ether acetals as electrophilic substrates for organocerium nucleophiles.[171] The organocerium reagents display higher reactivity and stereoselectivity than that of corresponding Grignard and organolithium reagents. Starting materials were recovered in the latter cases. The sense of asymmetric induction observed when organoceriums were utilized was explained on the basis of a chelation model (eq 262). The magnitude of asymmetric induction was generally higher for organoceriums derived from Grignard reagents than from organolithiums, although on the basis of the data presented solvent effects could not be excluded.



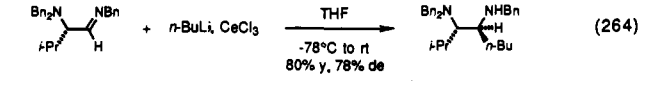
(262)

Chelation controlled addition of an organocerium reagent to an imine constituted the critical step in the synthesis of cyclohexylnorstatine, the key component of a promising renin inhibitor (eq 263).[172] Curiously, cyclohexylmagnesium bromide did not add at all to the imine, and cyclohexylmethylcopper(I) in the presence of $BF_3{\cdot}Et_2O$ provided the opposite diastereomer as the sole product of the reaction.



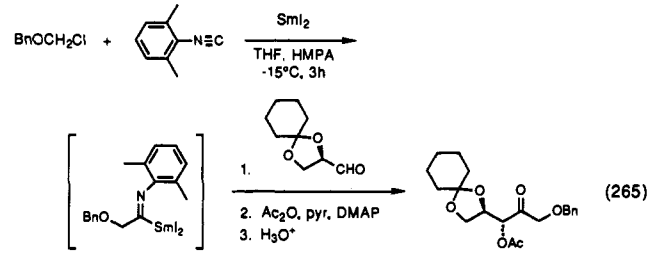
(263)

A stereoselective synthesis of vicinal diamines derives from chelation controlled addition of organoceriums to α-dibenzylamino-*N*-benzyl aldimines.[173] The latter are readily derived from amino acids, and thus the process provides a convenient entry to chiral, nonracemic materials. As in previous examples, organocerium reagents provide demonstrable advantages over more traditional organolithiums, organomagnesiums, and organocuprates, all of which failed to provide desired products in adequate yields and/or diastereoselectivities (eq 264).



(264)

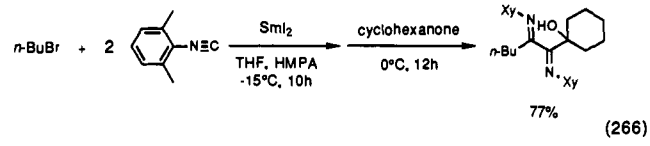
Processes based upon the SmI_2 promoted coupling reactions of isonitriles with organic halides provide unique new synthons for selective organic synthesis.[174] For example, treatment of benzyl chloromethyl ether with 2,6-dimethylphenyl isocyanide in the presence of SmI_2 leads to generation of an intermediate iminosamarium(III) species, which can be trapped by aldehyde and ketone electrophiles to provide α,α'-dialkoxy carbonyl derivatives (eq 265).[174a] Diastereoselectivity



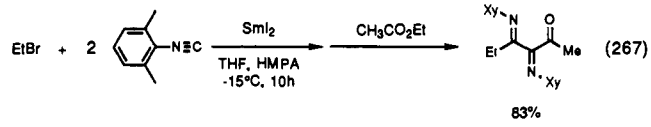
(265)

in the example shown was 10:1. Conjugated ketones undergo strict 1,2-carbonyl addition, and even readily enolizable ketones such as β-tetralone undergo reaction without significant competition from enolization. The organosamarium intermediate constitutes a novel α-hydroxyacetyl anion equivalent.

The method has been extended to include double isocyanide insertion, generating intermediate iminosamariums which can be capped by electrophilic quenching to provide a variety of useful diimines. The latter can be subsequently hydrolyzed to vicinal dicarbonyl compounds. Water, aldehydes, ketones, esters, and carbonates are all suitable electrophiles for the intermediate iminosamarium nucleophiles (eqs 266 and 267).[174c]



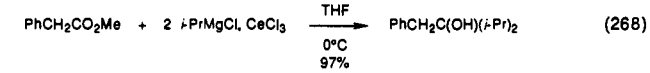
(266)



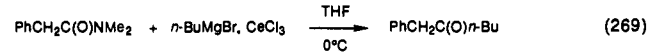
(267)

D. Nucleophilic Acyl Substitutions

Most organolanthanide reagents mimic organolithiums and organomagnesiums in their reactivity toward carboxylic acid halides, esters, and amides. There are a few exceptions, of course, and also some selectivity patterns warranting utilization of lanthanide reagents over their more common counterparts. One such example is nucleophilic acyl substitution of enolizable esters and amides. These substrates suffer competitive Claisen condensations and other side reactions when treated with Grignard reagents. Less basic organoceriums allow reasonable yields of desired tertiary alcohols from esters (even in highly hindered systems), and ketones from amides (eqs 268 and 269).[121e]

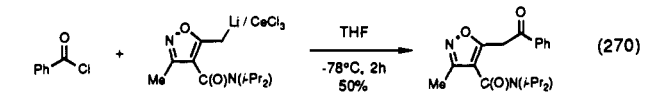


(268)

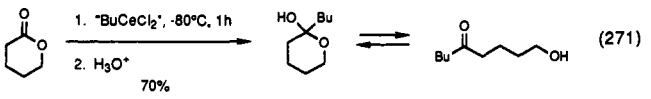


(269)

Cerium trichloride has been utilized in one instance to moderate the reactivity of organolithium reagents, permitting chemoselective generation of ketones (eq 270).[175] There is no clear indication as to whether this might be a general reactivity pattern of organoceriums.

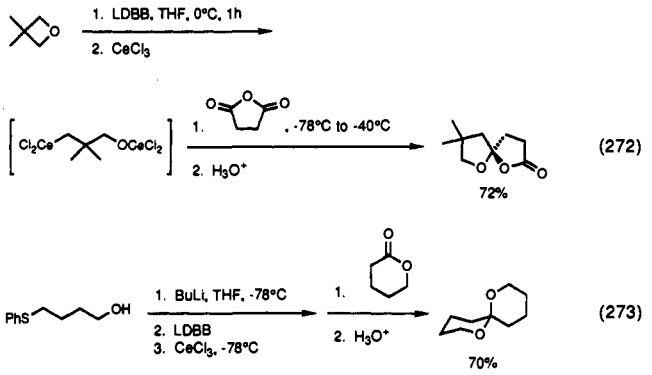


(270)



(271)

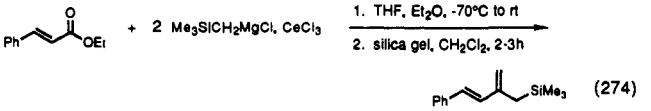
Selective reactions of organoceriums with lactones, providing the corresponding hydroxy ketones, can be achieved at low temperatures (eq 271).[176] Cohen and co-workers have utilized this fact to develop a simple one-pot synthesis of spiroketals and oxaspirolactones based upon addition of γ- and δ-cerioalkoxides to lactones and cyclic anhydrides, respectively (eqs 272 and 273). Lithium reagents required for these transformations are prepared by reductive cleavage of oxetanes with lithium *p,p'*-di-*tert*-butylbiphenylide (LDBB), or by treatment of 4-(phenylthio)butanol with the same reductant. Conversions to cerium reagents are accomplished by addition of $CeCl_3$.



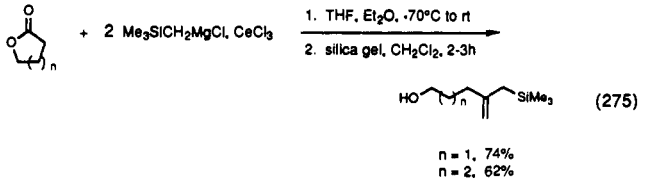
(272)

(273)

Cerium reagents provide a convenient route to functionalized allylsilanes via nucleophilic acyl substitution reactions. Thus the reagent derived from [(trimethylsilyl)methyl]magnesium chloride and $CeCl_3$ allows clean conversion of esters to tertiary alcohols, with subsequent elimination providing the desired allylsilanes (eq 274).[177] Functionalized esters provide entry to allylsilanes incorporating acetals, thioacetals, and halides difficult to prepare by other methods, and lactones lead to generation of hydroxy silanes (eq 275).

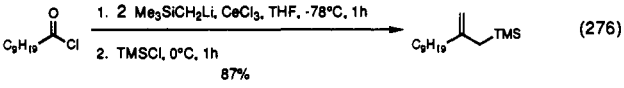


(274)



(275)

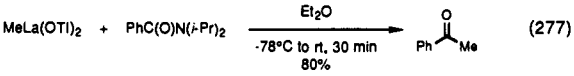
Curiously, reagents derived from [(trimethylsilyl)methyl]lithium and $CeCl_3$ show different properties in this process.[177a,178] Thus, although organolithium-derived reagents react poorly with esters (with unreacted starting material remaining), they provide excellent overall yields in reactions with carboxylic acid chloride substrates (eq 276). This demonstrates the dramatic



(276)

differences sometimes encountered in reactivity of organoceriums prepared from organomagnesium reagents on the one hand, and organolithium reagents on the other.

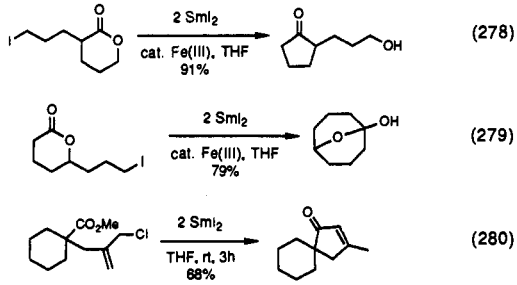
Alkyl- and aryllanthanum triflates [$RLa(OTf)_2$] react with tertiary amides to provide corresponding alkyl or aryl ketones in excellent yields (eq 277).[122a,179] It was not possible to add a single equivalent of these reagents cleanly to esters or carboxylic acid halides. In many



(277)

instances the procedure involving amides was found superior to those of more traditional methods utilizing organolithium reagents alone. Yields are generally higher with organolanthanum reagents, there is no metal–halogen exchange evident in reactions involving halogenated amides, and there is little if any enolization in amides prone to this side reaction. Highly hindered amides do not react, but otherwise the procedure is quite general. Ketones react much more rapidly with organolanthanum reagents than do corresponding amides in direct competition experiments. The success of the process is thus ascribed to the slow breakdown of an initially formed tetrahedral intermediate to the corresponding ketone.

Esters are normally unreactive under Barbier-type reaction conditions promoted by SmI_2. However, highly selective intramolecular nucleophilic acyl substitutions are accomplished under mild conditions when appropriately substituted halo esters are treated with SmI_2 (eqs 278–280).[180] Although it is perhaps not surprising that double addition to the carbonyl does not take place in such reactions, the complete absence of reduced (diol) products is somewhat unexpected.



(278)

(279)

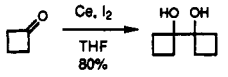
(280)

E. Reductive Coupling Reactions

1. Pinacolic Coupling and Related Reactions

A number of protocols employing lanthanide reagents have been utilized to effect pinacolic coupling reactions. Synthesis of pinacols from ketone or aldehyde precursors utilizing cerium reagents are best accomplished by employing what are postulated as low-valent cerium salts.[181] Treatment of cerium metal with iodine, di-

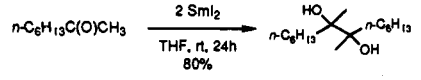
iodoethane, or iodobenzene, followed by addition of carbonyl substrate provides one entry to pinacol products. Alternatively, a reagent generated by reduction of CeI_3 with potassium can be utilized as a reductant for the pinacolic coupling. Neither cerium metal itself nor CeI_3 provide more than a trace of coupled product. A divalent cerium species has been implicated as the active species in the aforementioned protocols, although there is little direct evidence to establish this. Utilizing the Ce–I_2 procedure, a variety of aldehydes and ketones have been reductively coupled, providing the desired 1,2-diols (eq 281). Esters, nitriles, and alkenyl halides



(281)

are all tolerated under the reaction conditions, and ketones as well as aromatic aldehydes provide excellent yields of coupled products. Only two exceptions to this general reactivity pattern have been noted thus far. Benzophenone is unreactive under the conditions utilized, and cyclododecanone provides a 70% yield of cyclododecanol rather than pinacolic coupling.

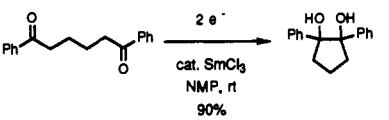
Pinacolic coupling reactions are also accomplished with considerable efficiency by SmI_2. Treatment of aldehydes or ketones with SmI_2 in the presence of a proton source such as methanol results in selective reduction to corresponding alcohols, and formation of pinacols is negligible. However, in the absence of a proton source, both aldehydes and ketones are cleanly coupled in the presence of SmI_2 to generate pinacols (eq 282).[182] Yields are excellent in nearly every case, and



(282)

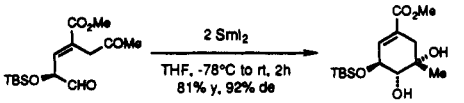
the method thus competes effectively with other established procedures for this process. Unfortunately, roughly equimolar ratios of threo and erythro isomers are generated in these reactions. Aromatic aldehydes and aromatic ketones couple within a few seconds at room temperature in THF. Aliphatic aldehydes require a few hours under these conditions, and a day is needed for complete reaction of aliphatic ketones. Amines, nitriles, and nitro groups are tolerated under these conditions. Surprisingly, carboxylic acids can also be incorporated into substrates with little attenuation in yields of pinacolic products. It is not clear why competitive reduction to alcohols is not observed in this instance, because a proton source is obviously provided by the acid under the reaction conditions.

Samarium(III)-catalyzed electrochemical dimerizations of aldehydes and ketones have been reported, and these provide an economical entry to symmetrical pinacols.[183] Sacrificial aluminum or magnesium electrodes are employed in the electrolyses, which are carried out in *N,N*-dimethylformamide (DMF) or *N*-methylpyrrolidone (NMP). The $SmCl_3$ utilized is essential for conversion: in the absence of this catalyst monomeric alcohols and aldol products are generated. In the catalytic cycle $SmCl_3$ is postulated to be electrochemically reduced to a Sm(II) species, which serves as the active electron transfer agent. In general, aromatic aldehydes and ketones perform better in these reactions than their aliphatic counterparts, and both intermolecular and intramolecular pinacolizations can be carried out employing this procedure (eq 283).

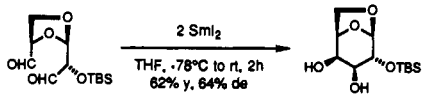


(283)

Considerable stereochemical control is achieved in intramolecular pinacolization reactions promoted by SmI_2. Hanessian and co-workers have studied cyclization of a variety of 1,5- and 1,6-dialdehydes, providing near exclusive formation of the cis diols.[184] Heterosubstituents α to the carbonyls do not interfere with the coupling process, indicating that reductive dimerization is much more rapid than reductive cleavage of these substituents. Furthermore, polar substituents α to the carbonyls end up anti to the diol stereocenters in the final product, providing a stereocontrol element as well (eqs 284 and 285).

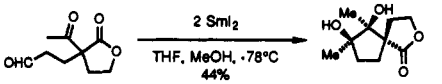


(284)

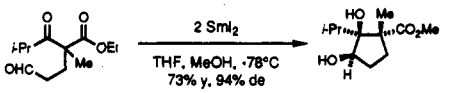


(285)

In suitably functionalized systems, excellent yields and diastereoselectivities over three contiguous stereocenters are achieved in intramolecular pinacolic coupling reactions promoted by SmI_2 (eqs 286 and 287).[185]

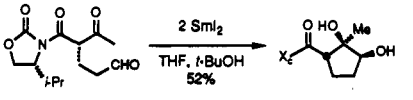


(286)



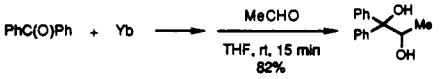
(287)

Both five- and six-membered rings can be generated by this process, but substantially lower yields and diastereoselectivities are observed for the latter. Yields obtained for β-keto amide substrates are also somewhat lower than those observed in the β-keto ester series, although a chiral, nonracemic oxazolidinone has been employed with great success, permitting entry to highly functionalized, enantiomerically pure dihydroxycyclopentanecarboxylate derivatives (eq 288).



(288)

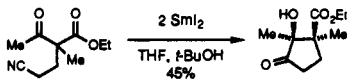
Pinacolic cross-coupling reactions are exceedingly difficult to achieve, and the only systems for which this is known to be effectively promoted by lanthanide reagents is in the case of diaryl ketone/carbonyl coupling reactions. Thus, ytterbium diaryl ketone dianions, generated by reaction of ytterbium metal with diaryl ketones, are effectively coupled with aldehydes and ketones to afford vicinal diols in very good yields (eq 289).[119a,b,186]



(289)

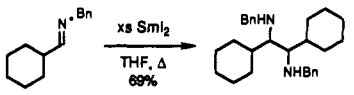
Procedures related to pinacolic coupling reactions are also promoted by lanthanide-based reductive coupling reagents. One such example is a ketone–nitrile reduc-

tive coupling process. This process permits construction of highly functionalized carbocycles with substantial control of stereochemistry,[185] although yields are somewhat diminished because of the reluctance of nitriles to undergo radical addition reactions (eq 290).



(290)

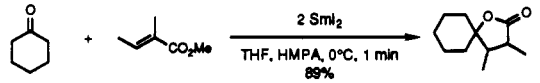
Vicinal diamines are synthesized by a procedure analogous to the pinacolic coupling reaction in which aldimines are reductively coupled with SmI_2 (eq 291).[187] The coupling is not highly diastereoselective and has not been applied to imines derived from ketones. Cross-coupling of diaryl imines with ketones is also possible by utilizing this protocol, although the scope of this process has not been extensively explored.[187b]



(291)

2. Ketone–Olefin Coupling

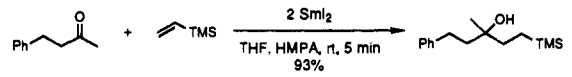
Ketyls derived from reduction of aldehydes or ketones with SmI_2 can be coupled to alkenes and alkynes in what amounts to radical addition reactions. Both intermolecular and intramolecular versions of this reaction have been described. In terms of intermolecular reactions, the ketone–olefin coupling process is apparently restricted to activated alkenes. Thus conjugated esters react with aldehydes and ketones in the presence of SmI_2, affording reasonable yields of butyrolactones (eq 292).[188] These reactions are best performed in the presence of HMPA, which dramatically enhances reactivity (and yields), permitting reactions to run to completion in minutes as opposed to 3–6 h without this additive. Mixtures of diastereomers are generated in



(292)

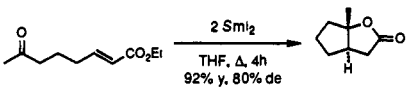
nearly all of the examples studied. Conjugated nitriles do not fare as well as their ester counterparts in these reactions. Yields of only 17–20% were reported for these substrates.[188a] In terms of the ketyl precursor, both aliphatic and aromatic ketones and aldehydes can be utilized,[188a] and even formaldehyde is effective to some degree.[188b]

Other conjugated olefins (e.g., styrene, 2,3-dimethylbutadiene), vinylsilanes, vinyl acetates, and allylic acetates serve as efficient ketyl acceptors in SmI_2-promoted coupling reactions (eq 293).[188d] The allylic radical generated by addition of ketyl to 2,3-butadiene leads to olefinic mixtures of coupled products, and allylic acetate coupling is also complicated by substantial β-elimination of acetate ion, leading to product mixtures.



(293)

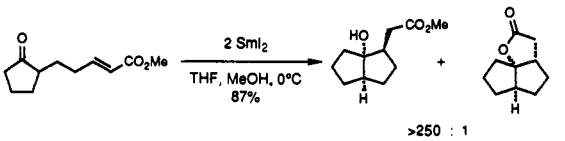
Bicyclic butyrolactones are generated when intramolecular versions of ketyl–olefin coupling reactions are carried out with unsaturated esters (eq 294).[188c,189] The method has been employed to form five-, six-, or seven-membered rings, although yields for the larger rings are modest (45–66%). Yields are marginally improved



(294)

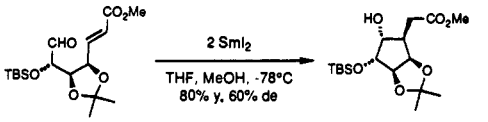
by addition of HMPA, which also permits reactions to be carried out under milder conditions. Addition of a catalytic amount of $FeCl_3$ has little effect on yields. In most cases, diastereoselectivities are low, ranging from 2.5:1 to 4:1.

Diastereoselectivities in intramolecular ketyl–olefin coupling reactions were demonstrated by Enholm and co-workers to be much higher in syntheses of conformationally restricted bicyclic systems, or when polar substituents are present to serve as stereochemical control elements for cyclization.[190] Olefin geometry plays a major role in terms of diastereoselection for the cyclization process leading to fused bicyclic systems. Whereas *E* olefinic isomers provide high diastereoselectivity in ring-forming processes (eq 295), *Z* isomer coupling reactions are virtually stereorandom. These dramatic differences were attributed to a combination of steric and electronic effects. A critical dependence

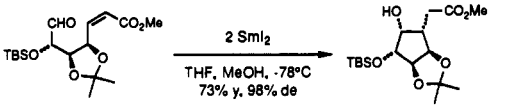


(295)

on olefin geometry is also observed in more highly functionalized systems derived from carbohydrates (eqs 296 and 297). For these substrates, relative asymmetric induction is often quite high.

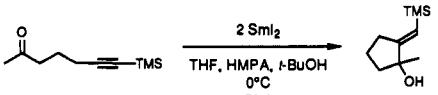


(296)

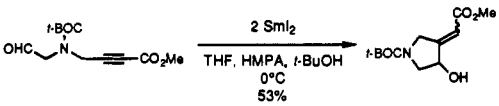


(297)

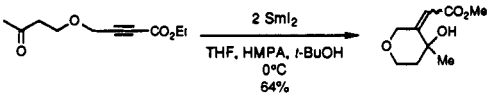
Carbocycles as well as oxygen and nitrogen heterocycles are generated by reaction of appropriately functionalized acetylenic ketones with SmI_2.[191] Although five- and six-membered rings could be accessed by this process, activated alkynes were necessary for construction of the cyclohexyl ring systems. Diastereocontrol was high in many cases (eqs 298–300).



(298)



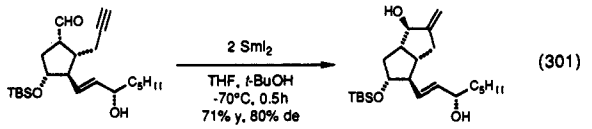
(299)



(300)

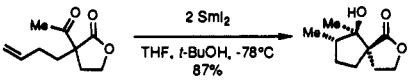
Although isolated alkenes and alkynes do not couple intermolecularly with ketyls in SmI_2-promoted reactions, these less reactive radical acceptors can be partners for intramolecular coupling processes.[191,192] This protocol has thus been utilized as a key step in the

synthesis of isocarbacyclin (eq 301). Samarium(II) iodide was found to be superior to several other reagents for conversion of the alkynyl aldehyde to the cyclic allylic alcohol.

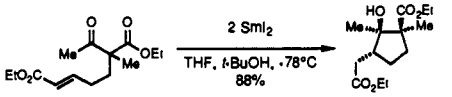


(301)

Highly diastereoselective processes are realized when olefinic β-keto ester and β-keto amide substrates are utilized in ketone–olefin reductive coupling processes. Both electron deficient and unactivated olefins can be utilized in these reactions (eqs 302 and 303).[185b,193] In



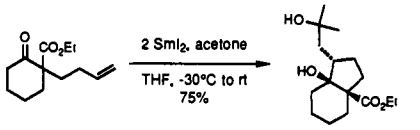
(302)



(303)

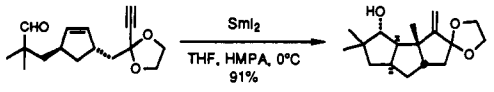
such examples, one can take advantage of chelation to control relative stereochemistry about developing hydroxyl and carboxylate stereocenters.

Because 2 equiv of SmI_2 are required for complete reaction, the reductive coupling must be a two-electron process overall. Cyclization appears to occur after transfer of a single electron, with Sm(III) controlling stereochemistry at this stage by chelation with the Lewis basic ester carbonyl. Subsequent reduction of the radical generated after cyclization to an organosamarium intermediate, followed by immediate protonation accounts for the observed products. The transient organosamarium intermediate can be trapped by added electrophiles such as aldehydes and ketones, providing a sequential radical cyclization/intermolecular carbonyl addition sequence (eq 304).[194]



(304)

Another type of tandem radical cyclization process has been described in which SmI_2 plays a critical role. Thus, an appropriately functionalized enynal, upon treatment with SmI_2, undergoes tandem cyclization to provide the key intermediate for the synthesis of (±)-hypnophilin and formal total synthesis of (±)-coriolin (eq 305).[195] Cyclization in this case again occurs



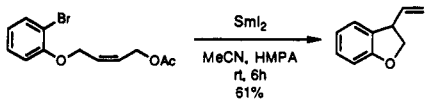
(305)

after transfer of a single electron, and in fact the entire process requires less than 2 equiv of SmI_2. When cyclizations were quenched with D_2O no deuterium was incorporated at the newly formed vinyl carbon, implying that the alkenyl radical produced after tandem cyclization abstracts a hydrogen from the solvent faster than it is reduced to the anion by SmI_2. This and the work by Molander and Kenny described above[185b,193,194] confirm observations of Inanaga and co-workers in their work on reduction of organic halides with SmI_2.[50,76] Thus, alkyl halides are reduced by SmI_2 to hydrocarbons by means of a transient organosamarium species (which can be trapped by D_2O), whereas aryl (and presumably alkenyl) halides show no deuterium incorporation upon reduction. Rather, the intermediate radicals simply abstract a hydrogen atom from THF solvent prior to further reduction to the anion.

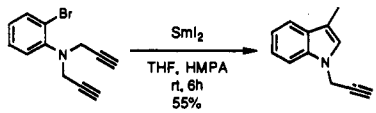
3. Radical Addition to Carbon–Carbon Unsaturated Systems

Samarium(II) iodide has proven effective for initiation of various radical addition reactions to alkenes and alkynes. In many cases, the SmI_2 protocol provides significant advantages over more traditional radical initiation procedures which are generally promoted by tin reagents. In particular, workup procedures are much easier in lanthanide promoted reactions; in tin promoted protocols complete removal of tin byproducts is often a considerable problem.

Cyclization reactions of aryl radicals are particularly well suited to promotion by SmI_2 because aryl radicals are not readily reduced to corresponding anions by the lanthanide reducing agent. As confirmation of this, general methods for synthesis of nitrogen and oxygen heterocycles have been developed which are based on SmI_2-mediated cyclization of aryl radicals onto alkene and alkyne acceptors (eqs 306 and 307).[196] Benzofuran, naphthofuran, and indole systems were all readily constructed utilizing the procedure outlined.

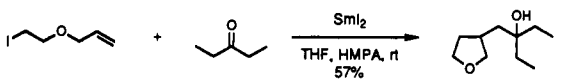


(306)

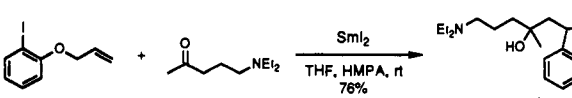


(307)

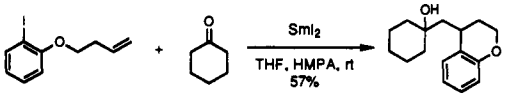
Unlike tin hydride promoted radical reactions, which leave products less highly functionalized than starting materials, the SmI_2-promoted procedure provides one with the opportunity to assemble more highly functionalized frameworks through a sequential radical cyclization/intermolecular carbonyl addition reaction.[197] Thus the intermediate radical formed after initial cyclization can be reduced by SmI_2, forming a transient organosamarium(III) intermediate. This can subsequently be trapped by added ketone electrophiles, affording products with functionality suitable for further manipulation (eqs 308–310). Analogous nitrogen heterocycles can also be prepared by this procedure, but yields in these processes are only modest.



(308)



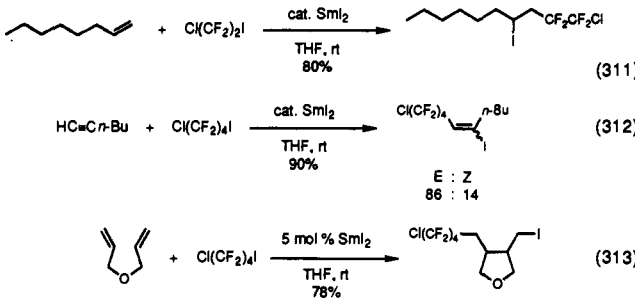
(309)



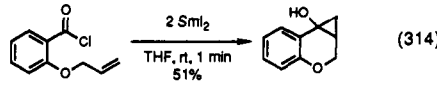
(310)

Samarium(II) iodide has been used to initiate addition of polyhaloalkanes to olefins and alkynes via radical

chain reactions.[198] For example, perfluoroalkylation reactions of alkenes and alkynes are catalyzed by SmI_2 (eqs 311 and 312), affording high yields of addition products and thereby providing a useful alternative to photochemical, thermal, electrochemical, and other metal-catalyzed routes to these molecules. Cyclization reactions initiated by this process can also be carried out (eq 313).

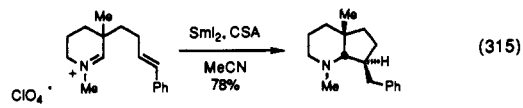


A unique double cyclization process has been reported by Kagan and co-workers.[199] When 2-(allyloxy)benzoyl chlorides are treated with SmI_2, an acyl radical is generated which undergoes intramolecular addition to the double bond, forming a new radical. This radical can then be reduced by a second equivalent of SmI_2, generating an anion. The organosamarium(III) intermediate thus generated intramolecularly adds to the ketone, forming a cyclopropanol (eq 314).



4. Miscellaneous Reductive Coupling Reactions

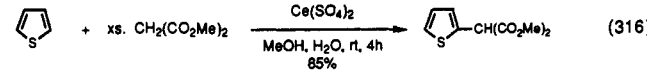
The reduction of ω-unsaturated iminium salts by single electron transfer from SmI_2 provides ω-unsaturated α-amino radicals which undergo radical cyclizations to provide nitrogen heterocycles.[200] Good diastereoselectivity is achieved in these processes in certain cases (eq 315), and the protocol thus may be useful for the stereocontrolled synthesis of alkaloid natural products.



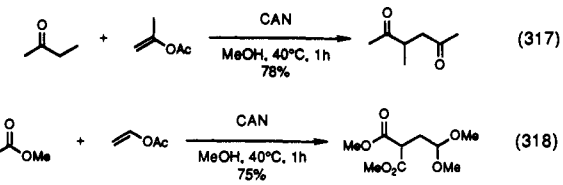
F. Oxidative Coupling Reactions

As with functional group oxidation chemistry employing lanthanide reagents, oxidative coupling reactions are dominated by Ce(IV) promoted processes. Several studies indicating the advantages of Ce(IV) oxidants have been published. These reports allude to the enhanced reactivity and general superiority of Ce(IV) over the more frequently utilized Mn(III) salts for such oxidative conversions.

A variety of oxidative carbon–carbon bond forming reactions can be carried out utilizing Ce(IV) reagents. One such class of transformations includes aromatic substitutions. In general, free-radical aromatic substitution reactions on benzene derivatives suffer from lack of regioselectivity on the aromatic ring.[201] This is not a problem in substitution reactions on electron-rich heteroaromatics such as thiophene and furan.[202] Malonylation can thus be carried out regioselectively in reasonable yields when the reaction is promoted by cerium(IV) sulfate (eq 316).

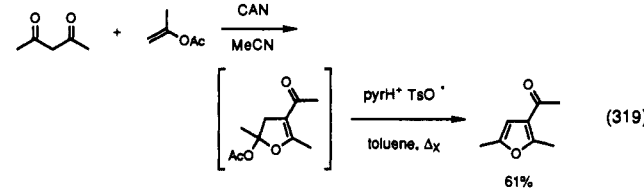


1,4-Dicarbonyl compounds or dimethyl acetals of 1,4-ketoaldehydes are readily synthesized by CAN-promoted reactions of ketones with vinyl or isopropenyl acetate, respectively (eqs 317 and 318).[203] The Ce(IV)



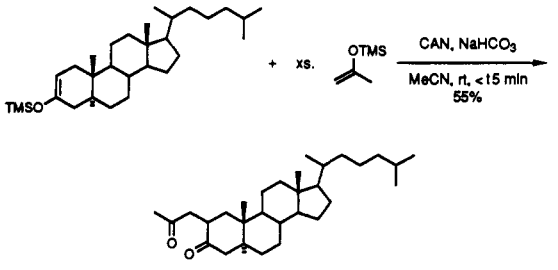
mediated reaction has several advantages over reported Mn(III) promoted oxidative coupling procedures, including higher yields and the ability to control regiochemistry in 2-alkanone coupling reactions. There are some limitations of the reaction. Perhaps the most serious is that the oxidation of ketones (especially acetone) is very slow, and thus the protocol requires utilization of carbonyl compound as solvent for the reaction. Therefore, solid or high molecular weight ketones cannot be used in the reaction. Furthermore, attempts to extend the reaction to 2-alkyl-substituted vinyl acetates failed with ketone substrates, but could be effected when 1,3-dicarbonyl compounds were used as radical precursors.

Subsequent development of these reactions has led to a convenient synthesis of 3-acyl and 3-carboalkoxyfurans. By performing the CAN reaction of 1,3-dicarbonyl substrates with alkenyl acetates in acetonitrile solvent instead of methanol, 5-acetoxy-4,5-dihydrofurans were generated in good yields (eq 319).[204] Heating these intermediates in toluene in the presence of pyridinium tosylate afforded 2-alkyl-3-acylfurans (from 1,3-diketones) or 2-alkyl-3-carboalkoxyfurans (from β-keto esters).



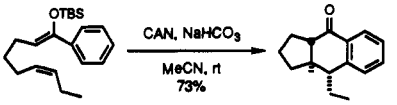
Trimethylsilyl enol ethers are cross-coupled in a CAN-promoted oxidative coupling process, providing another selective synthesis of 1,4-diketones.[205] Because silyl enol ethers are much more readily oxidized than their ketone precursors, they react at reasonable rates even in solution. This permits use of high molecular weight or solid substrates, thus solving one of the major problems mentioned above associated with oxidative coupling of ketones to alkenyl acetates in the synthesis of 1,4-diketones. The success of the cross-coupling resides in the ability to selectively oxidize 1,2-disubstituted silyl enol ethers in the presence of less highly substituted derivatives, and in the utilization of excess 1-substituted silyl enol ether to prevent homocoupling (eq 320).

Oxidative cyclization of unsaturated silyl enol ethers with CAN provides a stereoselective route to tricyclic



(320)

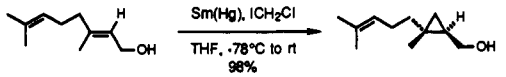
ketones (eq 321).[206] Although in some cases Cu(II)-mediated processes provide higher yields of products, usually the CAN and Cu(II) protocols can be utilized interchangeably. Questions concerning the scope and intimate mechanistic details of the reactions are still under study.



(321)

G. Cyclopropanation Reactions

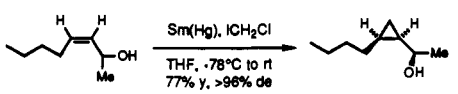
Probably the best method for preparing SmI_2 is to treat samarium metal with diiodomethane. Presumably, oxidative metalation occurs to provide a species best denoted as "$ISmCH_2I$". α-Elimination ensues, generating SmI_2 and methylene. This presumed sequence of events suggested the possibility of trapping the carbenoid intermediate with olefins, providing an alternative to the traditional Simmons–Smith procedure for preparation of cyclopropanes. In fact, the samarium-promoted route to cyclopropanes works very well in specific cases, providing a useful alternative to the more traditional zinc-mediated process.[207] In practice, a more efficient and economical cyclopropanation is achieved with Sm(Hg) in the presence of ICH_2Cl. Thus, reaction of geraniol with Sm(Hg)/ICH_2Cl provides a single diastereomeric product in excellent yield (eq 322). In contrast to the zinc-me-



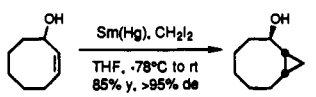
(322)

diated reaction, no byproducts resulting from cyclopropanation of the isolated olefin are detected. In fact, subjection of monocyclopropanated geraniol to the reaction conditions leads to complete recovery of starting material. This result and failed attempts to cyclopropanate other isolated olefins and even homoallylic alcohol substrates demonstrates the specificity of the Sm(Hg)/ICH_2Cl protocol for allylic alcohols.

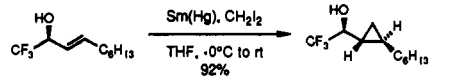
In addition to enhanced chemoselectivity, higher diastereoselectivity can often be achieved in samarium-promoted reactions than in classical Simmons–Smith reactions (eqs 323–325).[207,208] Perhaps a major reason for this is the initiation of Sm(Hg)-promoted reactions at –60 °C, whereas most zinc-mediated reactions are carried out in boiling ether.



(323)

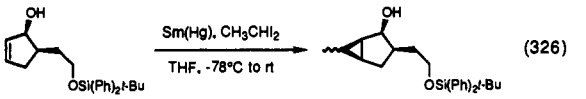


(324)



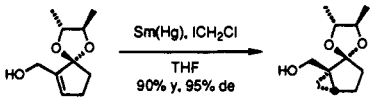
(325)

Ethylidenation reactions can also be performed utilizing Sm(Hg), allowing one to avoid use of pyrophoric diethylzinc for such processes.[207,209] In addition, the samarium-promoted reaction permits higher diastereoselectivities to be achieved in this transformation (eq 326).



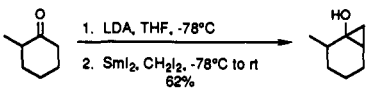
(326)

Samarium-promoted cyclopropanation of allylic alcohols incorporating a chiral (2*R*,3*R*)-butanediol ketal director provides high diastereoselectivity and yields in the desired conversion (eq 327).[210] Initial experiments carried out under standard Simmons–Smith conditions (CH_2I_2/Zn–Ag or Zn–Cu) proceed with poor chemical yields and modest diastereoselectivity.



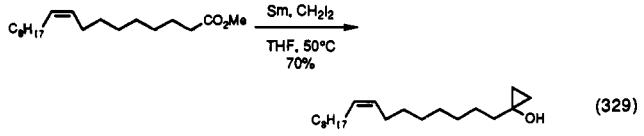
(327)

Treatment of enolates with the Simmons–Smith reagent system do not lead to cyclopropanes, but rather to α-methylated ketones. By contrast, cyclopropanation of enolates is achieved by utilizing SmI_2/CH_2I_2.[211] Thus, generation of the kinetic enolate with LDA followed by addition of SmI_2/CH_2I_2 provides a general route to cyclopropanols (eq 328).



(328)

Other routes to cyclopropanols are accomplished by the agency of lanthanide reagents. For example, when α-halo ketones are treated with diiodomethane and samarium at 0 °C, cyclopropanols are obtained in reasonable yields.[150a] Esters also react with CH_2I_2 in the presence of samarium to afford cyclopropanols, providing a one-carbon homologation route to these materials (eq 329).[212] Reactions are envisioned to proceed



(329)

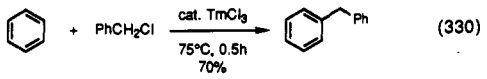
via an initial nucleophilic acyl substitution reaction, providing an α-iodo ketone. This is postulated to undergo reduction by Sm or SmI_2, generating an enolate. Cyclopropanation of the enolate then leads to the observed cyclopropanol.

H. Lanthanides as Lewis Acid Catalysts

1. Friedel Crafts Reactions

Lanthanide trichlorides were initially reported to be weak catalysts for Friedel–Crafts alkylation processes.[213] However, nearly all of the lanthanide trichlorides were subsequently shown to be quite effective in promoting this very important process.[214] The late lanthanide salts ($DyCl_3$, $TmCl_3$, and $LuCl_3$) demonstrate particularly high activity, whereas $LaCl_3$ possesses little catalytic

reactivity (eq 330). In these processes, the arene is used



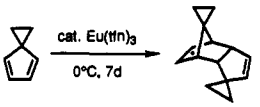
(330)

as the solvent. Only small amounts of dibenzylbenzenes are generated under these reaction conditions. A number of different alkyl halides can apparently be utilized, and the lanthanide catalysts can be reused after the usual aqueous workup of the reaction mixture. This is a great advantage over more traditional catalysts, such as $AlCl_3$, which cannot be recovered in active form after the desired reaction is complete.

2. Diels–Alder and Related Reactions

Numerous lanthanide complexes have served as highly selective catalysts for Diels–Alder reactions and related transformations. Lanthanide reagents thus provide access to unique reaction manifolds that appear difficult or impossible to achieve without catalysis or even utilizing other, less effective, Lewis acids.

Relatively few lanthanide-catalyzed examples of the traditional Diels–Alder reaction have been explored. In what is perhaps the first mention of lanthanide-promoted cycloaddition reactions, Eu(III) salts were reported to catalyze dimerization of spiro[2.4]hepta-4,6-diene by a Diels–Alder cycloaddition process (eq 331).[215] The catalyst utilized in this particular study was a shift reagent, tris[1,1,1,2,2,3,3,7,7,8,8,9,9,9-tetradecafluoro-4,6-nonanedionato]europium(III) [Eu(tfn)$_3$]. That the

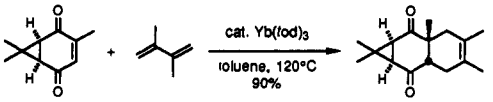


(331)

lanthanide complex was indeed catalyzing the reaction was evident because no dimerization took place in the absence of shift reagent.

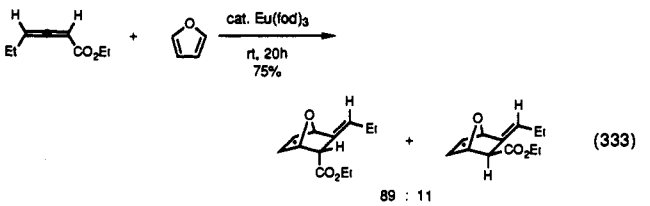
The effectiveness of lanthanide catalysts in promoting Diels–Alder reactions permits extension of the method to reactions where acid-sensitive components are to be combined. For example, Diels–Alder reactions employing acrolein or crotonaldehyde dienophiles are often problematical.[216] However, many dienes (even furan) react with acrolein at room temperature in 1–2 days in the presence of catalytic Yb(fod)$_3$, providing the expected cycloaddition products with minimal side reactions. Crotonaldehyde is condensed with cyclopentadiene, providing adducts in which the endo isomer predominates by a factor of 10:1.

In an effort to study the effect of *gem*-dimethylcyclopropane rings on regio- and stereoselectivities of Diels–Alder cycloadditions of carenone derivatives, Yb(fod)$_3$ was utilized as a catalyst to promote the desired reactions.[217] Use of this mild lanthanide Lewis acid prevented decomposition of these acid labile carenone derivatives (eq 332).



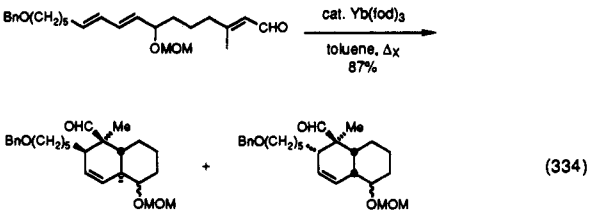
(332)

Allenes comprise another set of dienophiles benefiting by lanthanide catalysis in Diels–Alder reactions. Allenes normally exhibit low dienophilicity in cycloaddition reactions, and yet under forcing conditions they undergo substantial polymerization. Gandhi and co-workers developed a protocol employing lanthanide Lewis acid catalysis which permits the smooth condensation of electron-deficient allenes with cyclopentadiene and furans.[218] Lanthanide catalysts significantly improved the yields of cycloadducts and did so under much milder conditions than in uncatalyzed reactions. Furthermore, stereoselectivity (endo addition and π-facial addition to the dienophile) in the [4 + 2] cycloaddition was also enhanced (eq 333).



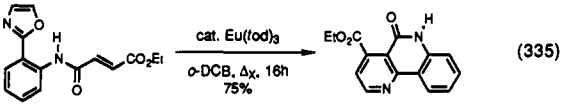
(333)

An approach to the synthesis of chlorothricolide takes advantage of a lanthanide-catalyzed intramolecular Diels–Alder reaction to assemble the octalin ring system of the molecule.[219] Unfortunately, stereochemistry is not efficiently controlled in this process (eq 334); however, to some extent the rapid assembly of the carbon skeleton makes up for this deficiency.



(334)

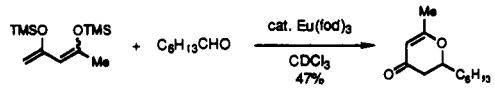
Another type of intramolecular Diels–Alder reactions has greatly benefited by lanthanide catalysis. Thus, intramolecular reactions involving oxazole dienes proceed in the presence of Eu(fod)$_3$ to provide substituted 5*H*-[1]benzopyrano[4,3-*b*]pyridines and benzo[*h*]-1,6-naphthyridines in reasonable yields (eq 335).[220] The reaction is notable because 2-aryloxazole heterodienes are extremely reluctant to undergo cycloaddition reactions owing to both steric and electronic factors. For example, starting materials were recovered when reactions were run without a catalyst, and use of $ZnBr_2$ caused decomposition of the starting materials with no apparent product formation.



(335)

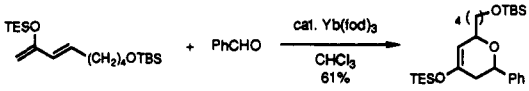
Perhaps the most dramatic examples of lanthanide Lewis acid catalysis have resulted from applications to hetero-Diels–Alder reactions. The combined efforts of several research groups have led to unprecedented entries to highly substituted, stereodefined dihydropyran derivatives. In the reaction scheme first outlined by Danishefsky, oxophilic lanthanide salts complex with aldehyde substrates, generating potent heterodienophiles for the desired cyclocondensation. Many examples of this reactivity pattern attest to the generality of the method. For example, the reaction of 1-alkyl 1,3-dioxygenated dienes with aldehydes affords a simple, one-step route to 6-substituted 2,3-dihydropyrones (eq 336).[221]

Appropriately functionalized 1-alkyl-3-oxygenated dienes also react very efficiently.[222] The catalyst of



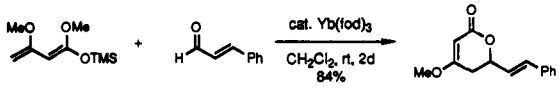
(336)

choice for this hetero-Diels–Alder process is Yb(fod)$_3$. Less than 5% of this Yb(III) catalyst is required for the process, whereas a full equivalent of $ZnCl_2$ is necessary for complete reaction in analogous cases (eq 337). The Yb(fod)$_3$ catalyst is also more effective than the corresponding Eu(fod)$_3$ species, perhaps because of the former's enhanced Lewis acidity.



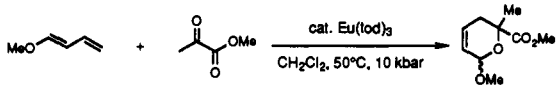
(337)

Several groups have exploited the hetero-Diels–Alder chemistry to provide efficient routes to dihydropyrones.[220,223] Thus, 1,1,3-trialkoxy dienes treated with appropriate aldehydes in the presence of lanthanide(III) catalysts provide excellent yields of desired 2-alkoxy-5,6-dihydro-γ-pyrones. Remarkably, even unsaturated aldehydes can be utilized as heterodienophiles in the reaction, despite potential cycloaddition reactivity at either the carbonyl unit or the dienophilic carbon–carbon double bond in these substrates (eq 338). In the absence of lanthanide catalysts, mixtures of the desired product and the product resulting from cycloaddition to the carbon–carbon bond are generated. Thus lanthanide catalysts serve not only to improve yields and provide a single regioisomeric product in these processes, but also direct cyclocondensation to the activated carbonyl subunit of conjugated enal systems. In these instances the stronger Lewis acid catalyst, Yb(III), again provides higher yields than either Eu(III) or stoichiometric $ZnCl_2$.

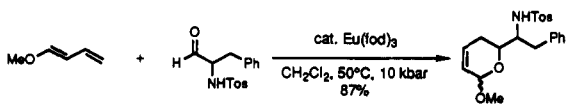


(338)

Although many dienes undergo cycloaddition with carbonyl substrates under very mild conditions with Lewis acid catalysis, some less reactive educts require a combination of lanthanide complex catalysis and high pressure to effect complete conversion to products.[224] 1-Methoxy-1,3-butadiene is one such example. This diene polymerizes immediately in the presence of $ZnCl_2$, $BF_3{\cdot}Et_2O$, and $(RO)_2AlCl$, but can be utilized successfully in high-pressure hetero-Diels–Alder reactions when suitable ketone substrates are activated by Eu(fod)$_3$ catalysts. The most suitable dienophiles are carbonyl substrates possessing α- or β-heterosubstituents (eqs 339 and 340).

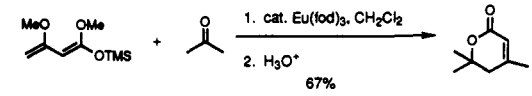


(339)



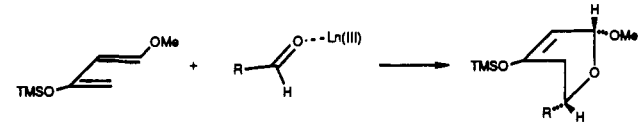
(340)

Initially, only highly electrophilic aldehydes received attention as dienophiles for the hetero-Diels–Alder reaction. However, 1,3-dimethoxy-1-(silyloxy)butadiene (Brassard's diene) was shown to undergo hetero-Diels–Alder reactions with reactive aldehydes as well as unactivated ketones (eq 341).[223c] In fact, regiospecific condensation was achieved utilizing a variety of Lewis acid promoters, including Eu(fod)$_3$ and tris[3-((heptafluoropropyl)hydroxymethylene)-*d*-camphorato]europium(III) [Eu(hfc)$_3$].



(341)

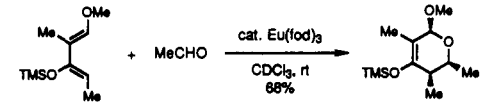
The value of lanthanide catalysts in hetero-Diels–Alder reactions does not end with their ability to promote reactions of sensitive substrates or to provide higher yields under milder conditions. Lanthanide complexes also serve in several capacities to control stereochemistry.[225] Somewhat surprisingly, the lanthanide promoted reaction of achiral aldehydes with 1,3-dialkoxybutadienes provides the product resulting from endo addition of the aldehyde to the diene (eq 342). Because there are no obvious secondary orbital



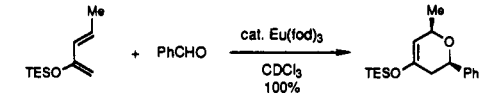
(342)

interactions placing a simple alkyl group of the aldehyde endo in the transition structure, steric effects associated with the Lewis acid complex were suggested as control elements in the overall stereochemistry of the process. Thus, the lanthanide cation is proposed to bind anti to the alkyl group of the aldehyde. If the effective size of the cation–solvent array is greater than that of the alkyl group of the aldehyde, then one could explain the observed endo selectivity as a consequence of exo directivity of the catalyst–solvent ensemble. Interestingly, this "endo selectivity" is a function of the substitution pattern about the diene, and stereoselectivity erodes to a large extent for some simpler dienes.[226]

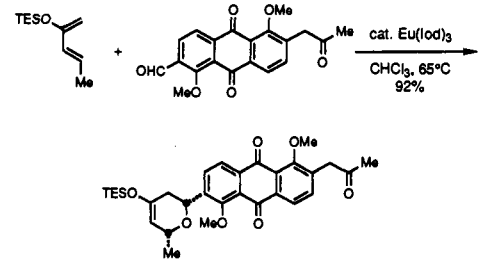
The endo selectivity provided by lanthanide-catalyzed hetero-Diels–Alder reactions has been demonstrated in a variety of diverse systems, some examples of which are depicted below (eqs 343–346).[221,226,227] One



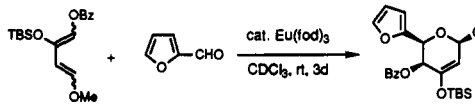
(343)



(344)



(345)

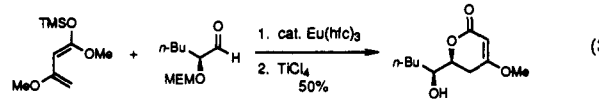


(346)

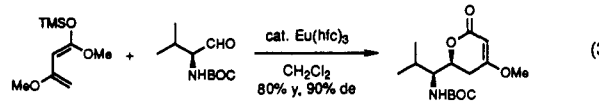
advantage in utilizing a lanthanide catalyst for this process is the ability to retain sensitive silyl enol ether

functionalities in the final products under the mild reaction conditions allowed by use of these Lewis acids.

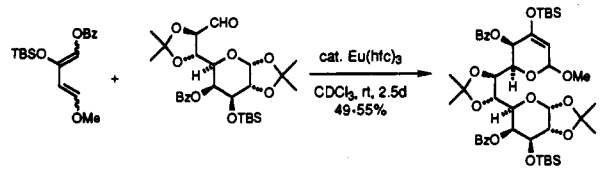
Under optimized conditions, high diastereoselectivity is achieved in hetero–Diels–Alder reactions between chiral aldehydes and active dienes. Aldehydes with α-stereocenters incapable of chelation provide only low levels of asymmetric induction in the Cram or Felkin–Anh sense.[223c] Aldehydes bearing chelating substituents at the α-stereocenter engender high diastereoselectivity in a chelation controlled process, so long as the proper lanthanide Lewis acid is chosen, and provided substituents on the aldehyde are not so large as to prevent complete complexation of the lanthanide ion (eqs 347–349).[223c,225,227b,228] Chelation-controlled processes in which the sense of asymmetric induction is derived from β-stereogenic centers have also been observed (eq 350).[229]



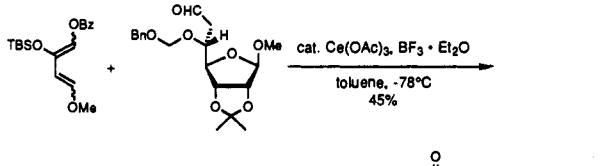
(347)

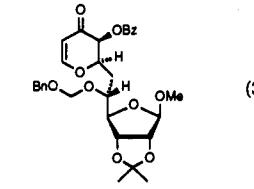


(348)



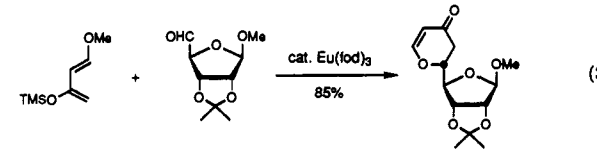
(349)



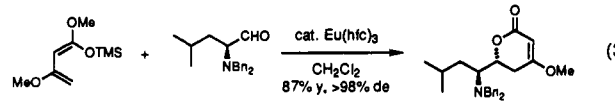


(350)

In substrates bearing α-heterosubstituents incapable of chelation (for either steric or electronic reasons[228b,c]), high diastereoselectivity is achieved in the Felkin–Anh sense (eqs 351 and 352).[228a,229]

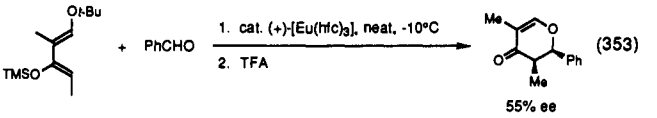


(351)



(352)

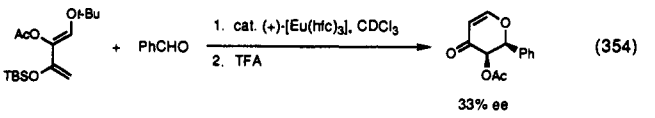
Variable success has been achieved in utilizing chiral, nonracemic lanthanide catalysts for absolute asymmetric induction in cyclocondensation processes. In general, enantiomeric excesses range from 18–36% in simple systems with chiral catalysts.[223c,230] A substantial improvement in enantioselectivity comes by modifying reaction conditions. Although essentially no change in enantiomeric excess was noted by increasing the proportion of chiral catalyst, conducting the reaction in the absence of solvent at reduced temperatures improved chiral induction to 55% ee (eq 353).



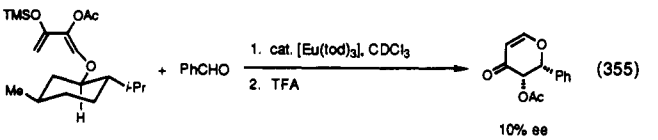
(353)

The source of asymmetric induction in these systems is unknown, and no model with predictive value has been proposed. Other diene–heterodienophile systems have been reported to exhibit modest[231] or negligible asymmetric induction utilizing the same chiral lanthanide catalyst.[223c]

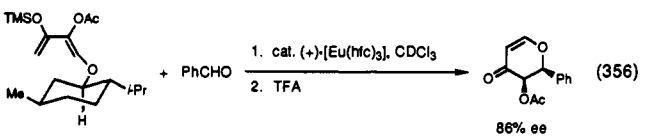
A new concept in asymmetric induction was introduced as a result of hetero-Diels–Alder reaction studies employing chiral catalysts in conjunction with dienes containing chiral auxiliaries.[232] Termed "specific interactivity" of chiral catalysts and chiral auxiliaries, the method resulted in diastereofacial excesses of 95% in select cases. Equations 354–356 serve to illustrate the concept. By utilizing a chiral lanthanide catalyst



(354)



(355)

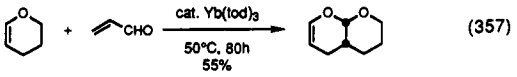


(356)

(eq 354), modest enantioselectivity for the L-isomeric product was achieved in the cyclocondensation reaction. A chiral (menthyl) auxiliary attached to the diene permits modest selectivity for the D-isomeric pyranose derivative (eq 355). The "mismatched" pair [i.e., L-selective (+)-Eu(hfc)$_3$ and D-selective diene as illustrated in eq 356], produces a strikingly high diastereomeric ratio in desired products. The diastereomeric excesses clearly do not reflect a simple numerical factoring of individual biases of these reagents (simple double stereodifferentiation), but are a consequence of "specific interactivity" inherent in the process itself. This protocol shows promise in the hetero-Diels–Alder chemistry described herein and could prove important in other transformations as well.

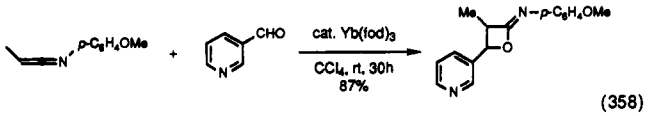
As mentioned previously, lanthanide catalysts often permit reactions of dienes and dienophiles containing sensitive functional groups. A particularly good illustration of this is the inverse electron demand Diels–Alder reaction reported by Danishefsky and Bednarski.[233] In this version of the hetero-Diels–Alder reaction, heterodienes (acrolein, crotonaldehyde, and cinnamaldehyde) and enol ethers combine to generate dihydropyrans (eq 357). These reactions are again stereospecific, providing only products resulting from endo addition. The reaction is quite sensitive to steric and/or

electronic effects, as more highly substituted enol ethers provide somewhat lower yields of desired cyclocondensation products.



(357)

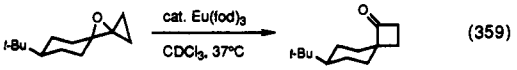
One example has been reported of a formal [2 + 2] cycloaddition reaction which benefits by lanthanide catalysis. Reaction of ketene imines with aldehydes under thermal conditions fails because of rapid oligomerization of the ketene imines. Attempts to catalyze the reaction with several Lewis acids (e.g., $AlCl_3$, Et_2AlCl, BF_3, $TiCl_4$) also failed, presumably for the same reason. By contrast, use of catalytic lanthanide complexes effectively promotes the reaction, permitting isolation of desired 2-iminooxetanes in reasonable yields (eq 358).[234] Mixtures of stereoisomers generally arise in these reactions, indicating the lack of concertedness in the process.



(358)

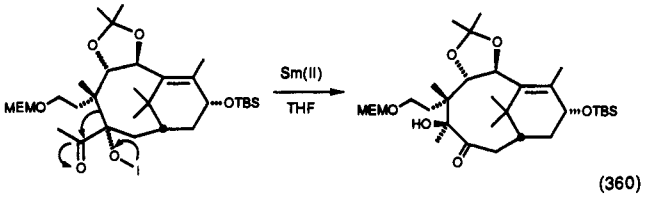
3. Lewis Acid Promoted Rearrangements

Two lanthanide promoted rearrangement reactions have been reported which involve the formation of carbon–carbon bonds. In the first, oxaspiropentanes were found to rearrange cleanly to cyclobutanones through the agency of $Eu(fod)_3$ (eq 359).[235] Aqueous acids and other Lewis acids (e.g., $LiClO_4$) also promote the rearrangement, but with significant loss of stereochemistry. This rearrangement forms the cornerstone of carbonyl spiroannulation and general dialkylation processes developed by Trost and co-workers in the 1970s.



(359)

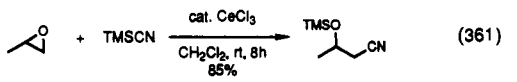
A novel Sm(III)-mediated ring expansion was encountered during studies aimed toward the total synthesis of taxusin.[236] Thus, treatment of an α-hydroxy ketone substrate with Sm(III) species induces rearrangement to a ring expanded product in high yields (eq 360). The structural (stereoelectronic) features of this substrate may be unique, as the α-hydroxy ketone epimer does not undergo an analogous transformation.



(360)

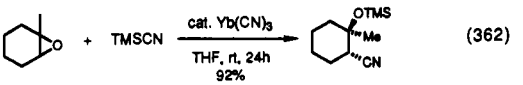
4. Lewis Acid Promoted Reactions of Oxiranes and Aziridines

Epoxides undergo efficient ring opening when treated with trimethylsilyl cyanide in the presence of lanthanide Lewis acid catalysts (eq 361).[160] Although some feeling for regioselectivity to be expected can be gained from this example, no data is available on stereoselectivity of the process when unsymmetrical epoxides are subjected to these reaction conditions.

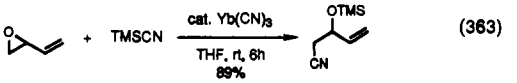


(361)

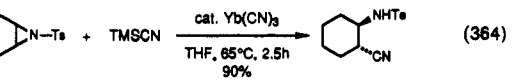
In more extensive studies, $Yb(CN)_3$ proved to be a mild, highly effective catalyst for regio- and stereoselective ring opening of oxiranes with trimethylsilyl cyanide.[237] A variety of epoxides react smoothly with this reagent, providing desired β-trimethylsiloxy nitriles in excellent yields (eqs 362 and 363). The same combination of reagents also effects ring cleavage of aziridines, providing a regio- and stereocontrolled entry to β-amino nitriles (eq 364).[238]



(362)



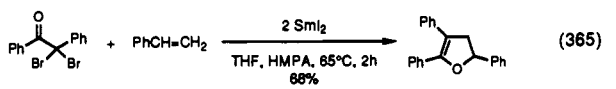
(363)



(364)

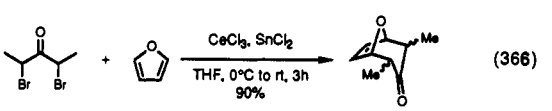
I. Miscellaneous Carbon–Carbon Bond Forming Reactions

Ketocarbenoids are generated from α,α-dibromodeoxybenzoin by reaction with SmI_2. Reactive intermediates produced in this fashion undergo a formal 1,3-dipolar cycloaddition with activated alkenes, resulting in formation of dihydrofurans (eq 365).[239] The same procedure utilizing zinc as reductant requires 2 days in benzene heated at reflux to proceed to completion, and very low yields are realized. Most aryl-substituted alkenes and isoprene provide good conversions to desired products. However, aliphatic alkenes such as cyclohexene and 1-hexene provide little, if any, dihydrofurans.



(365)

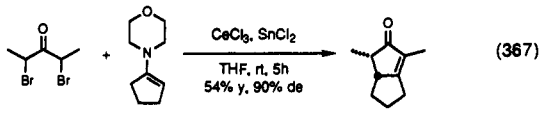
α,α'-Dibromo ketones react with 1,3-dienes in the presence of $CeCl_3$–$SnCl_2$, providing [3 + 4] cycloadducts in modest yields.[240] Although both $CeCl_3$ and $SnCl_2$ are necessary for the reaction, mechanistic details of the transformation are sketchy. Furans and cyclopentadiene provide very good yields of the expected cycloaddition products, but acyclic 1,3-dienes (isoprene and 2,3-dimethyl-1,3-butadiene) afford 4-cyclohepten-1-ones in only modest yields. The lack of diastereoselectivity further detracts from the method (eq 366).



(366)

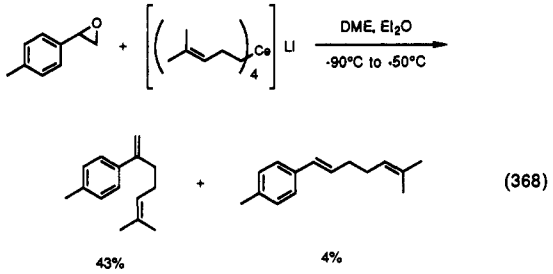
Although isolated alkenes do not produce [3 + 2] cycloaddition products under similar reaction conditions, nucleophilic enamines can be utilized to generate 2-cyclopenten-1-ones by a formal [3 + 2] process.[240] Diastereoselectivity in the limited examples attempted is quite good (eq 367).

Lithium tetraalkylcerium "ate" complexes react with epoxides, providing alkylated olefins in a process pos-



(367)

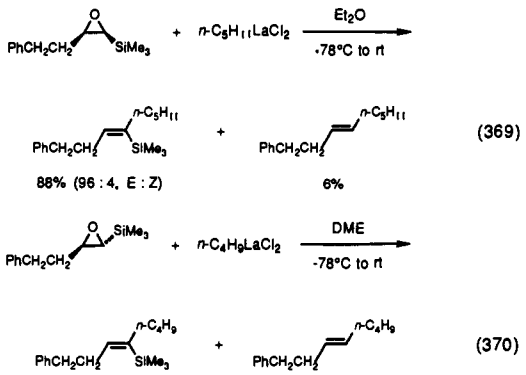
tulated to involve initial formation of oxiranyl organometallics.[241] α-Elimination of this anion to an alkoxy carbene ensues, with subsequent alkylation by a second equivalent of organometallic. Elimination of "cerium oxide" completes the process, affording the observed alkenes (eq 368). Although organolithiums undergo the



(368)

same reaction, yields with these organometallics are much lower than those employing the lanthanide reagents. Mixtures of regio- and stereoisomers are generally observed in both cases.

The reaction has been applied to trialkylsilyl-substituted epoxides, providing vastly different reaction manifolds depending on the stereochemistry of initial oxiranes. Thus the trialkylsilyl group of (*Z*)-1-(trialkylsilyl)oxiranes acidifies the α-proton, facilitating metalation. The resulting α-silyloxiranyl anion undergoes a reaction pathway very similar to that described for the simple oxiranes above. Good yields of stereodefined alkenylsilanes result (eq 369). On the



(369)

(370)

other hand, steric factors make (*E*)-1-(trialkylsilyl)oxiranes much more difficult to metalate. Desilylation thus becomes the preferred reaction pathway, affording a desilylated oxiranyl anion. α-Elimination, alkylation of the resulting alkoxy carbene, and β-elimination of "cerium oxide" this time leads to desilylated alkene (eq 370). Organolithiums and organolanthanide dihalides have been utilized interchangeably in both of these isomeric series of substrates.

IV. Acknowledgments

I wish to acknowledge my co-workers, whose dedicated efforts have sustained our program in the application of lanthanide reagents to selective organic synthesis and made these studies enormously pleasurable. Their many valuable contributions are recognized in the text and reference section of this review. In addition, we are very grateful to the National Institutes of Health, who have steadfastly supported our work since its inception.

V. References

(1) (a) Natale, N. R. *Org. Prep. Proced. Int.* **1983**, *15*, 387. (b) Kagan, H. B.; Namy, J. L. In *Handbook on the Physics and Chemistry of the Rare Earths*; Gschneidner, K. A., Eyring, L., Eds.; Elsevier: Amsterdam, 1984; p 525. (c) Kagan, H. B. In *Fundamental and Technological Aspects of Organo-f-Element Chemistry*; Marks, T. J., Fragalà, I. L., Eds.: Reidel: Dordrecht, 1985; p 49. (d) Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573. (e) Long, J. R. In *Handbook on the Physics and Chemistry of the Rare Earths*; Gschneidner, K. A., Eyring, L., Eds.; Elsevier: Amsterdam, 1986; p 335. (f) Kagan, H. B. *Inorg. Chim. Acta* **1987**, *140*, 3. (g) Kagan, H. B.; Sasaki, M.; Collin, J. *Pure Appl. Chem.* **1988**, *60*, 1725. (h) Kagan, H. B.; Collin, J. In *Proceedings of the NATO Advanced Research Workshop on Paramagnetic Organometallic Species in Activation/Selectivity, Catalysis*; Chanon, M., Julliard, M., Poite, J. C., Eds.; Kluwer Academic Publishers: Dordrecht, 1989; p 131. (i) Molander, G. A. In *The Chemistry of the Metal-Carbon Bond*; Hartley, F. R., Ed.; John Wiley & Sons: Chichester, 1989; Vol. 5, Chapter 8. (j) Kagan, H. B. *New J. Chem.* **1990**, *14*, 453. (k) Soderquist, J. A. *Aldrichim. Acta* **1991**, *24*, 15.
(2) (a) Ho, T.-L. *Synthesis* **1973**, 347. (b) Ho, T.-L. In *Organic Syntheses by Oxidation with Metal Compounds*; Mijs, W. J., de Jonge, C. R. H. I., Eds.; Plenum Press: New York, 1986.
(3) Periasamy, M.; Bhatt, M. V. *Synthesis* **1977**, 330.
(4) Balanikas, G.; Hussain, N.; Amin, S.; Hecht, S. S. *J. Org. Chem.* **1988**, *53*, 1007.
(5) (a) Kreh, R. P.; Spotnitz, R. M.; Lundquist, J. T. *Tetrahedron Lett.* **1987**, *28*, 1067. (b) Kreh, R. P.; Spotnitz, R. M.; Lundquist, J. T. *J. Org. Chem.* **1989**, *54*, 1526.
(6) Fisher, A.; Henderson, G. N. *Synthesis* **1985**, 641.
(7) Ho, T.-L. *Synth. Commun.* **1979**, *9*, 237.
(8) (a) Firouzabadi, H.; Iranpoor, N.; Parham, H.; Toofan, J. *Synth. Commun.* **1984**, *14*, 631. (b) Firouzabadi, H.; Iranpoor, N. *Synth. Commun.* **1984**, *14*, 875. (c) Firouzabadi, H.; Iranpoor, N.; Kiaeezadeh, F.; Toofan, J. *Synth. Commun.* **1984**, *14*, 973.
(9) Laatsch, H. *Liebigs Ann. Chem.* **1986**, 1655.
(10) Tanoue, Y.; Terada, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2039.
(11) Obol'nikova, E. A.; Kozlova, I. V.; Filippova, T. M.; Samakhvalov, G. I. *Zh. Org. Khim.* **1986**, *22*, 2258.
(12) Takeuchi, Y.; Sudani, M.; Yoshii, E. *J. Org. Chem.* **1983**, *48*, 4151.
(13) (a) Corey, E. J.; Tramantano, A. *J. Am. Chem. Soc.* **1981**, *103*, 5599. (b) Itoh, S.; Kato, J.; Inoue, T.; Kitamura, Y.; Komatsu, M.; Ohshiro, Y. *Synthesis* **1987**, 1067.
(14) (a) Fukuyama, T.; Frank, R. K.; Jewell, C. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 2122. (b) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.
(15) Yamaura, M.; Suzuki, T.; Hashimoto, H.; Yoshimura, J.; Okamoto, T.; Shin, C. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1413.
(16) (a) Syper, L. *Tetrahedron Lett.* **1966**, 4493. (b) Laing, S. B. *J. Chem. Soc. C* **1968**, 2915.
(17) Imamoto, T.; Koide, Y.; Hiyama, S. *Chem. Lett.* **1990**, 1445.
(18) Torii, S.; Tanaka, H.; Inokuchi, T.; Nakane, S.; Akada, M.; Saito, N.; Sirakawa, T. *J. Org. Chem.* **1982**, *47*, 1647.
(19) Sydnes, L. K.; Hansen, S. H.; Burkow, I. C.; Saethre, L. J. *Tetrahedron* **1985**, *41*, 5205.
(20) Baciocchi, E.; Della Cort, A.; Eberson, L.; Mandolini, L.; Rol, C. *J. Org. Chem.* **1986**, *51*, 4544.
(21) Della Cort, A.; Barbera, A. L.; Mandolini, L. *J. Chem. Res. (S)* **1983**, 44.
(22) Baciocchi, E.; Rol, C.; Sebastiani, G. V.; Serena, B. *Tetrahedron Lett.* **1984**, *25*, 1945.
(23) (a) Trahanovsky, W. S.; Young, L. B. *J. Chem. Soc.* **1965**, 5777. (b) Trahanovsky, W. S.; Young, L. B.; Brown, G. L. *J. Org. Chem.* **1967**, *32*, 3865. (c) Firouzabadi, H.; Iranpoor, N. *Synth Commun.* **1983**, *13*, 1143. (d) Hwang, D.-R.; Helquist, P.; Shekhani, M. S. *J. Org. Chem.* **1985**, *50*, 1264. (e) Oi, R.; Takenaka, S. *Chem. Lett.* **1988**, 1115. (f) Fisher, T. H.; Dershem, S. M.; Schultz, T. P. *J. Org. Chem.* **1988**, *53*, 1504.
(24) Ho, T. *Synthesis* **1978**, 936.
(25) Hatanaka, Y.; Imamoto, T.; Yokoyama, M. *Tetrahedron Lett.* **1983**, *24*, 2399.
(26) (a) Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 539. (b) Kanemoto, S.; Saimoto, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 3317. (c) Kanemoto, S.; Tomioka, H.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1986**, *58*, 105.
(27) (a) Trahanovsky, W. S.; Young, M. G.; Nave, P. M. *Tetrahedron Lett.* **1969**, 2501. (b) Fujise, Y.; Kobayashi, E.; Tsu-

chida, H.; Ito, S. *Heterocycles* **1978**, *11*, 351. (c) Balasubramanian, V.; Robinson, C. H. *Tetrahedron Lett.* **1981**, *22*, 501.
(28) (a) Trahanovsky, W. S.; Himstedt, A. L. *J. Am. Chem. Soc.* **1974**, *96*, 7974. (b) Wilson, S. R.; Zucker, P. A.; Kim, C.; Villa, C. A. *Tetrahedron Lett.* **1985**, *26*, 1969.
(29) Olah, G. A.; Gupta, B. G. B.; Fung, A. P. *Synthesis* **1980**, 897.
(30) Maione, A. M.; Romeo, A. *Synthesis* **1987**, 250.
(31) Baciocchi, E.; Giacco, T. D.; Murgia, S. M.; Sebastiani, G. V. *Tetrahedron* **1988**, *44*, 6651.
(32) Salomon, M. F.; Pardo, S. N.; Salomon, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 2473.
(33) Salomon, R. G.; Roy, S.; Salomon, M. F. *Tetrahedron Lett.* **1988**, *29*, 769.
(34) Maknon'kov, D. I.; Cheprakov, A. V.; Rodkin, M. A.; Mil'chenko, A. Y.; Beletskaya, I. P. *Zh. Org. Khim.* **1986**, *22*, 30.
(35) Horiuchi, C. A.; Kiji, S. *Chem. Lett.* **1988**, 31.
(36) (a) Asakura, J.; Robins, M. J. *Tetrahedron Lett.* **1988**, *29*, 2855. (b) Asakura, J.; Robins, M. J. *J. Org. Chem.* **1990**, *55*, 4928.
(37) Olah, G. A.; Gupta, B. G. B. *Synthesis* **1980**, 44.
(38) Cookson, R. C.; Ray, P. S. *Tetrahedron Lett.* **1982**, *23*, 3521.
(39) Riley, D. P.; Smith, M. R.; Correa, P. E. *J. Am. Chem. Soc.* **1988**, *110*, 177.
(40) Baciocchi, E.; Piermattei, A.; Ruzziconi, R. *Synth. Commun.* **1988**, *18*, 2167.
(41) Ho, T.-L.; Ho, H. C.; Wong, C. M. *J. Chem. Soc., Chem. Commun.* **1972**, 791.
(42) Ho, H. C.; Ho, T.-L.; Wong, C. M. *Can. J. Chem.* **1972**, *50*, 2718.
(43) Sepulchre, A. M.; Vass, G.; Gero, S. D. *Tetrahedron Lett.* **1973**, 3619.
(44) Girard, P.; Kagan, H. B. *Tetrahedron Lett.* **1975**, 4513.
(45) Ouertani, M.; Girard, P.; Kagan, H. B. *Bull. Soc. Chim. Fr. 2* **1982**, 327.
(46) (a) Namy, J. L.; Souppe, J.; Collin, J.; Kagan, H. B. *J. Org. Chem.* **1984**, *49*, 2045. (b) Collin, J.; Namy, J.-L.; Kagan, H. B. *Nouv. J. Chim.* **1986**, *10*, 229.
(47) Yokoo, K.; Mine, N.; Taniguchi, H.; Fujiwara, Y. *J. Organomet. Chem.* **1985**, *279*, C19.
(48) White, J. D.; Larson, G. L. *J. Org. Chem.* **1978**, *43*, 4555.
(49) (a) Imamoto, T.; Mita, T.; Yokoyama, M. *J. Chem. Soc., Chem. Commun.* **1984**, 163. (b) Imamoto, T.; Mita, T.; Yokoyama, M. *J. Org. Chem.* **1987**, *52*, 5695. (c) Imamoto, T. *Rev. Heteroat. Chem.* **1990**, *3*, 87.
(50) Inanaga, J. *Rev. Heteroat. Chem.* **1990**, *3*, 75.
(51) (a) Evans, W. J.; Meadows, J. H.; Hunter, W. E.; Atwood, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 1291. (b) Jeske, G.; Lauke, H.; Mauermann, H.; Schumann, H.; Marks, T. J. *J. Am. Chem. Soc.* **1985**, *107*, 8111. (c) Qian, C.; Xie, Z.; Huang, Y. *J. Organomet. Chem.* **1987**, *323*, 1987. (d) Qian, C.; Ge, Y.; Deng, D.; Gu, Y.; Zhang, C. *J. Organomet. Chem.* **1988**, *344*, 175.
(52) (a) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (b) Luche, J.-L.; Rodriguez-Hahn, L.; Crabbé, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601. (c) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(53) (a) Hua, D. H.; Venkataraman, S.; King, R. C.-Y.; Paukstelis, J. V. *J. Am. Chem. Soc.* **1988**, *110*, 4741. (b) Hatakeyama, S.; Sakurai, K.; Numata, H.; Ochi, N.; Takano, S. *J. Am. Chem. Soc.* **1988**, *110*, 5201. (c) Calverley, M. J. *Tetrahedron* **1987**, *43*, 4609. (d) Nakata, T.; Saito, K.; Oishi, T. *Tetrahedron Lett.* **1986**, *27*, 6341.
(54) (a) Sakairi, N.; Hayashida, M.; Kuzuhara, H. *Tetrahedron Lett.* **1987**, *28*, 2871. (b) Jefford, C. W.; Rossier, J.-C.; Boukouvalas, J. *J. Chem. Soc., Chem. Commun.* **1987**, 1593. (c) Kato, N.; Kataoka, H.; Ohbuchi, S.; Tanaka, S.; Takeshita, H. *J. Chem. Soc., Chem. Commun.* **1988**, 354. (d) Fleming, I.; Higgins, D. *Tetrahedron Lett.* **1989**, *30*, 5777.
(55) (a) Raphael, R. A.; Telfer, S. J. *Tetrahedron Lett.* **1985**, *26*, 489. (b) Mori, K.; Kisida, H. *Tetrahedron* **1986**, *42*, 5281. (c) Yates, P.; Burnell, D. J.; Freer, V. J.; Sawyer, J. F. *Can. J. Chem.* **1987**, *65*, 69. (d) Clarke, T.; Stewart, J. D.; Ganem, B. *Tetrahedron Lett.* **1987**, *28*, 6253. (e) Paquette, L. A.; Ham, W. H. *J. Am. Chem. Soc.* **1987**, *109*, 3025.
(56) (a) Zoretic, P. A.; Chambers, R. J.; Marbury, G. D.; Riebiro, A. A. *J. Org. Chem.* **1985**, *50*, 2981. (b) Iwata, C.; Takemoto, Y.; Kubota, H.; Kuroda, T.; Imanishi, T. *Tetrahedron Lett.* **1985**, *26*, 3231. (c) Pearson, A. J.; Bansal, H. S. *Tetrahedron Lett.* **1986**, *27*, 283. (d) Danishefsky, S. J.; DeNinno, M. P.; Chen, S. *J. Am. Chem. Soc.* **1988**, *110*, 3929. (e) DeShong, P.; Waltermire, R. E.; Ammon, H. L. *J. Am. Chem. Soc.* **1988**, *110*, 1901. (f) Abelman, M. M.; Overman, L. E.; Tran, V. D. *J. Am. Chem. Soc.* **1990**, *112*, 6959.
(57) (a) Lieb, F.; Wendisch, D. *Liebigs Ann. Chem.* **1986**, 1528. (b) Boutin, R. H.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5320. (c) Smit, V. A.; Gybin, A. S.; Veretenov, S. O.; Shashkov, A. S. *Izv. Akad. Nauk SSSR* **1987**, 232. (d) Paterson, I.; Laffan, D. D. P.; Rawson, D. J. *Tetrahedron Lett.* **1988**, *29*, 1461. (e) Kawada, K.; Dolence, E. K.; Morita, H.; Kometani, T.; Watt, D. S.; Balapure, A.; Fritz, T. A.; Orlicky, D. J.; Gerschenson, L. E. *J. Med. Chem.* **1989**, *32*, 256. (f) Ikota, N. *Heterocycles* **1989**, *29*, 1469. (g) Coxon, J. M.; van Eyk, S. J.; Steel, P. J. *Tetrahedron* **1989**, *45*, 1029. (h) Sardina, F. J.; Howard, M. H.; Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 4654.
(58) Nimkar, S.; Manaldino, D.; Merrill, A. H.; Liotta, D. *Tetrahedron Lett.* **1988**, *29*, 3037.
(59) (a) Wender, P. A.; Schaus, J.; White, A. W. *Heterocycles* **1987**, *25*, 263. (b) Krief, A.; Surleraux, D.; Frauenrath, H. *Tetrahedron Lett.* **1988**, *29*, 6157. (c) Ishizuka, T.; Ishibuchi, S.; Kunieda, T. *Tetrahedron Lett.* **1989**, *30*, 3449. (d) Tatsuta, K.; Hayakawa, J.; Tatsuzawa, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 490.
(60) (a) Rücher, G.; Hörster, H.; Gajewski, W. *Synth. Commun.* **1980**, *10*, 623. (b) Friedrich, D.; Bohlmann, F. *Tetrahedron* **1988**, *44*, 1369. (c) Hatakeyama, S.; Numata, H.; Osanai, K.; Takano, S. *J. Org. Chem.* **1989**, *54*, 3515. (d) Bartel, S.; Bohlmann, F. *Tetrahedron Lett.* **1989**, *30*, 685.
(61) (a) Gemal, A. L.; Luche, J.-L. *J. Org. Chem.* **1979**, *44*, 4187. (b) Luche, J.-L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848. (c) Gemal, A. L.; Luche, J.-L. *Tetrahedron Lett.* **1981**, *22*, 4077. (d) Rokach, J.; Adams, J.; Perry, R. *Tetrahedron Lett.* **1983**, *24*, 5185. (e) Suemune, H.; Kawahara, T.; Sakai, K. *Chem. Pharm. Bull.* **1986**, *34*, 550. (f) Zamboni, R.; Rokach, J. *Tetrahedron Lett.* **1982**, *23*, 4751. (g) Furukawa, J.; Morisaki, N.; Kobayashi, H.; Iwasaki, S.; Nozoe, S.; Okuda, S. *Chem. Pharm. Bull.* **1985**, *33*, 440. (h) Comins, D. L.; Mantlo, N. B. *J. Org. Chem.* **1986**, *51*, 5456. (i) Leblanc, Y.; Fitzsimmons, B. J.; Adams, J.; Perez, F.; Rokach, J. *J. Org. Chem.* **1986**, *51*, 789. (j) Compagnone, R. S.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 1713. (k) Leblanc, Y.; Fitzsimmons, B. J.; Rokach, J.; Ueda, N.; Yamamoto, S. *Tetrahedron Lett.* **1987**, *28*, 3449. (l) White, J. D.; Jayasinghe, L. R. *Tetrahedron Lett.* **1988**, *29*, 2139. (m) LeMerrer, Y.; Bonnet, A.; Depezay, J. C. *Tetrahedron Lett.* **1988**, *29*, 2647. (n) Mehta, G.; Krishnamurthy, N.; Karra, S. R. *J. Chem. Soc., Chem. Commun.* **1989**, 1299. (o) Howard, M. H.; Sardina, F. J.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 2829.
(62) Jung, M. E.; Usui, Y.; Vu, C. T. *Tetrahedron Lett.* **1987**, *28*, 5977.
(63) Lakshmy, K. V.; Mehta, P. G.; Sheth, J. P.; Trivedi, G. K. *Org. Prep. Proced. Int.* **1985**, *17*, 251.
(64) (a) Lakhvich, F. A.; Lis, L. G.; Pap, A. A.; Zheldakova, T. A.; Akhrem, A. A. *Zh. Org. Khim.* **1988**, *24*, 956. (b) Matsuda, F.; Matsumoto, T.; Ohsaki, M.; Terashima, S. *Tetrahedron Lett.* **1989**, *30*, 4259.
(65) Fukuzawa, S.; Fujinami, T.; Yamauchi, S.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1929.
(66) (a) Starodubtseva, E. V.; Konenko, I. R.; Klabunovskii, E. I.; Savitskii, E. M.; Mordovich, V. P.; Savost'yanova, T. P. *Izv. Akad. Nauk SSSR* **1984**, 758. (b) Starodubtseva, E. V.; Konenko, I. R.; Fedorovskaya, E. A.; Klabunovskii, E. I.; Mordovin, V. P. *Izv. Akad. Nauk SSSR* **1986**, 1960.
(67) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.
(68) Yamamoto, Y.; Matsuoka, K.; Nemoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 4475.
(69) Singh, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 6187.
(70) Takeuchi, S.; Ohgo, Y. *Chem. Lett.* **1988**, 403.
(71) Okano, T.; Matsuoka, M.; Konishi, H.; Kiji, J. *Chem. Lett.* **1987**, 181.
(72) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.
(73) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.
(74) (a) Poulton, G. A.; Cyr, T. D. *Synth. Commun.* **1980**, *10*, 581. (b) Abouelfida, A.; Pradère, J.-P.; Rozé, J.-C.; Jubault, M. *Tetrahedron Lett.* **1990**, *31*, 4019.
(75) Imamoto, T.; Takeyama, T.; Kusumoto, T. *Chem. Lett.* **1985**, 1491.
(76) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485.
(77) Kagan, H. B.; Namy, J. L.; Girard, P. *Tetrahedron* **1981**, *37*, 175, Suppl. 1.
(78) Ananthanarayan, T. P.; Gallagher, T.; Magnus, P. *J. Chem. Soc., Chem. Commun.* **1982**, 709.
(79) Crombie, L.; Rainbow, L. J. *Tetrahedron Lett.* **1988**, *29*, 6517.
(80) Ho, T.-L. *Synth. Commun.* **1979**, *9*, 241.
(81) (a) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135. (b) Smith, A. B., III; Dunlap, N. K.; Sulikowski, G. A. *Tetrahedron Lett.* **1988**, *29*, 439. (c) Castro, J.; Sörenson, H.; Riera, A.; Morin, C.; Moyano, A.; Pericàs, M. A.; Greene, A. E. *J. Am. Chem. Soc.* **1990**, *112*, 9388.
(82) (a) White, J. D.; Somers, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 4424. (b) Holton, R. A.; Williams, A. D. *J. Org. Chem.* **1988**, *53*, 5981.
(83) Pratt, D. V.; Hopkins, P. B. *Tetrahedron Lett.* **1987**, *28*, 3065.
(84) Kusuda, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1989**, *30*, 2945.

(85) (a) Yoneda, R.; Harusawa, S.; Kurihara, T. *Tetrahedron Lett.* **1989**, *30*, 3681. (b) Yoneda, R.; Harusawa, S.; Kurihara, T. *J. Org. Chem.* **1991**, *56*, 1827.
(86) (a) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 2596. (b) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 4437.
(87) Molander, G. A.; La Belle, B. E.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 5259.
(88) Imamoto, T.; Kusumoto, T.; Suzuki, N.; Sato, K. *J. Am. Chem. Soc.* **1985**, *107*, 5301.
(89) Matsukawa, M.; Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 2101.
(90) Honda, Y.; Inanaga, J.; Yamaguchi, M. *J. Chem. Soc., Chem. Commun.* **1989**, 298.
(91) Zhang, Y.; Lin, R. *Synth. Commun.* **1987**, *17*, 329.
(92) Murahashi, S.-I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.* **1990**, *55*, 1736.
(93) (a) Souppe, J.; Danon, L.; Namy, J. L.; Kagan, H. B. *J. Organomet. Chem.* **1983**, *250*, 227. (b) Kende, A. S.; Mendoza, J. S. *Tetrahedron Lett.* **1991**, *32*, 1699.
(94) (a) Denmark, S. E.; Sternberg, J. A.; Lueoend, R. *J. Org. Chem.* **1988**, *53*, 1251. (b) Denmark, S. E.; Ares, J. J. *J. Am. Chem. Soc.* **1988**, *110*, 4432.
(95) Natale, N. R. *Tetrahedron Lett.* **1982**, *23*, 5009.
(96) (a) Johnson, C. R.; Senanayake, C. H. *J. Org. Chem.* **1989**, *54*, 735. (b) Feldman, K. S.; Simpson, R. E. *Tetrahedron Lett.* **1989**, *30*, 6985.
(97) Harring, L. S. Unpublished results.
(98) Kende, A. S.; Mendoza, J. S. *Tetrahedron Lett.* **1990**, *31*, 7105.
(99) (a) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 601. (b) Moriya, T.; Handa, Y.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1988**, *29*, 6947.
(100) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5237.
(101) Prandi, J.; Namy, J. L.; Menoret, G.; Kagan, H. B. *J. Organomet. Chem.* **1985**, *285*, 449.
(102) Luche, J.-L.; Gemal, A. L. *J. Chem. Soc., Chem. Commun.* **1978**, 976.
(103) Mori, S.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1986**, *27*, 6111.
(104) (a) Taylor, M. D.; Minaskanian, G.; Winzenberg, K. N.; Santone, P.; Smith, A. B. III. *J. Org. Chem.* **1982**, *47*, 3960. (b) Satoh, T.; Kaneko, Y.; Okuda, T.; Uwaya, S.; Yamakawa, K. *Chem. Pharm. Bull.* **1984**, *32*, 3452. (c) Cockerill, G. S.; Kocienski, P.; Treadgold, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2101. (d) Arai, Y.; Yamamoto, M.; Koizumi, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 467. (e) Kuo, D. L.; Money, T. *Can. J. Chem.* **1988**, *66*, 1794. (f) Brandes, E.; Grieco, P. A.; Garner, P. *J. Chem. Soc., Chem. Commun.* **1988**, 500. (g) Baudouy, R.; Prince, P. *Tetrahedron* **1989**, *45*, 2067.
(105) Tobe, Y.; Yamashita, D.; Takahashi, T.; Inata, M.; Sato, J.; Kakiuchi, K.; Kobiro, K.; Odaira, Y. *J. Am. Chem. Soc.* **1990**, *112*, 775.
(106) Lawson, K. R.; McDonald, B. P.; Mills, O. S.; Steele, R. W.; Sutherland, J. K.; Wear, T. J.; Brewster, A.; Marsham, P. R. *J. Chem. Soc., Perkin Trans. 1* **1988**, 663.
(107) Brandes, S. J.; Katzenellenbogen, J. A. *Mol. Pharmacol.* **1987**, *32*, 391.
(108) Golubovskaya, L. E.; Piritskii, K. K. *Zh. Obshch. Khim.* **1985**, *55*, 427.
(109) Garlaschelli, L.; Vidari, G. *Tetrahedron Lett.* **1990**, *31*, 5818.
(110) Ukaji, Y.; Koumoto, N.; Fujisawa, T. *Chem. Lett.* **1989**, 1623.
(111) Vougioukas, A. E.; Kagan, H. B. *Tetrahedron Lett.* **1987**, *28*, 6065.
(112) Fujisawa, T.; Tanaka, A.; Ukaji, Y. *Chem. Lett.* **1989**, 1255.
(113) (a) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 215. (b) Fukuzawa, S.; Fujinami, T.; Sakai, S. *Chem. Lett.* **1990**, 927.
(114) Syutkina, O. P.; Rybakova, L. F.; Petrov, E. S.; Beletskaya, I. P. *J. Organomet. Chem.* **1985**, *280*, C67.
(115) Corey, E. J.; Mehrotra, M. M. *Tetrahedron Lett.* **1988**, *29*, 57.
(116) (a) Sigalov, A. B.; Rybakova, L. F.; Beletskaya, I. P. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1983**, 1692. (b) Yokoo, K.; Fukagawa, T.; Yamanaka, Y.; Taniguchi, H.; Fujiwara, Y. *J. Org. Chem.* **1984**, *49*, 3237. (c) Rybakova, L. F.; Syutkina, O. P.; Garbar, A. V.; Petrov, E. S. *Zh. Obshch. Khim.* **1988**, *58*, 1053.
(117) Collin, J.; Namy, J.-L.; Bied, C.; Kagan, H. B. *Inorg. Chim. Acta* **1987**, *140*, 29.
(118) Mukerji, I.; Wayda, A.; Dabbagh, G.; Bertz, S. H. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 760.
(119) (a) Hou, Z.; Takamine, K.; Aoki, O.; Shiraishi, H.; Fujiwara, Y.; Taniguchi, H. *J. Chem. Soc., Chem. Commun.* **1988**, 668. (b) Hou, Z.; Takamine, K.; Aoki, O.; Shiraishi, H.; Fujiwara, Y.; Taniguchi, H. *J. Org. Chem.* **1988**, *53*, 6077. (c) Takaki, K.; Tanaka, S.; Beppu, F.; Tsubaki, Y.; Fujiwara, Y. *Chem. Lett.* **1990**, 1427.
(120) Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1985**, *107*, 6137.
(121) (a) Imamoto, T.; Kusumoto, K.; Yokoyama, M. *J. Chem. Soc., Chem. Commun.* **1982**, 1042. (b) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904. (c) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233. (d) Imamoto, T.; Sugiura, Y. *J. Organomet. Chem.* **1985**, *285*, C21. (e) Imamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763. (f) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.
(122) (a) Collins, S.; Hong, Y.; Hoover, G. J.; Veit, J. R. *J. Org. Chem.* **1990**, *55*, 3565. (b) Utimoto, K.; Nakamura, A.; Matsubara, S. *J. Am. Chem. Soc.* **1990**, *112*, 8189.
(123) (a) Suzuki, M.; Kimura, Y.; Terashima, S. *Chem. Lett.* **1984**, 1543. (b) Tamura, Y.; Sasho, M.; Ohe, H.; Akai, S.; Kita, Y. *Tetrahedron Lett.* **1985**, *26*, 1549. (c) Blagg, J.; Coote, S. J.; Davies, S. G.; Mobbs, B. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2257. (d) Suzuki, M.; Kimura, Y.; Terashima, S. *Chem. Pharm. Bull.* **1986**, *34*, 1531. (e) Grewal, R. S.; Hayes, P. C.; Sawyer, J. F.; Yates, P. *J. Chem. Soc., Chem. Commun.* **1987**, 1290. (f) Tamura, Y.; Akai, S.; Kishimoto, H.; Kirihara, M.; Sasho, M.; Kita, Y. *Tetrahedron Lett.* **1987**, *28*, 4583. (g) Tamura, Y.; Sasho, M.; Akai, S.; Kishimoto, H.; Sekihachi, J.; Kita, Y. *Chem. Pharm. Bull.* **1987**, *35*, 1405. (h) Tamura, Y.; Akai, S.; Kishimoto, H.; Sasho, M.; Kirihara, M.; Kita, Y. *Chem. Pharm. Bull.* **1988**, *36*, 3897. (i) Yates, P.; Grewal, R. S.; Hayes, P. C.; Sawyer, J. F. *Can. J. Chem.* **1988**, *66*, 2805. (j) Kelly, T. R.; Chandrakumar, N. S.; Saha, J. K. *J. Org. Chem.* **1989**, *54*, 980. (k) Nagasawa, K.; Ito, K. *Heterocycles* **1989**, *28*, 703. (l) Larock, R. C.; Stinn, D. E.; Kuo, M.-Y. *Tetrahedron Lett.* **1990**, *31*, 17.
(124) (a) Chen, C.-P.; Swenton, J. S. *J. Org. Chem.* **1985**, *50*, 4569. (b) Jisheng, L.; Gallardo, T.; White, J. B. *J. Org. Chem.* **1990**, *55*, 5426. (c) Robson, J. N.; Rowland, S. J. *Tetrahedron Lett.* **1988**, *29*, 3837.
(125) Johnson, C. R.; Tait, B. D. *J. Org. Chem.* **1987**, *52*, 281.
(126) (a) Paquette, L. A.; Learn, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 7873. (b) Paquette, L. A.; Learn, K. S.; Romine, J. L. *Tetrahedron* **1987**, *43*, 4989. (c) Paquette, L. A.; Romine, J. L.; Lin, H.-S. *Tetrahedron Lett.* **1987**, *28*, 31. (d) Sugimura, T.; Paquette, L. A. *J. Am. Chem. Soc.* **1987**, *109*, 3017. (e) Paquette, L. A.; Learn, K. S.; Romine, J. L.; Lin, H.-S. *J. Am. Chem. Soc.* **1988**, *110*, 879. (f) Paquette, L. A.; DeRussy, D. T.; Pegg, N. A.; Taylor, R. T.; Zydowsky, T. M. *J. Org. Chem.* **1989**, *54*, 4576. (g) Paquette, L. A.; DeRussy, D. T.; Gallucci, J. C. *J. Org. Chem.* **1989**, *54*, 2278. (h) Paquette, L. A.; He, W.; Rogers, R. D. *J. Org. Chem.* **1989**, *54*, 2291. (i) Paquette, L. A.; Pegg, N. A.; Topps, D.; Maynard, G. D.; Rogers, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 277. (j) Paquette, L. A.; DeRussy, D. T.; Vamdemjeste, T.; Rogers, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 5562. (k) Paquette, L. A.; Romine, J. L.; Lin, H.-S.; Wright, J. *J. Am. Chem. Soc.* **1990**, *112*, 9284. (l) Paquette, L. A. *Synlett* **1990**, 67.
(127) (a) Fox, C. M. J.; Hiner, R. N.; Warrier, U.; White, J. D. *Tetrahedron Lett.* **1988**, *29*, 2923. (b) Ziegler, F. E.; Nangia, A.; Schulte, G. *Tetrahedron Lett.* **1988**, *29*, 1669. (c) Gössinger, E.; Müller, R.; Patterna, T. *Tetrahedron* **1990**, *46*, 407.
(128) (a) Kawauchi, N.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1441. (b) Kawauchi, N.; Sato, K.; Yoshimura, J.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1433. (c) Takeda, K.; Yano, S.; Sato, M.; Yoshii, E. *J. Org. Chem.* **1987**, *52*, 4137. (d) Martin, S. F.; Pacofsky, G. J.; Gist, R. P.; Lee, W.-C. *J. Am. Chem. Soc.* **1989**, *111*, 7634. (e) Chamberlain, T.; Fu, X.; Pechacek, J. T.; Peng, X.; Wheeler, D. M. S.; Wheeler, M. M. *Tetrahedron Lett.* **1991**, *32*, 1707.
(129) (a) Mash, E. A. *J. Org. Chem.* **1987**, *52*, 4142. (b) Suzuki, T.; Sato, E.; Matsuda, Y.; Tada, H.; Koizumi, S.; Unno, K.; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1988**, 1531.
(130) (a) Suzuki, K.; Ohkuma, T.; Tsuchihashi, G. *Tetrahedron Lett.* **1985**, *26*, 861. (b) Kawasaki, M.; Matsuda, F.; Terashima, S. *Tetrahedron Lett.* **1985**, *26*, 2693. (c) Sato, T.; Kato, R.; Gokyu, K.; Fujisawa, T. *Tetrahedron Lett.* **1988**, *29*, 3955. (d) Fujisawa, T.; Funabora, M.; Ukaji, Y.; Sato, T. *Chem. Lett.* **1988**, 59. (e) Kawasaki, M.; Matsuda, F.; Terashima, S. *Tetrahedron* **1988**, *44*, 5695. (f) Lett, R. M.; Overman, L. E.; Zablocki, J. *Tetrahedron Lett.* **1988**, *29*, 6541. (g) Corey, E. J.; Ha, D.-C. *Tetrahedron Lett.* **1988**, *29*, 3171. (h) Garigipati, R. S.; Weinreb, S. M. *J. Org. Chem.* **1988**, *53*, 4143. (i) Weinreb, S. M.; Garigipati, R. S. *Pure Appl. Chem.* **1989**, *61*, 435. (j) Garigipati, R. S.; Tschaen, D. M.; Weinreb, S. M. *J. Am. Chem. Soc.* **1990**, *112*, 3475. (k) Fujisawa, T.; Fujimura, A.; Ukaji, Y. *Chem. Lett.* **1988**, 1541. (l) Miyashita, M.; Hoshino, M.; Yoshikoshi, A. *Chem. Lett.* **1990**, 791.
(131) Molander, G. A.; Burkhardt, E. R.; Weinig, P. *J. Org. Chem.* **1990**, *55*, 4990.
(132) (a) Liebeskind, L. S.; Mitchell, D.; Foster, B. S. *J. Am. Chem. Soc.* **1987**, *109*, 7908. (b) Braish, T. F.; Saddler, J. C.; Fuchs,

P. L. *J. Org. Chem.* **1988**, *53*, 3647. (c) Zheng, J.; Undheim, K. *Acta Chem. Scand.* **1989**, *43*, 816. (d) Horiguchi, Y.; Kataoka, Y.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 3327. (e) Mitchell, D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 291. (f) Herndon, J. W.; McMullen, L. A.; Daitch, C. E. *Tetrahedron Lett.* **1990**, *31*, 4547. (g) Jasperse, C. P.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 5601. (h) Mitchell, D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 291.

(133) (a) Guo, B.-S.; Doubleday, W.; Cohen, T. *J. Am. Chem. Soc.* **1987**, *109*, 4710. (b) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152. (c) Abraham, W. D.; Cohen, T. *J. Am. Chem. Soc.* **1991**, *113*, 2313. (d) Mudryk, B.; Cohen, T. *J. Am. Chem. Soc.* **1991**, *113*, 1866.

(134) Fukuzawa, S.; Sato, K.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1990**, 939.

(135) Otsubo, K.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 1487.

(136) (a) Souppe, J.; Namy, J. L.; Kagan, H. B. *Tetrahedron Lett.* **1982**, *23*, 3497. (b) Namy, J. L.; Souppe, J.; Collin, J.; Kagan, H. B. *J. Org. Chem.* **1984**, *49*, 2045.

(137) Namy, J. L.; Collin, J.; Zhang, J.; Kagan, H. B. *J. Organomet. Chem.* **1987**, *328*, 81.

(138) Molander, G. A.; Etter, J. B. *Synth. Commun.* **1987**, *17*, 901.

(139) Berks, A. H. Ph.D. Thesis, University of Colorado, Boulder, 1988.

(140) (a) Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1986**, *51*, 1778. (b) Zoretic, P. A.; Yu, B. C.; Caspar, M. L. *Synth. Commun.* **1989**, *19*, 1859. (c) Daniewski, A. R.; Uskokovic, M. R. *Tetrahedron Lett.* **1990**, *31*, 5599.

(141) Suginome, H.; Yamada, S. *Tetrahedron Lett.* **1987**, *28*, 3963.

(142) (a) Lannoye, G.; Cook, J. M. *Tetrahedron Lett.* **1988**, *29*, 171. (b) Lannoye, G.; Sambasivarao, K.; Wehrli, S.; Cook, J. M.; Weiss, U. *J. Org. Chem.* **1988**, *53*, 2327.

(143) Barner, B. A.; Liu, Y.; Rahman, M. A. *Tetrahedron* **1989**, *45*, 6101.

(144) (a) Sosnowski, J. J.; Danaher, E. B.; Murray, R. K., Jr. *J. Org. Chem.* **1985**, *50*, 2759. (b) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1991**, *56*, 4112.

(145) Molander, G. A.; Etter, J. B.; Zinke, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 453.

(146) Araki, S.; Hatano, M.; Ito, H.; Butsugan, Y. *J. Organomet. Chem.* **1987**, *333*, 329.

(147) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 1195.

(148) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 2275.

(149) Imamoto, T.; Takeyama, T.; Yokoyama, M. *Tetrahedron Lett.* **1984**, *25*, 3225.

(150) (a) Imamoto, T.; Takeyama, T.; Koto, H. *Tetrahedron Lett.* **1986**, *27*, 3243. (b) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3891. (c) Imamoto, T.; Takiyama, N. *Tetrahedron Lett.* **1987**, *28*, 1307.

(151) (a) Fukuzawa, S.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1986**, 475. (b) Fukuzawa, S.; Sumimoto, T.; Fujinami, T.; Sakai, S. *J. Org. Chem.* **1990**, *55*, 1628.

(152) (a) Souppe, J.; Namy, J.-L.; Kagan, H. B. *Tetrahedron Lett.* **1984**, *25*, 2869. (b) Collin, J.; Namy, J.-L.; Dallemer, F.; Kagan, H. B. *J. Org. Chem.* **1991**, *56*, 3118.

(153) Collin, J.; Kagan, H. B. *Tetrahedron Lett.* **1988**, *29*, 6097.

(154) Zinke, P. W. Ph.D. Thesis, University of Colorado, Boulder, 1987.

(155) Collin, J.; Dallemer, F.; Namy, J. L.; Kagan, H. B. *Tetrahedron Lett.* **1989**, *30*, 7407.

(156) Sasaki, M.; Collin, J.; Kagan, H. B. *Tetrahedron Lett.* **1988**, *29*, 4847.

(157) Matsukawa, M.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 5877.

(158) Imamoto, T.; Kusumoto, T.; Yokoyama, M. *Tetrahedron Lett.* **1983**, *24*, 5233.

(159) Nagasawa, K.; Kanbara, H.; Matsushita, K.; Ito, K. *Tetrahedron Lett.* **1985**, *26*, 6477.

(160) Vougioukas, A. E.; Kagan, H. B. *Tetrahedron Lett.* **1987**, *28*, 5513.

(161) Fukuzawa, S.; Tsuruta, T.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1473.

(162) Zhang, Y.; Liu, T.; Lin, R. *Synth. Commun.* **1988**, *18*, 2003.

(163) Harada, T.; Mukaiyama, T. *Chem. Lett.* **1982**, 467.

(164) (a) Tabuchi, T.; Kawamura, K.; Inanga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3889. (b) Vedejs, E.; Ahmad, S. *Tetrahedron Lett.* **1988**, *29*, 2291. (c) Moriya, T.; Handa, Y.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1988**, *29*, 6947.

(165) Molander, G. A.; Etter, J. B. *J. Am. Chem. Soc.* **1987**, *109*, 6556.

(166) Thorel, P.-J. Unpublished results.

(167) Harring, L. S. Ph.D. Thesis, University of Colorado, Boulder, 1991.

(168) (a) Fry, A. J.; Susla, M.; Weltz, M. *J. Org. Chem.* **1987**, *52*, 2496. (b) Fry, A. J.; Susla, M. *J. Am. Chem. Soc.* **1989**, *111*, 3225.

(169) Lipshutz, B. H.; Huff, B.; Vaccaro, W. *Tetrahedron Lett.* **1986**, *27*, 1986.

(170) (a) Denmark, S. E.; Weber, T.; Piotrowski, D. W. *J. Am. Chem. Soc.* **1987**, *109*, 2224. (b) Weber, T.; Edwards, J. P.; Denmark, S. E. *Synlett* **1989**, 20.

(171) Fujioka, H.; Fuji, M.; Okaichi, Y.; Yoshida, T.; Annoura, H.; Kita, Y.; Tamura, Y. *Chem. Pharm. Bull.* **1989**, *37*, 602.

(172) Matsumoto, T.; Kobayashi, Y.; Takemoto, Y.; Ito, Y.; Kamijo, T.; Harada, H.; Terashima, S. *Tetrahedron Lett.* **1990**, *31*, 4175.

(173) Reetz, M. T.; Jaeger, R.; Drewlies, R.; Hübel, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 103.

(174) (a) Murakami, M.; Kawano, T.; Ito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 2437. (b) Ito, Y.; Murakami, M. *Synlett* **1990**, 245. (c) Murakami, M.; Masuda, H.; Kawano, T.; Nakamura, H.; Ito, Y. *J. Org. Chem.* **1991**, *56*, 1.

(175) Natale, N. R.; Yocklovich, S. G.; Mallet, B. M. *Heterocycles* **1986**, *24*, 2175.

(176) Mudryk, B.; Shook, C. A.; Cohen, T. *J. Am. Chem. Soc.* **1990**, *112*, 6389.

(177) (a) Narayanan, B. A.; Bunnelle, W. H. *Tetrahedron Lett.* **1987**, *28*, 6261. (b) Lee, T. V.; Porter, J. R.; Roden, F. S. *Tetrahedron Lett.* **1988**, *29*, 5009. (c) Lee, T. V.; Channon, J. A.; Cregg, C.; Porter, J. R.; Roden, F. S.; Yeoh, H. T.-L. *Tetrahedron* **1989**, *45*, 5877.

(178) Anderson, M. B.; Fuchs, P. L. *Synth. Commun.* **1987**, *17*, 621.

(179) Collins, S.; Hong, Y. *Tetrahedron Lett.* **1987**, *28*, 4391.

(180) Molander, G. A.; McKie, J. A. Submitted for publication.

(181) Imamoto, T.; Kusumoto, T.; Hatanaka, Y.; Yokoyama, M. *Tetrahedron Lett.* **1982**, *23*, 1353.

(182) (a) Namy, J. L.; Souppe, J.; Kagan, H. B. *Tetrahedron Lett.* **1983**, *24*, 765. (b) Fürstner, A.; Csuk, R.; Rohrer, C.; Weidmann, H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1729.

(183) Léonard, E.; Duñbach, E.; Périchon, J. *J. Chem. Soc., Chem. Commun.* **1989**, 276.

(184) Chiara, J. L.; Cabri, W.; Hanessian, S. *Tetrahedron Lett.* **1991**, *32*, 1125.

(185) (a) Molander, G. A.; Kenny, C. *J. Org. Chem.* **1988**, *53*, 2132. (b) Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236.

(186) Hou, Z.; Takamine, K.; Aoki, O.; Shiraishi, H.; Fujiwara, Y.; Taniguchi, H. *J. Chem. Soc., Chem. Commun.* **1988**, 668.

(187) (a) Enholm, E. J.; Forbes, D. C.; Holub, D. P. *Synth. Commun.* **1990**, *20*, 981. (b) Imamoto, T.; Nishimura, S. *Chem. Lett.* **1990**, 1141.

(188) (a) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1986**, 624. (b) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5763. (c) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1669. (d) Ujikawa, O.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1989**, *30*, 2837.

(189) Fukuzawa, S.; Iida, M.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1987**, 920.

(190) (a) Enholm, E. J.; Trivellas, A. *Tetrahedron Lett.* **1989**, *30*, 1063. (b) Enholm, E. J.; Satici, H.; Trivellas, A. *J. Org. Chem.* **1989**, *54*, 5841. (c) Enholm, E. J.; Trivellas, A. *J. Am. Chem. Soc.* **1989**, *111*, 6463.

(191) Shim, S. C.; Hwang, J.-T.; Kang, H.-Y.; Chang, M. H. *Tetrahedron Lett.* **1990**, *31*, 4765.

(192) Bannai, K.; Tanaka, T.; Okamura, N.; Hazato, A.; Sugiura, S.; Manabe, K.; Tomimori, K.; Kato, Y.; Kurozumi, S.; Noyori, R. *Tetrahedron* **1990**, *46*, 6689.

(193) Molander, G. A.; Kenny, C. *Tetrahedron Lett.* **1987**, *28*, 4367.

(194) Molander, G. A.; Kenny, C. *J. Org. Chem.* **1991**, *56*, 1439.

(195) Fevig, T. L.; Elliott, R. L.; Curran, D. P. *J. Am. Chem. Soc.* **1988**, *110*, 5064.

(196) Inanaga, J.; Ujikawa, O.; Yamaguchi, M. *Tetrahedron Lett.* **1991**, *32*, 1737.

(197) Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1990**, *55*, 6171.

(198) (a) Lu, X.; Ma, S.; Zhu, J. *Tetrahedron Lett.* **1988**, *29*, 5129. (b) Ma, S.; Lu, X. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2031.

(199) Sasaki, M.; Collin, J.; Kagan, H. B. *Tetrahedron Lett.* **1988**, *29*, 6105.

(200) Martin, S. F.; Yang, C.-P.; Laswell, W. L.; Rüeger, H. *Tetrahedron Lett.* **1988**, *29*, 6685.

(201) (a) Kurz, M. E.; Ngoviwatchai, P. *J. Org. Chem.* **1981**, *46*, 4672. (b) Baciocchi, E.; Dell'Aira, D.; Ruzziconi, R. *Tetrahedron Lett.* **1986**, *27*, 2763.

(202) Weinstock, L. M.; Corley, E.; Abramson, N. L.; King, A. O.; Karady, S. *Heterocycles* **1988**, *27*, 2627.

(203) Baciocchi, E.; Civitarese, G.; Ruzziconi, R. *Tetrahedron Lett.* **1987**, *28*, 5357.

(204) Baciocchi, E.; Ruzziconi, R. *Synth. Commun.* **1988**, *18*, 1841.

(205) Baciocchi, E.; Casu, A.; Ruzziconi, R. *Tetrahedron Lett.* **1989**, *30*, 3707.

(206) Snider, B. B.; Kwon, T. *J. Org. Chem.* **1990**, *55*, 4786.

(207) (a) Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1987**, *52*, 3942. (b) Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1989**, *54*, 3525.
(208) Yamazaki, T.; Lin, J. T.; Takeda, M.; Kitazume, T. *Tetrahedron: Asymmetry* **1990**, *1*, 351.
(209) (a) Clive, D. L. J.; Daigneault, S. *J. Chem. Soc., Chem. Commun.* **1989**, 333. (b) Clive, D. L. J.; Daigneault, S. *J. Org. Chem.* **1991**, *56*, 3801.
(210) Uskokovic, M. R. Private communication.
(211) Imamoto, T.; Takiyama, N. *Tetrahedron Lett.* **1987**, *28*, 1307.
(212) Imamoto, T.; Kamiya, Y.; Hatajima, T.; Takahashi, H. *Tetrahedron Lett.* **1989**, *30*, 5149.
(213) Olah, G. A.; Kobayashi, S.; Tashiro, M. *J. Am. Chem. Soc.* **1972**, *92*, 7448.
(214) Mine, N.; Fujiwara, Y.; Taniguchi, H. *Chem. Lett.* **1986**, 357.
(215) Morrill, T. C.; Clark, R. A.; Bilobran, D.; Youngs, D. S. *Tetrahedron Lett.* **1975**, 397.
(216) Danishefsky, S.; Bednarski, M. *Tetrahedron Lett.* **1985**, *26*, 2507.
(217) Minuti, L.; Radics, L.; Taticchi, A.; Venturini, L.; Wenkert, E. *J. Org. Chem.* **1990**, *55*, 4261.
(218) (a) Gandhi, R. P.; Ishar, M. P. S.; Wali, A. *J. Chem. Soc., Chem. Commun.* **1988**, 1074. (b) Ishar, M. P. S.; Wali, A.; Gandhi, R. P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2185.
(219) Takeda, K.; Igarashi, Y.; Okazaki, K.; Yoshii, E.; Yamaguchi, K. *J. Org. Chem.* **1990**, *55*, 3431.
(220) Levin, J. I. *Tetrahedron Lett.* **1989**, *30*, 2355.
(221) Danishefsky, S. J.; Harvey, D. F.; Quallich, G.; Uang, B. J. *J. Org. Chem.* **1984**, *49*, 392.
(222) Danishefsky, S. J.; Pearson, W. H. *J. Org. Chem.* **1983**, *48*, 3865.
(223) (a) Castellino, S.; Sims, J. J. *Tetrahedron Lett.* **1984**, *25*, 2307. (b) Castellino, S.; Sims, J. J. *Tetrahedron Lett.* **1984**, *25*, 4059. (c) Midland, M. M.; Graham, R. S. *J. Am. Chem. Soc.* **1984**, *106*, 4294.
(224) (a) Jurczak, J.; Golebiowski, A.; Bauer, T. *Synthesis* **1985**, 928. (b) Golebiowski, A.; Izdebski, J.; Jacobsson, U.; Jurczak, J. *Heterocycles* **1986**, *24*, 1205.
(225) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F. *J. Am. Chem. Soc.* **1984**, *106*, 2456.
(226) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716.
(227) (a) Danishefsky, S. J.; Uang, B. J.; Quallich, G. *J. Am. Chem. Soc.* **1984**, *106*, 2453. (b) Danishefsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.* **1989**, *111*, 2193.
(228) (a) Midland, M. M.; Afonso, M. M. *J. Am. Chem. Soc.* **1989**, *111*, 4368. (b) Midland, M. M.; Koops, R. W. *J. Org. Chem.* **1990**, *55*, 4647. (c) Midland, M. M.; Koops, R. W. *J. Org. Chem.* **1990**, *55*, 5058.
(229) Danishefsky, S.; Barbachyn, M. *J. Am. Chem. Soc.* **1985**, *107*, 7761.
(230) Bednarski, M.; Maring, C.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 3451.
(231) Quimpère, M.; Jankowski, K. *J. Chem. Soc., Chem. Commun.* **1987**, 676.
(232) (a) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 6968. (b) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1986**, *108*, 7060.
(233) Danishefsky, S.; Bednarski, M. *Tetrahedron Lett.* **1984**, *25*, 721.
(234) Barbaro, G.; Battaglia, A.; Giorgianni, P. *J. Org. Chem.* **1988**, *53*, 5501.
(235) (a) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 2038. (b) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5321.
(236) Holton, R. A.; Williams, A. D. *J. Org. Chem.* **1988**, *53*, 5983.
(237) Matsubara, S.; Onishi, H.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 6209.
(238) Matsubara, S.; Kodama, T.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 6379.
(239) Fukuzawa, S.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1987**, 919.
(240) Fukuzawa, S.; Fukushima, M.; Fujinama, T.; Sakai, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2348.
(241) (a) Ukaji, Y.; Fujisawa, T. *Tetrahedron Lett.* **1988**, *29*, 5165. (b) Ukaji, Y.; Yoshida, A.; Fujisawa, T. *Chem. Lett.* **1990**, 157.