Reagent-Controlled Transition-Metal-Catalyzed Radical Reactions

Andreas Gansäuer* and Harald Bluhm

Institut für Organische Chemie und Biochemie der Albert-Ludwigs-Universität, Albertstr. 21, 79104 Freiburg, Germany

Received November 26, 1999

Contents

I. Introduction and Scope

Over the past decades radical chemistry has developed into an important and integral part of organic chemistry. Although the first example of an organic radical **(1)** was observed as early as 1900 by Gomberg,[1] the pace of development was rather slow over the next couple of decades and radicals were rarely used in synthesis. The development of efficient chain

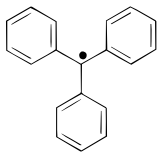
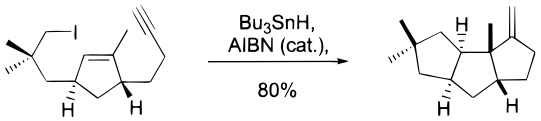


Figure 1. Gomberg's triphenyl methyl radical.

reactions constituted an important breakthrough in the application of radical chemistry in organic synthesis.[2] An important and very attractive feature of these reactions is their high degree of functional group tolerance. Since radicals are usually stable under protic conditions, alcohols or even water can, in principle, be used as solvents in radical chemistry. Consequently, protic functional groups do not need protection. As soon as the underlying principles of the kinetic and thermodynamic behavior of free radicals were firmly established, efficient synthetic applications became feasible.[3] The use of chain reactions has resulted in a number of very impressive total syntheses of natural products. An example is shown in eq 1.[4] The characteristic features of free radicals can by now be deduced from ESR data.[5] The course of some radical reactions can be understood by theoretical means.[6]



(1)

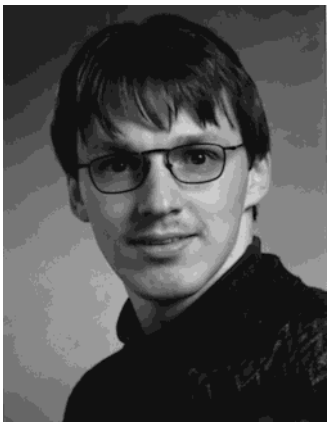
However, because the crucial intermediates are free radicals, no influence of the ligand sphere of the reagent generating the radical on the selectivities of the reaction is usually observed. These transformations are, therefore, classical examples of substrate-controlled reactions.

An alternative approach to radical chemistry is constitued by controlling the course of the radical reaction by a suitably designed reagent both during radical generation and the ensuing transformation of the metal-bound radical. This concept of reagent control has been applied with excellent success in organometallic chemistry and in catalysis.[7] Until recently, use of this otherwise very successfull approach to radical chemistry has been rare.[8] The purpose of this review is to describe exactly these novel emerging concepts in C−C and C−H bond forming reactions. The literature is covered until November 1999. Examples where the element of stereocontrol depends on chiral auxiliaries on the starting material will not be dealt with here. The existing excellent reviews and book chapters on this topic should be consulted by the interested reader.[3b,9] Metal-initiated reactions leading to transformations of free radicals will not be treated because no metal-bound radicals are obtained. Thus, vitamin B_{12}-initiated reactions[10] and cobaloxime chemistry[11] will not be discussed here. The recently described living radical polymerizations initiated by well-designed metal complexes[12] are also thought to proceed via chain reactions of free radicals. The selectivity determining step of allylic oxidations catalyzed by chiral copper complexes is thought to proceed through an organocopper(III) reagent.[13] Thus, these oxidations will not be treated here. C−H activation by manganese porphyrins,[14] DNA cleavage by metal complexes,

* To whom correspondence should be addressed. E-mail: agansaeu@organik.chemie.uni-freiburg.de.

10.1021/cr9902648 CCC: $35.00 © 2000 American Chemical Society
Published on Web 07/14/2000

Andreas Gansäuer was born in 1966 in Paris, France. After studying chemistry at the universities of Bonn, Germany, and Oxford, GB, he obtained his diploma under the supervision of Professor J. E. Baldwin, Oxford. He completed his Ph.D. degree under the guidance of Professor M. T. Reetz at the Max-Planck-Institut für Kohlenforschung in 1994 and spent a postdoctoral year in 1995 with Professor B. M. Trost at Stanford as a Feodor-Lynen fellow of the Alexander von Humboldt-Stiftung. He began his Habilitation in Göttingen in early 1996 under the mentorship of Professor Brückner, which was completed in 1999. During this time he was supported by a the Liebig-Stipendium des Fonds der Chemischen Industrie and a Habilitationsstipendium der Deutschen Forschungsgemeinschaft. In 1999 he won the annual ADUC-prize and the Gerhard Hess-Preis der Deutschen Forschungsgemeinschaft in 2000. Since 1999 he has been working at the University of Freiburg im Breisgau, Germany, and will move as Professor to the University of Bonn, Germany. His research interests include the chemistry of metal-bound radicals, enantioselective synthesis, and novel catalytic methods. In addition, he enjoys travelling and staying with his wife and daughter.



Harald Bluhm was born in 1972 in Westrhauderfehn, Germany. He studied chemistry at the University of Göttingen, Germany, and graduated in the group of Dr. Gansäuer with a thesis entitled "Catalytic, Regio and Chemoselective Opening of Epoxides via Radicals: A new Strategy in Transition Metal Catalysis". Since then he has started working toward his Ph.D. degree in the same group and moved to Freiburg, Germany. His research interests include the development of novel organometallic methods and their application in organic synthesis. In his rare spare time he breeds "Ostfriesische Möven", a traditional chicken breed of Ostfriesland, his native county.

e.g., bleomycin,[15] and DNA foot-printing[16] are not included because the radicals formed have not been used in C−C bond forming reactions.

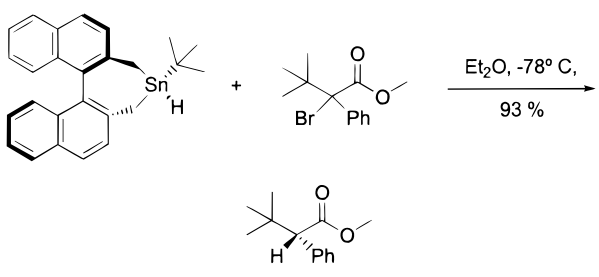
In principle, reagent control can be excercised at different stages in a radical reaction. (a) The first step in the series of transformations of a radical reaction is constituted by the generation of the radical from a suitable precursor. The usual selectivities of this generation, e.g., by electron transfer, can be controlled by the electron transfer reagent and its ligand sphere. Clearly, the radical precursor needs to have a functional group that allows for binding of the reagent in close proximity of the newly generated radical prior to its formation. (b) In the subsequent transformation of the radical, the selectivities of the reaction, e.g., addition to carbon−carbon multiple bonds, should, in principle, also be amenable to reagent control if the metal complex remains bound to the radical. Here one is, of course, not dealing with the chemistry of intermediates usually described as free radicals but with metal-bound radicals. (c) In the case of a free radical reaction, reagent control is possible if the radical or the radical trap are complexed by a carefully designed reagent. The stereochemical course of the following transformation is thus amenable to reagent control by the metal and its ligand.

Although at the stage the reagent-controlled radical reaction is completed, an additional attractive feature of the desired process becomes immediately apparent. If the reagent determining the course of the overall transformation can be cleaved off the reaction product and recycled, a catalytic reaction emerges. This is obviously of great economic advantage if the reagent contains an expensive metal or a ligand that has to be synthesized in a multistep sequence.

Metal-initiated radical reactions with suitable radical precursors allow for reagent control in both of the above-mentioned two points, a and b. Although these radical reactions have been applied to demanding synthetic reactions with great success for some time,[17] attempts to influence the usual selectivities by ligand variations have appeared in the literature only recently. These emerging novel concepts and reactions will be the subject of this review. The focus will be on the use of carbonyl- and epoxide-containing molecules as radical precursors for reagent control in radical chemistry.

The concepts outlined as point c were reviewed by Renaud[18] in late 1998 and by Sibi and Porter[19] in early 1999. Diastereoselective and enantioselective reactions in these fields have been realized during the last 5 years. Therefore, this subject will not be covered comprehensively in this article and only recent examples will be discussed here.

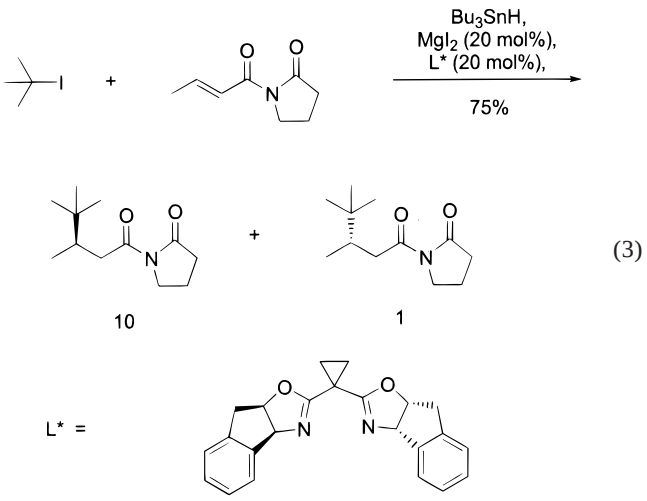
Chiral, nonracemic stannanes have been used to enantioselectively reduce radicals by Schumann[20] and later independently by Curran[21] and Metzger (eq 2).[22]



(2)

(*S*) : (*R*) = 76 : 24

An intriguing extension of this work has been reported by Schiesser only recently.[23] It was demonstrated that the performance of chiral, nonracemic stannanes in these transformations can be significantly improved in the presence of enantiomerically pure Lewis acids for substrates containing carbonyl groups. Obviously this concept of double stereocontrol is very promising for future applications. Since the first reports on the activation of prochiral radical traps by enantioselective Lewis acid catalysis by Porter and Sibi (eq 3), this exiting field has developed at a rapid pace.[24] The interested reader is referred to the review by these authors.[19]



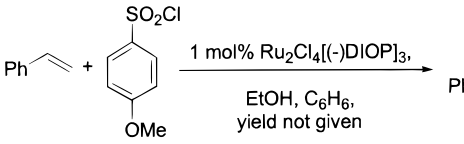
(3)

II. Reagent Control in Transition-Metal-Initiated Radical Reactions

Interesting classes of radical sources in transition-metal-initiated reactions are aldehydes and ketones. Carbonyl compounds are good ligands for Lewis-acidic metal complexes, and thus, reagent control during the formation of ketyl anions seems possible.[8] Moreover, the ketyl anions formed during electron transfer enables binding of the metal ions or complexes via oxygen. Control of the following radical transformations can, therefore, be achieved. Ketyl radicals are, of course, interesting intermediates in organic synthesis. They can either dimerize to give 1,2-diols in pinacol coupling[25] or add to carbon−carbon multiple bonds in inter- or intramolecular reactions.[26] In these classes of transformations, reagent control can be excercised in directing the diastereo- and enantioselectivity of the products derived from the ketyl anions by variation of the ligands and the metal ions of the electron-transfer reagent.

Another intriguing class of radical precursors that is to date used rarely and is thus probably less well established than carbonyl compounds are epoxides.[8] The epoxide oxygen is well-suited for complexation by a metal complex. Therefore, the regio- and stereoselectivity of epoxide opening via electron transfer can be influenced by the ligands. The initial product of the opening via electron transfer is a β-metal oxy radical. These radicals that are bound to the metal via the oxygen can participate in the usual reactions of carbon-centered radicals, e.g., hydrogen-atom abstraction, cyclizations, and intermolecular addition reactions to activated olefins. The course of these transformations should be amenable to reagent control if a properly chosen metal complex is utilized. Therefore, these metal-bound radicals constitute an interesting class of intermediates for a number of synthetically useful transformations.

An example of a reaction of reagent control in radical chemistry without using carbonyl compounds or epoxides was reported by Kamigata.[27] It was demonstrated that addition of sulfonyl chlorides to styrene and phenylpropene is catalyzed by chiral ruthenium complexes (eq 4). The enantioselectivities



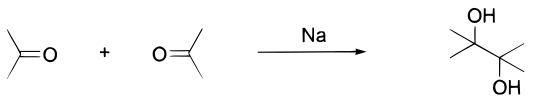
(4)

obtained were low. A reaction mechanism involving a radical redox transfer chain has been proposed. The exact reason for the stereochemical induction is still unclear, however.

III. Carbonyl Compounds as Radical Sources: Pinacol Couplings

A. Stoichiometric Reagent-Controlled Couplings

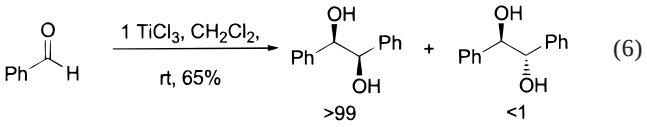
The reductive coupling of two carbonyl compounds, the pinacol coupling, is probably the most direct way for the formation of the C−C bond of 1,2-diols.[25] Since the first report of the reaction of acetone with sodium in 1858 by Fittig from Göttingen[28] (eq 5), considerable effort has been devoted to the development of milder and more selective ways to achieve this important transformation.



(5)

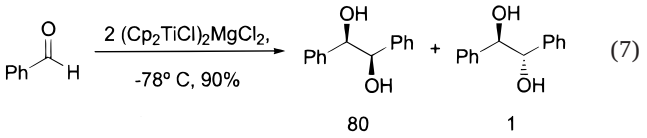
Pinacol couplings have been used as key steps in a number of elegant syntheses of natural products.[29] A complete coverage of modern methods is beyond the scope of this article. The emerging catalytic variations will be emphasized.

Stoichiometric titanium-based complexes have turned out to be excellent reagents for the pinacol coupling of aromatic and α,β-unstaurated aldehydes.[30] Seebach reported that titanium trichloride generated in situ from titanium tetrachloride and butyllithium was an excellent reagent for highly diastereoselective couplings of aromatic aldehydes to racemic C_2-symmetrical 1,2-diols.[31] Aliphatic aldehydes and aromatic ketones were not affected. Thus, the chemoselectivity of this mild reagent is high. Later, Porta showed (eq 6) that commercial titanium trichloride in THF/CH_2Cl_2 solution also was an efficient reagent for this transformation.[32]



(6)

Diastereoselectivities were similar to the titanium(III) reagent generated in situ. Unfortunately, addition of a tartrate-derived ligand did not induce significant enantioselectivities (ee < 5). It remains to be seen whether this conceptually simple and attractive approach is to be successful in enantioselective synthesis. In 1987, Inanaga and Handa disclosed their results on the pinacol coupling of aromatic and α,β-unsaturated aldehydes.[33] They found that reduction of titanocene dichloride with Grignard reagents lead to a green trinuclear titanium(III) reagent that was formulated as $(Cp_2TiCl)_2MgCl_2$. This complex coupled the aldehydes in high yield and with high diastereoselectivities to give the racemic C_2-symmetrical 1,2-diols (eq 7).



(7)

The mechanistic rationale offered for the high diastereoselectivity of this process is shown in Figure 2. Both ketyl anions are coordinated in a trinuclear

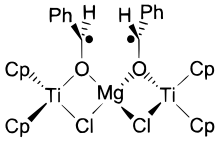
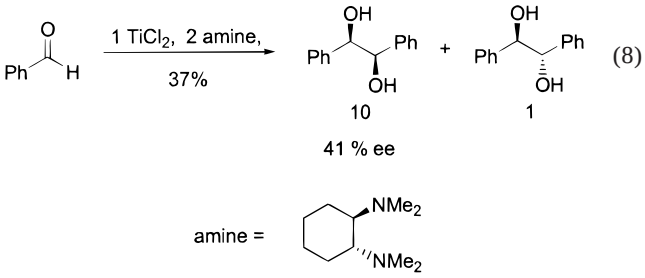


Figure 2. Possible decisive intermediate in titanocene-mediated pinacol couplings.

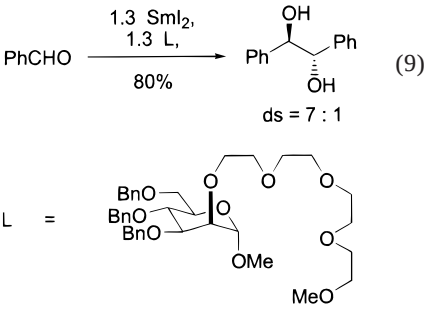
complex consisting of two titanocene(IV) units and a central magnesium ion. Each ketyl anion is bound to one titanium atom and to magnesium. This arrangement results in the depicted orientation of the phenyl groups minimizing steric interactions.

In this case, aliphatic aldehydes and ketones were unreactive. Clearly, this highly ordered trinuclear complex should allow for control of diastereo- and enantioselectivity of the pinacol coupling if the cyclopentadienyl ligands are chosen properly.[34] Titanocene(III)-initiated pinacol couplings were later reinvestigated by Schwartz.[35] It was found that reduction of Cp_2TiCl_2 with aluminum powder[34] lead, after washing with diethyl ether, to the dimeric $(Cp_2TiCl)_2$ as active reagent for the highly diastereoselective coupling of activated aldehydes. Interestingly, the coupling could be performed in the presence of water without significant loss in diastereoselectivity. However, more than 50 equiv of NaCl had to be added to the reaction mixture to conserve the high selectivities. This observation is nevertheless an intriguing manifestation of the stability of radicals in protic environment. A common feature of all titanium(III) reagents reported to date is their high chemoselectivity. Obviously simple titanium(III) reagents are incapable of transferring an electron to nonactivated carbonyl compounds, e.g., simple aldehydes and ketones. To achieve this goal, titanium(II) reagents have been developed by Mukaiyama. In this manner, ketones can be coupled to the 1,2-diols in moderate to excellent diastereoselectivities without significant formation of the deoxygenation products.[36] An important achievement in this area is Matsubara's observation that addition of chelating diamines greatly improves the performance of the titanium(II) reagent.[37] It was not established if the amine lead to an acceleration of the reaction or simply tamed Lewis-acid species initiating side reactions. The goal of an enantioselective coupling was also pursued by addition of diamines and amino alcohols to the reaction mixture by Matsubara (eq 8). The enantioselectivity obtained (44% ee) so far is not yet fully satisfying. However, this simple and efficient concept still seems very promising.



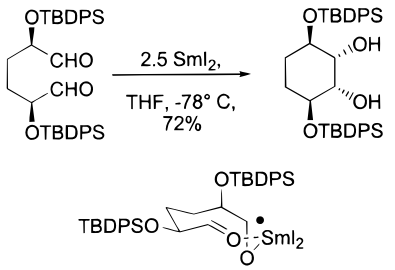
(8)

Interesting modifications of the selectivity of samarium diiodide-based reagents have been reported by Skrydstrup.[38] Addition of chelating ligands allowed for distinct improvements in diastereoselectivity of the pinacol coupling (eq 9).



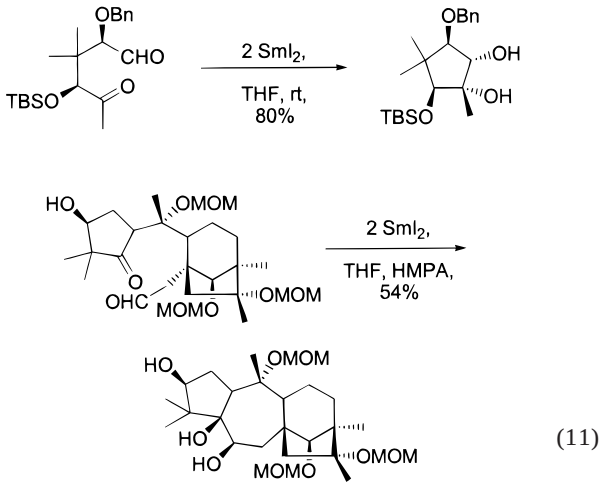
(9)

Samarium diiodide has also been employed in stereocontrolled pinacol cyclizations.[39] Examples are shown in eq 10 and 11. The origin of stereocontrol



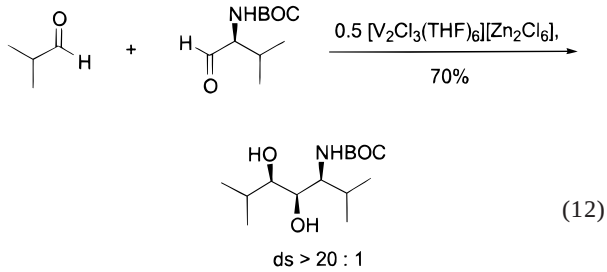
(10)

in the first example is thought to be the formation of a nine-membered cyclic ketyl radical. The other transformations also proceed under chelation control.



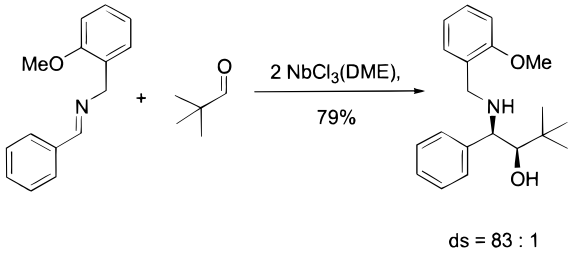
(11)

Low-valent vanadium reagents constitute a very interesting class of reagents in pinacol couplings. Pedersen demonstrated as early as 1989 that crossed pinacol couplings are readily achieved using $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$[40] with substrates allowing for chelation.[41] Excellent diastereoselectivities were sometimes achieved (eq 12).



(12)

This important methodology can also be applied to pharmacologically important α-amino aldehydes.[42] Although variations of the ligand sphere have not yet been reported, reagent control is excercised in binding the substrates in a chelation-controlled manner.[43] Intriguing applications of low-valent niobium complexes[44] have been found in the reductive coupling of imines and in the crossed pinacol coupling of imines and aldehydes by Pederson in one of the earliest examples of highly selective couplings in 1987[45] (eq 13).

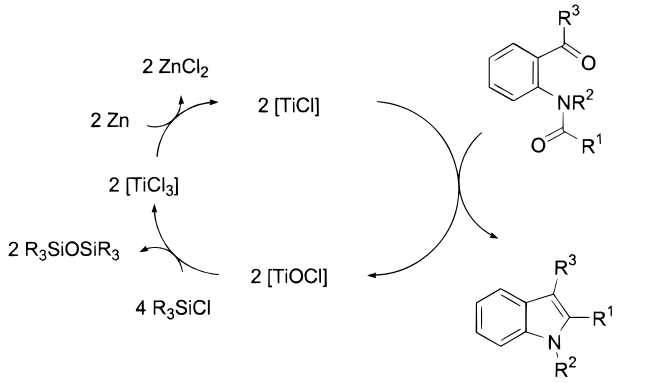


(13)

B. From Stoichiometric to Catalytic Pinacol Couplings

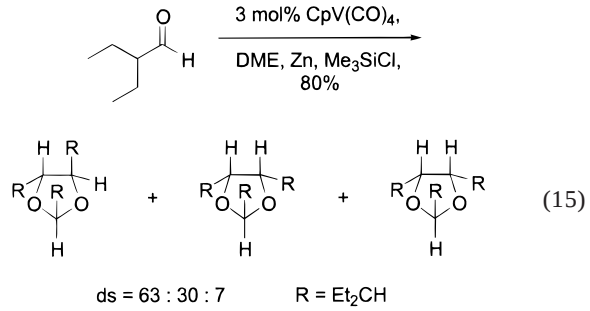
1. Chlorosilanes as Mediators

Although some of the reagents discussed above allow for excellent results, they all suffer from the principal drawback of having to be employed in stoichiometric amounts. This is especially disadvantageous when more complex and expensive reagents are to be used to obtain reagent control. Clearly a catalytic reaction would circumvent this problem and result in a more efficient use of resources. In 1995, Fürstner and Hupperts reported their McMurry reaction (eq 14) catalytic in titanium and introduced a novel concept for conducting catalyzed redox reactions.[46] Independently, Hirao developed a vanadium-



(14)

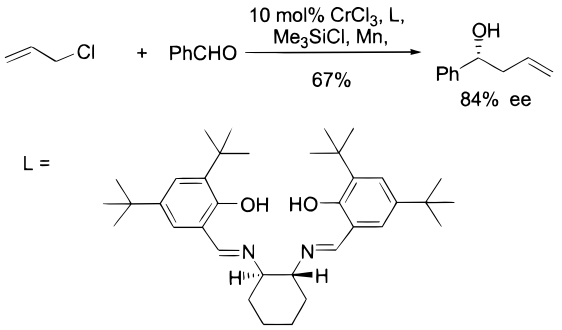
catalyzed pinacol coupling based on the same considerations.[47] However, in this reaction the initially formed diolate was cleaved off the vanadium catalyst by formation of a dioxolane. Thus, a third of the aldehyde was consumed for catalyst regeneration. The role of Me_3SiCl seems to be the activation of the aldehyde for dioxolane formation. The diastereoselectivities of the pinacol coupling were moderate (eq 15).



(15)

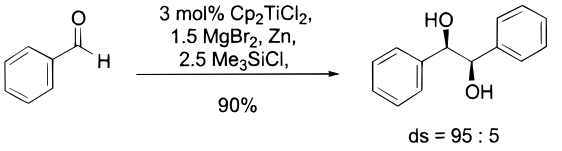
No further investigations concerning ligand variations were undertaken. Later, this concept[48] has also been applied to the synthetically very useful Nozaki–Hiyama reactions by Fürstner and Shi.[49] The essential novel step in both catalytic cycles consists of the removal of oxo or alkoxides from metal complexes for the regeneration of metal chloride species that could be reduced to the redox-active reagent in situ. Metal chloride formation was achieved by adding chlorosilanes to the reaction mixture. The redox-active reagent was simply recovered by reduction with zinc or manganese dust. A catalytic enantioselective variation of the Nozaki–Hiyama reaction was very recently reported by Cozzi[50] (eq 16).

Ephritikhine demonstrated that cleavage of the metal oxo species can also be achieved by adding aluminum trichloride instead of chlorotrimethyl-



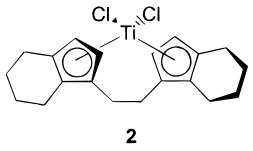
(16)

silane.[51,52] The catalysts used in these reactions were titanium trichloride and uranium tetrachloride. In 1996, Endo reported the samarium-catalyzed pinacol coupling of aldehydes and ketones using chlorotrimethylsilane.[53] Diastereoselectivities in the intermolecular reaction were moderate, and no attempts were made to change the ligands on samarium to alter the course of the reaction. Another study bearing promise for a reagent-controlled catalytic pinacol coupling was the titanocene-catalyzed pinacol coupling of aromatic aldehydes as shown in eq 17.[54]



(17)

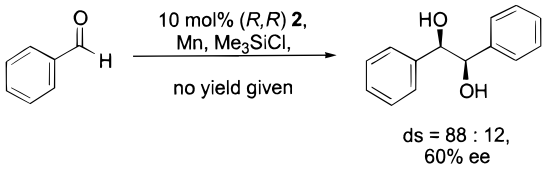
It turned out to be essential that the aldehyde, Me_3SiCl, and $MgBr_2$ were added slowly to a mixture of Cp_2TiCl_2 and zinc dust in THF. In this manner, the uncatalyzed coupling of aromatic aldehydes in the presence of $ClSiMe_3$ was supressed.[55] $MgBr_2$ was necessary to obtain a tight trinuclear complex ensuring high diastereoselectivity.[33,34] It was established that silylation was the slowest step in the catalytic cycle. Without the catalyst, the reaction was slower and yielded the 1,2-diols with substantially reduced diastereoselectivity. A drawback of these conditions was that aldehydes that are reduced only slowly for steric reasons, e.g., *o*-tolyl aldehyde, or electronic reasons, e.g., anisaldehyde, were not coupled by the catalyst but by the stoichiometric reductive system. Although acetophenone was transformed to product under the catalytic conditions, this was not due to the titanocene reagent. In the absence of the catalyst, essentially the same results were obtained. Thus, a chlorotrimethylsilane-initiated coupling was taking place.[55] If the proper reaction conditions and substrates, i.e., unhindered aromatic aldehydes, were chosen, the catalytic system delivered the reaction products in good yields and with reasonable diastereoselectivity (90:10 up to 95:5). THF constituted the best solvent. Later, Nicholas reported a similar reaction using manganese dust as stoichiometric reductant.[56] With the titanocene reagents, control of diastereoselectivity is readily accomplished by variation of the ligand sphere. Using Brintzinger's *ansa*-titanocene **2**[57] (Figure 3) in racemic form as catalyst lead to a distinct improvement of diastereoselectivity compared to titanocene dichloride with zinc as reductant.[58] Nicholas reported the first catalytic enantioselective pinacol coupling using enantiomerically pure **2** as catalyst with manganese as reductant.[56]



2

Figure 3. Brintzinger's *ansa*-metallocene.

Although reasonably high levels of enantioselection were observed (ee = 60% for benzaldehyde), the reaction suffered from a decrease in diastereoselectivity (8:1 vs 13:1) compared to Cp_2TiCl_2 (eq 18).

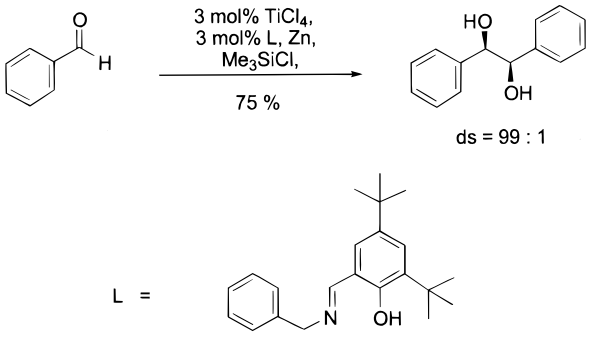


(18)

This effect was even more pronounced in the presence of zinc dust.[59] The trinuclear complex responsible for the binding of both ketyl radicals probably could not be formed with the enantiomerically pure **2**. It remains to be seen if this problem can be circumvented by employing different titanocene complexes as catalysts. However, titanocene(III) complexes constitute the catalysts allowing for the highest enantioselectivities in pinacol couplings so far. Hirao reported the pinacol coupling of aliphatic aldehydes using the titanocene dichloride, $ClSiMe_3$, zinc dust system.[60] Diastereoselectivities were usually substantially lower than for aromatic aldehydes. The authors claim that the titanium(III) reagent tranfers an electron to an aldehyde activated by the strong Lewis acid $ClSiMe_3$. The silyl-bound neutral ketyl radicals then coupled with low selecticity. Thus, the system does not offer obvious potential for controlling selectivity by the ligands of the metal. A similar observation has been made by Svatos and Boland using chromium(II) compounds as electron-transfer catalysts.[61] They found that using bulkier chlorosilanes leads to greatly enhanced selectivity, albeit at the expense of lower yields. These reports clearly demonstrate the major disadvantage of chlorosilane-mediated catalytic pinacol couplings. The high Lewis acidity of the employed silanes allows for activation of the carbonyl-containing substrates toward electron transfer and thus a background reaction through silyl bound ketyl radicals. Therefore, the reaction conditions have to be carefully controlled. A milder way of cleaving the metal−oxygen bonds prior to in situ reduction of the catalyst is therefore desirable. A solution to this problem will be discussed in the next section.

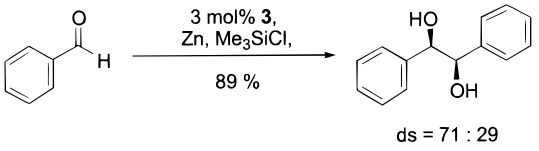
Three other titanium-catalyzed pinacol couplings based on silylation reactions to recycle the catalyst have recently been described. Nelson developed a catalyst based on titanium trichloride.[62] Interestingly, protic additives, e.g., *tert*-butyl alcohol, and donor ligands, e.g., 1,3-diethyl-1,3-diphenyl urea, showed distinct improvements in yield and selectivity. Salen ligands have been employed by Cozzi in

titanium-catalyzed reactions.[63] Aromatic and aliphatic aldehydes could be coupled (eq 19).



(19)

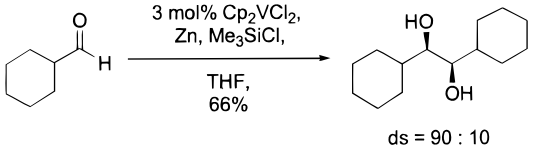
Diastereoselectivities were excellent in many cases. A single example of a chiral ligand was reported resulting in low enantioselectivity (10% ee). Therefore, the titanocene catalysts still seem to bear greater promise for enantioselective catalysis. The intriguing catalyst phenyl titanocene(III) **(3)** was employed by Itoh[64] (eq 20).



(20)

However, for benzaldehyde, diastereoselectivities (71:29) are somewhat lower than with titanocene chloride. Phenyltitanocene is a more active electron-transfer reagent than titanocene(III) chloride. The phenyl group constitutes a less electron-withdrawing substitutent on titanium than chloride. Thus, aliphatic dialdehydes could be coupled intramolecularly. This attractive novel approach toward selective catalysis offers an additional element of reagent control in radical reactions through variation of the aryl group attached to titanium.

Hirao further optimized his vanadium catalysts for the coupling of aldehydes and imines.[65] Varying the ligands on vanadium and changing the solvent lead to dramatic improvements in diastereoselectivity of the reaction (eq 21). It turned out that vanadocene



(21)

dichloride in THF constituted by far the most efficient system for catalysis. This catalytic system has been used by Hirao for a coupling of imines also.[66] No enantioselective reactions using vanadocenes have been reported so far.

2. Protonation of Metal–Oxygen Bonds in Catalytic Radical Reactions

As indicated above, silylation is not always an ideal way to regenerate the redox-active complexes in situ. The problem to be solved is the cleavage of metal−oxygen bonds to yield metal halides by an oxophilic reagent without activating carbonyl compounds toward electron transfer. It has to be kept in mind that the reactive intermediates dealt with in pinacol couplings are radicals. Thus, any reagent employed should be tailor-made to account for the stability of radicals. Protonation is, in principle, the simplest way of cleaving metal oxides and alkoxides. Protonation also seems to be well-suited in radical reactions. Radicals are usually stable under protic conditions, and alcohols and even water are suitable solvents for radical reactions.[3] The reason for this stability is the low tendency for homolytic cleavage of O−H bonds. It should not be forgotten, however, that even addition reactions to carbonyl compounds where classical carbanionic species have until now not been ruled out as intermediates, e.g., magnesium compounds under Barbier conditions, can be performed in aqueous acidic media.[67] Bearing these general considerations in mind, we decided to screen buffered forms of hydrochloric acid as mediators in titanocene-catalyzed pinacol couplings. Neat hydrochloric acid as the ultimate proton source is desirable because titanocene dichloride is readily reduced by zinc or manganese dust to the corresponding titanium(III) reagents.[34] Except for the bromide and iodide, this is not readily achieved with other ions. Chloride constitutes the most convinient choice among the halides. The catalytic cycle is depicted in Figure 4.

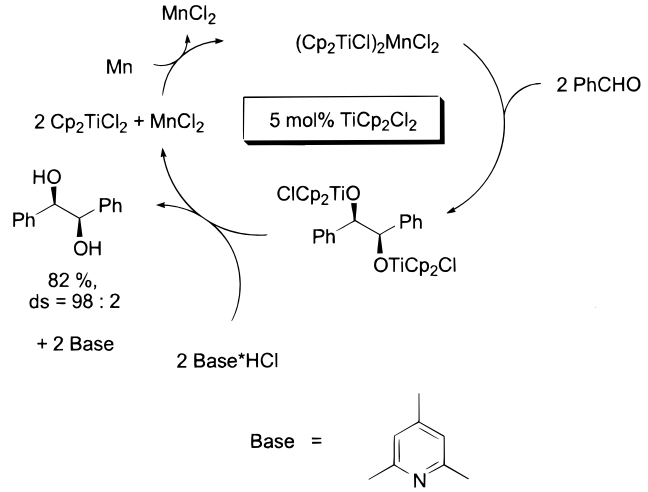


Figure 4. Titanocene-catalyzed pinacol coupling employing protic conditions.

Some features of the acid and the stoichiometric reductant, i.e., the metal powder, to be employed to achieve catalytic turnover become immediately apparent. (1) The acid must be strong enough to protonate a metal−oxygen bond. The acid's pK_a in water should thus be lower than that of typical alcohols (CH_3OH, 15.5; *t*-BuOH, 19.2).[68] To ensure complete protonation, the pK_a should, therefore, be at most 12.5. Also, protonation should occur fast to exclude any undesired side reactions. (2) Neither the stoichiometric reductant, i.e., the metal powder, nor the active titanium(III) reagent may be oxidized by the acid. Therefore, neat hydrochloric acid cannot be employed directly. (3) The corresponding base must not complex and deactivate any titanium species in the catalytic cycle. (4) The employed acid should not activate the aldehyde strongly toward electron trans-

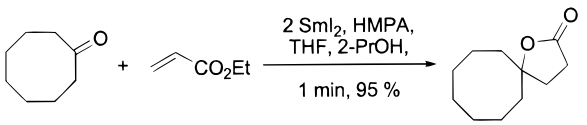
fer by protonation. (5) The metal salt formed during the reduction of titanocene dichloride should not act as Lewis acid, initiating uncatalyzed electron transfer to the carbonyl compound.

Another feature of the catalytic cycle is that free 1,2-diols are formed as compared to the silyl ethers obtained in silylations. The free diol can, in principle, act as ligand for titanium, and care has to be taken to avoid product inhibition. With these considerations in mind, we decided to use pyridine hydrochlorides as acids. Both the pK_a and steric demand of the acid and the corresponding base can be readily altered by variation of the substituents.[68] 2,4,6-Collidine hydrochloride was an appropriate acid to achieve catalytic turnover.[69] Manganese as a stoichiometric reductant was distinctly superior to zinc with respect to both yield and diastereoselectivity of the coupling.

It should be noted that under the catalytic conditions, diastereoselectivity is almost the same as in the stoichiometric parent system.[33] Product inhibition did not seem to pose serious problems. Under the optimized conditions, hardly any benzyl alcohol was formed. The stoichiometric reductive system is, therefore, exceptionally mild. *o*-Tolyl and *p*-anisaldehyde gave the desired product in good yields and with excellent diastereoselectivities. Both aldehydes reacted with distinctly lower selectivity when Me_3SiCl was used as the mediator for catalysis. The chemoselectivity of the system was high. Neither aliphatic aldehydes nor aromatic ketones were affected under the reaction conditions. These findings indicate the almost complete absence of uncatalyzed electron transfer from manganese to the aldehydes. Our mild stoichiometric reducing agent is, thus, clearly superior to the systems employing zinc or manganese and chlorotrimethylsilane. It remains to be seen if this reagent combination will be of value in other catalytic reactions. Although no attempts have been made to investigate ligand variations, this area of research certainly remains promising.

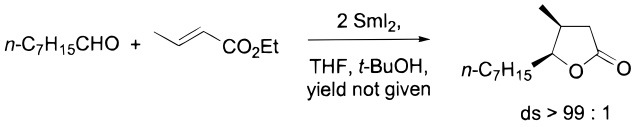
IV. Carbonyl Compounds as Radical Precursors: Additions of Ketyl Radicals to C–C and C–X Bonds

A very productive part of radical chemistry during the last 20 years has been addition reactions of ketyl radicals to olefins. It is fair to say that the rapid development of this field is due to the introduction of samarium diiodide as electron-transfer reagent to organic synthesis by Kagan and Namy in 1980.[70] Application of low-valent complexes in ketyl anion chemistry of samarium has resulted in a number of impressive applications in synthesis.[17,71] Among the best acceptors in the coupling reactions are α,β-unsaturated esters.[72] Both aldehydes and ketones can be used as carbonyl partners in these reactions (eq 22).



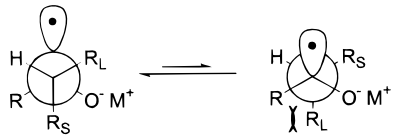
(22)

Interestingly, even formaldehyde in aqueous solutions constitutes a good precursor for the ketyl radicals.[73] The products of these transformations, γ-lactones and γ-hydroxyesters, are a common structural motif in natural product synthesis and are valuable synthetic intermediates. Addition of simple aldehydes to crotonates has been reported to be highly diastereoselective.[72b] However, the results are somewhat confusing because in closely related systems substantially different selectivities have been observed[72c,d] (eq 23).



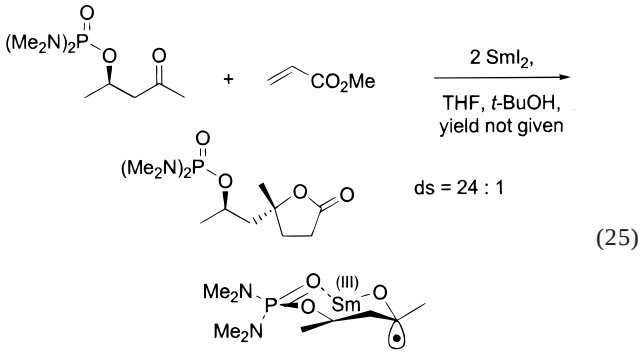
(23)

The reactivity of samarium diiodide can be dramatically increased if hexamethylphosphoric acid triamide (HMPA) is added as ligand for samarium to the reaction mixture.[72c,73] Lewis- acid cocatalysis has been reported as an efficient means to accelerate ketyl additions reaction by Inanaga.[74] Diastereoselectivity of the addition reactions of ketyl radicals seems to be governed by the preferred configuration of the ketyl radical as deduced from theoretical studies[75] (eq 24). One would expect reagent control by addition of ligands to be an interesting means to influence the selectivity.



(24)

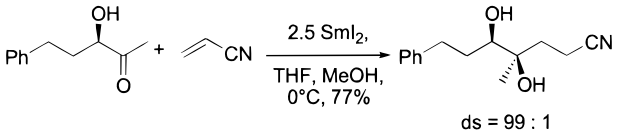
The high oxophilicity of samarium allows for excellent results in chelation-controlled ketyl olefin couplings.[74d] Diastereoselectivity can be very high if the properties of the reagent and the substrate are suitably adjusted. An instructive example is shown in eq 25. An eight-membered chelate containg the



(25)

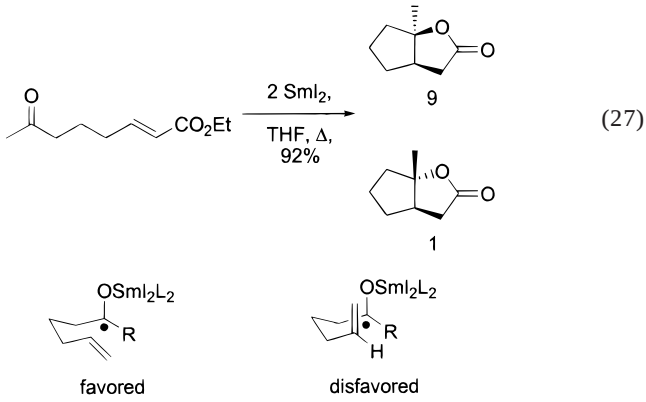
[P(O)(NMe$_2$)$_2$] group has been postulated as the decisive intermediate in the coupling of the protected hydroxyketone and acrylic acid ethyl ester.[63d]

Simple hydroxyketones yielded excellent results also by forming a five-membered chelate[67a,b] (eq 26). Thus matching of the steric and electronic features of both substrate and the reagent samarium diiodide, a typical scenario of reagent control, can lead to excellent results.



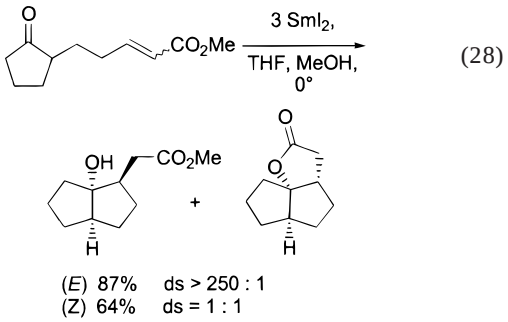
(26)

An important class of ketyl couplings are cyclization reactions. With simple substrates and in reactions giving bicyclic products, low to reasonable diastereoselectivities can be obtained[72b,77] (eq 27).



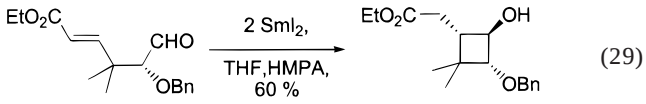
(27)

Chairlike transition structures have been proposed minimizing interactions with the samarium complex and the pseudoaxial substituent of the olefin. Olefin geometry can be an important factor[77] (eq 28).



(28)

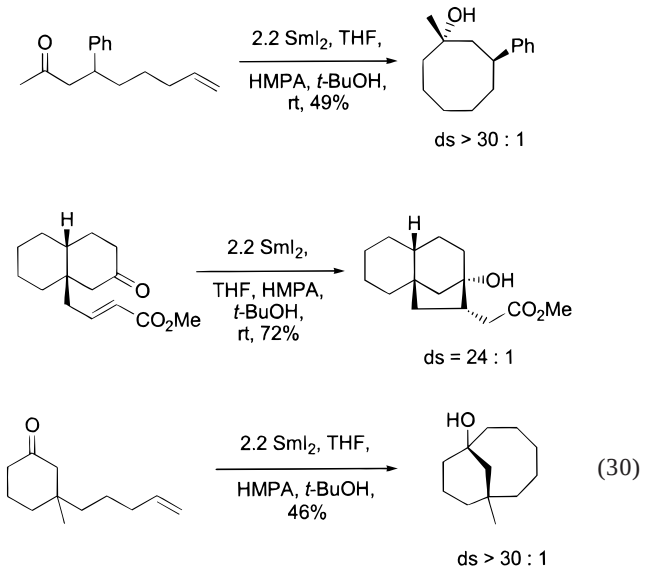
Substrates allowing for chelation usually react with exceedingly high diastereoselectivity.[78] For these reactions, convincing transition-state models have been proposed. It should be noted, though, that proper choice and positioning of the chelating group can be essential for optimizing the steric interactions in the respective transition states.[79] In this manner, even four-membered rings can be obtained in reasonable yields[80] (eq 29). Seven-[73a] and eight-membered



(29)

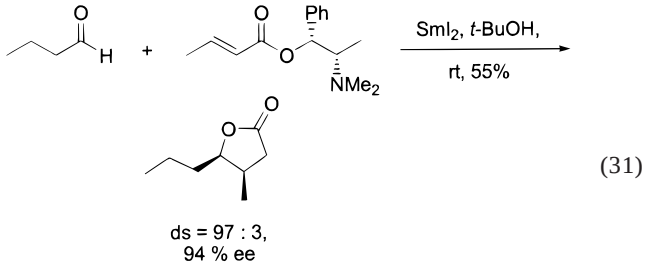
rings[81] and bicyclic and bridged systems[81] are readily accessible using this methodology (eq 30).

Two efficient systems for the intermolecular addition of ketyl radicals to acrylates and for ketyl cyclizations employing chiral auxiliaries have recently been described by Fukuzawa[82] and Molander.[83] Although the use of auxiliaries does not fit the subject of reagent control in a strict sense, these examples



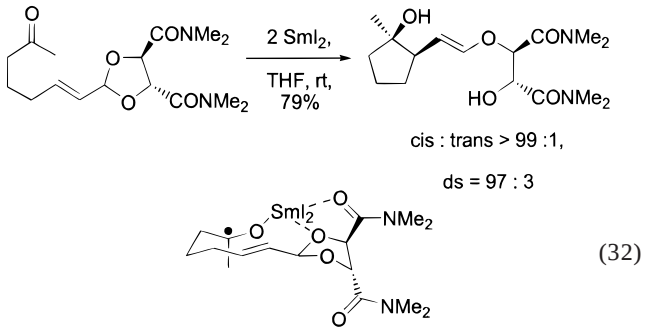
(30)

will be discussed here because they reveal important aspects of the coordination chemistry of samarium. Fukuzawa demonstrated that (1*R*,2*S*)-*N*-methyl ephedrine is an excellent chiral auxiliary for the addition of a wide variety of ketyl radicals to acrylates (eq 31).



(31)

The ephedrine is vastly superior to esters containing no groups for binding samarium, e.g., menthol. It has been postulated that the auxiliary enables binding of both the acrylate and the ketyl radical to samarium in a sterically well-defined manner. In this manner, excellent stereoselectivity is achieved. This assumption is supported by the observation that addition of HMPA results in complete loss of selectivity. No structures of the chelates were proposed. Molander reported chiral auxiliaries for cyclization reactions based on tartaric acid amides.[83] A typical example with the best auxiliary is shown in eq 32.

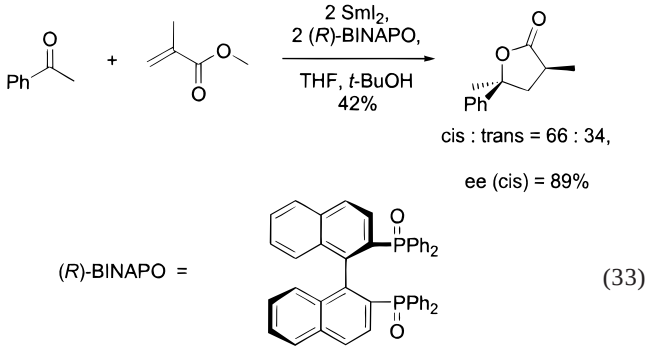


(32)

The improved donor ability of the amide compared to ester groups is crucial for the success of the reaction. Both relative stereoselectivity and stereo-

induction from the chiral auxiliary are usually excellent. It should be noted that the sense of relative stereoselectivity is reversed compared to samarium diiodide-induced cyclization containing no auxiliary ligand system. The effect of the auxiliary acting as ligand for the reactivity of samarium is therefore dramatic.

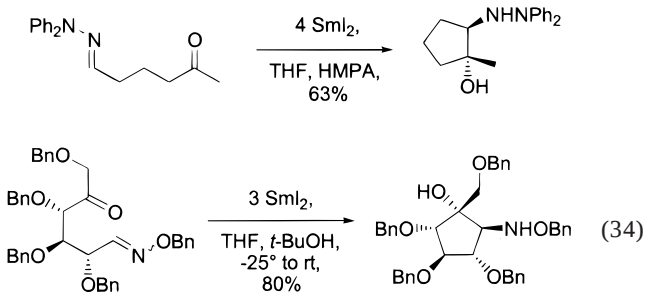
Recently, the first example of chiral ligand control in intermolecular ketyl additions was described by Mikami and Yamaoka.[84] This report constitutes a very interesting example of an enantioselective addition of ketyl radicals to acrylates. A number of ligands containing the highly polar P−O bond were examined. This approach is based on the beneficial effects of HMPA on samarium chemistry. By using "chiral HMPA", the coordination sphere of samarium was modified to allow for enantioselective synthesis. The best ligand described was the oxide of the well-established (*R*)-BINAP (eq 33).



(33)

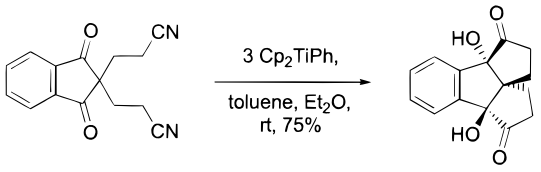
Enantiomeric excesses of up to 89% were obtained. However, diastereoselectivities were modest in some cases. This was due to an essentially nonstereoselective protonation of the obtained enolates. Using different protic acids could result in further improvements. This promising approach is very interesting in connection with the recently developed reactions catalytic in samarium.[85]

Another application of ketyl cyclizations is the addition to nitriles, hydrazones, and oximes. These transformations are possible using samarium diiodide[86−88] (eq 34). As in the addition to carbon−carbon multiple bonds, diastereoselectivities are high, although the yields are not always as satisfying.



(34)

Itoh described an intriguing titanocene-based system for the addition of ketones to nitriles.[89] As in the pinacol coupling, the phenyl ligand on titanium is essential for the ability of the reagent to transfer electrons (eq 35). The authors convincingly demonstrated that the reagent is also necessary to activate



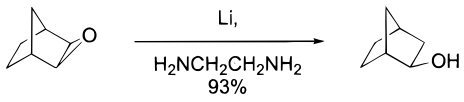
(35)

the nitrile group by complexation toward attack by the ketyl radical. Both the cyclopentadienyl and the phenyl ligands offer potential for enantioselective synthesis.

V. Epoxides as Radical Precursors

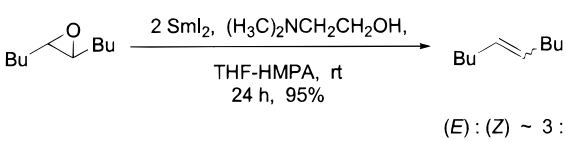
A. Stoichiometric Reagents

Probably the first examples of epoxide opening via electron transfer were reported by Birch in 1950.[90] An example of this type of transformation is shown in eq 36.



(36)

It was originally proposed that the reactions proceed through a nucleophilic opening of the epoxide via a solvated electron to yield the radical anion, a β-lithium oxyradical. However, it seems more likely that as in the formation of ketyl anions, an electron is transferred to the epoxide with concomitant opening of the radical anion. Clearly the use of solvated electrons does not readily allow for a reagent-controlled course of the reaction, and thus, structurally more complex electron-transfer reagents are desirable. The first convincing evidence that β-metaloxy radicals can be obtained from epoxides via electron transfer emerged from investigations by Kochi, Singleton, and Andrews in 1968.[91] Deoxygenation of cyclohexene oxide and styrene oxide in the presence of chromium(II) reagents yielded cyclohexene and styrene in high yields. This finding was explained by the presence of a long-lived intermediate trapped by a second equivalent of the chromium(II) reagent. The resulting species, a β-metaloxy metal compound, fragmented to give the olefin. To achieve C−C bond formation or reduction of the β-metaloxy radical with hydrogen-atom donors, it is essential that the subsequent reaction of the β-metaloxy radical is faster than the trapping with a second equivalent of the electron-transfer reagent and concomitant β-elimination. Thus, highly active electron donors such as SmI_2 were, as yet, not suitable for this purpose and lead to clean deoxygenation.[92] As expected, this elimination yielded mixtures of the (*E*)- and (*Z*)-olefins (eq 37). This observation can be

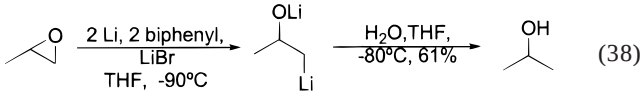


(37)

readily explained by assuming a β-metaloxy radical as intermediate that is long-lived enough to rotate

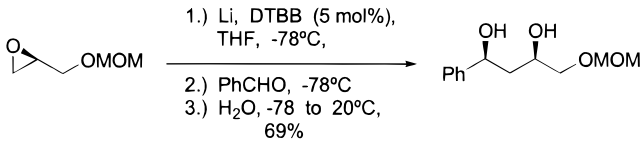
around the C−C bond before being trapped by a second equivalent of SmI_2.

An important discovery was made in 1986 by Bartmann.[93] He demonstrated that epoxides could be reductively opened to β-lithio lithiumoxy compounds at low temperatures by radical anions of aromatic compounds, e.g., of biphenyl. These organometallic intermediates generally did not decompose instantaneously due to the low tendency to eliminate the ionic "O^{2-}" group. Epoxides are opened to give the less substituted organolithium compound. These species could be trapped with reactive electrophiles, e.g., protons, allylic halides, and aldehydes, as shown in eq 38.



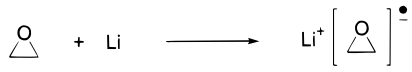
(38)

However, the low thermal stability of these intermediates and their high reactivity makes them somewhat difficult to use in the synthesis of complex organic molecules. Interesting applications have nevertheless been reported by Cohen[94] and Yus.[95] Especially attractive substrates employed in these studies are "Sharpless epoxides"[96] (eq 39). In this manner, a number of 1,3-diols can be readily obtained.



(39)

The mechanism of these transformations has been studied in some detail by Houk and Cohen.[97] Calculations suggest that an electron is transferred from lithium to the epoxide to yield the epoxide radical anion as shown in eq 40.



(40)

This unstable intermediate fragments to yield a β-lithio oxy radical that is subsequently trapped by a second equivalent of the aromatic radical anion. The crucial β-lithio lithiumoxy compound is obtained. The reason for the formation of the less stable radical during these transformations is explained by the formation of the more stable higher substituted alkoxide. The difference in stability between a secondary and primary alkoxide is obviously greater than the difference in stability of a primary and secondary radical! Interestingly the lithium ion was postulated to have very little influence on the course of the reaction. Therefore, reagent control is unfortunately difficult to achieve in these reactions also.

Important steps toward reagent-controlled epoxide openings were achieved between 1988 and 1994 when Nugent and RajanBabu discovered that titanocene(III) complexes are useful stoichiometric reagents for the reductive opening of epoxides with or without deoxygenation.[98] Obviously the reduced redox potential of the titanium(III) reagent compared to samarium diiodide combined with the higher steric demand of the cyclopentadienyl ligands can, if desired, prevent trapping of the β-metaloxy radicals with the titanium reagent under properly chosen conditions. The usual reactivity of carbon-centered radicals toward radical traps can be exploited in synthetically useful reactions. Therefore, the cyclopentadienyl ligands of titanium determine the chemoselectivity of the reaction by tuning the redox properties and the steric demand of the metal complex. Reagent control is also excercised in the formation of the higher substitued radical, i.e., regioselectivity of epoxide opening. It seems that after complexation of the epoxide by the titanocene(III) reagent, the resulting adduct, presumably the radical anion of the epoxide bound to a titanocene(IV) species,[97] avoids substantial unfavorable steric interactions between the metal complex and the bulky substituent on the epoxide in opening the epoxide. Thus, the higher substituted β-titanoxy radical is formed. This selectivity is complemetary to the above-mentioned Bartmann opening with aromatic radical anions, although one can also imagine a reversible epoxide opening with the titanocene(III) reagent leading to the more stable radical (Figure 5). This typical Curtin−Hammet scenario[99] seems unlikely.

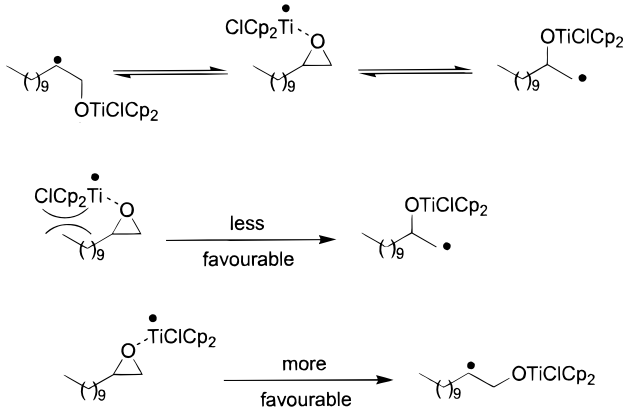


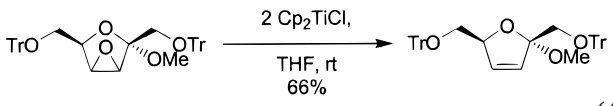
Figure 5. Possible mechanisms of titanocene-initiated epoxide opening.

If an equilibrium existed, the ratio of the products formed should depend on the radical trap employed. This is, however, not the case. *tert*-Butyl acrylate, acrylonitrile, and 1,4-cyclohexadiene give the same ratio of products derived from decene oxide.[98] Thus, it seems that the regioselectivity of epoxide opening is determined by the interaction of the metal's ligand sphere with the substrate, the typical scenario of reagent control.

Epoxides can be readily deoxygenated in the presence of low-valent titanocene reagents under extremly mild conditions. Schobert,[100] and independently Nugent and RajanBabu[98] provided convincing evidence that β-metaloxyradicals are indeed intermediates in these reactions. Both *cis*- and *trans*-5,6-epoxy decane yield the same 27:73 mixture of (*E*)- and (*Z*)-5-decene as products.[98] Both deoxygenations are thought to proceed via the same long-lived β-titanoxy radical that can rotate freely around the adjacent carbon−carbon bond to yield the same

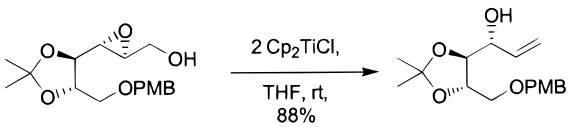
mixture of β-metal metaloxy species. After elimination, both (*E*)- and (*Z*)-5-decenes are obtained.

This very mild deoxygenation procedure[98] has been used in the synthesis of a number of highly acid sensitive products (eq 41) that are not readily accessible via different methods.



(41)

The method is especially useful in the synthesis of deoxy sugar derivatives since the corresponding epoxides are readily accessible. An elegant application of the deoxygenation reaction is the synthesis of enantiomerically pure allylic alcohols from "Sharpless epoxides" as demonstrated in eq 42.[101] It should be noted that the disadvantage of the loss of one-half the allylic alcohol as in the kinetic resolutions of allylic alcohols is not a problem when this protocol is employed.



(42)

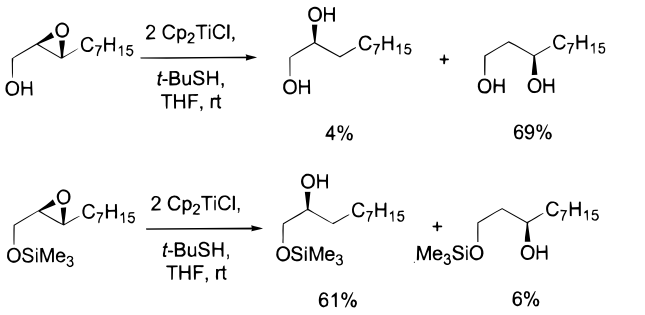
PMB = *p*-MeOC$_6$H$_4$CH$_2$

Considering these results, it is obvious that titanocene(III) chloride is a superior reagent compared to samarium diiodide in terms of chemoselectivty and yields for the deoxygenation of epoxides.

An interesting and preparatively important extension of the deoxygenation emphasizing the radical character of the pivotal intermediates is the reduction of the β-metaloxy radical with hydrogen-atom donors, e.g., 1,4-cyclohexadiene or *tert*-butyl thiol.[99] This useful transformation has a number of attractive features. Epoxides are opened with high regioselectivity opposite to that of S_N2 reactions to yield the corresponding alcohols. It is highly chemoselective, e.g., ketones, tosylates, and halides are not reduced and it is applicable in the synthesis of complex and sensitive molecules. The use of properly functionalized "Sharpless epoxides"[96] as substrates allows for an efficient synthesis of 1,2- and 1,3-diols. Tuning of the alcohol's protecting group allows the choice between a chelating and nonchelating binding mode of the epoxide by the titanium reagent. In this manner, it is possible to open the epoxide and obtain either the 1,2- or 1,3-diol with a high level of regioselectivity (eq 43).

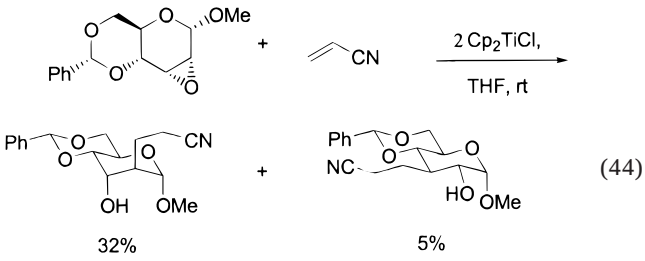
As in the deoxygenation reactions, the synthesis of sensitive molecules has been demonstrated. Deoxysugars are an interesting class of compounds readily accessible by this methodology.

Efficient C−C bond forming reactions being even more important than the formation of C−H bonds become available too. The first class of these reactions to be discussed here are the intermolecular additions to α,β-unsaturated carbonyl compounds.[98] After reductive epoxide opening, the resulting radical readily adds to esters of acrylic and methacrylic acid. The



(43)

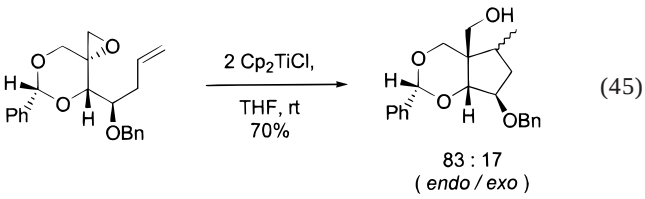
resulting compounds, δ-hydroxyesters, can be lactonized, thus allowing a convenient entry to the synthesis of δ-lactones from epoxides in a single step. Yields are usually high. The corresponding esters can be readily obtained by using *tert*-butyl acrylate. Unfortunately β-substitution of the ester is not tolerated. Diastereoselectivities in carbohydrate systems are the same as those in related systems using free radical methodology (eq 44).



(44)

Using "Sharpless epoxides" as substrates, derivates of 1,3-diols incorporating the additional ester group are readily obtained. This intriguing approach to hydroxyesters and lactones still offers synthetic potential. Acrylonitrile and methacrylnitrile are also useful radical traps in these reactions. The corresponding hydroxynitriles are valuable intermediates in organic synthesis.

Arguably one of the synthetically most important applications of radicals is the 5-exo-cyclization reaction.[102,103] Suitably unsaturated epoxides are good substrates for titanocene(III)-initiated cyclization reactions as shown in eq 45.

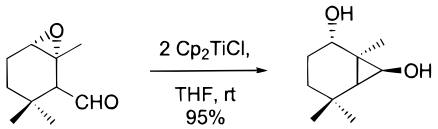


(45)

The desired products are obtained in good to high yields, and diastereoselectivities are in the usual range for radical cyclizations.[104] Optically pure carbocyclic compounds can thus be readily obtained from carbohydrates. The resulting densely functionalized products are important intermediates for organic synthesis. In similar carbohydrate systems of free radicals studied by Giese, comparable results were obtained.[105]

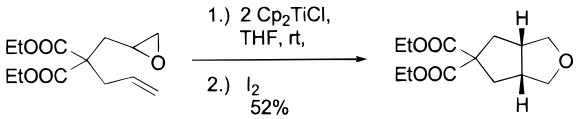
Recently, the scope of the cyclization reactions was further increased by Fernández-Mateos through in-

tramolecular additions to aldehydes and ketones.[106] In the example shown in eq 46, a rare example of a highly efficient 3-exo-cyclization has been realized.



(46)

An intriguing aspect of titanocene- mediated reactions is the reductive trapping of the radical formed after the cyclization step by a second equivalent of the titanium(III) reagent. This is clearly advantageous compared to free radical cyclization reactions conducted in the presence of stannanes and silanes. In these latter cases, no further functionalization of the cyclization product can be achieved in situ. In the titanocene-initiated reductions, tandem reactions are readily possible. The nucleophilic titanium species obtained after reductive termination can be reacted with electrophiles other than protons, e.g., iodine, to yield iodoalcohols. These compounds can be readily transformed to other useful products, e.g., tetrahydrofuran derivatives (eq 47).



(47)

In principle, this approach combines the advantages of radical chemistry, e.g., high functional group tolerance, mildness of the reaction conditions, with the advantages of organometallic chemistry, e.g., determining the course of reactions by ligand variations. Unfortunately the applicability of these reactions is somewhat limited for practical use by the need to employ at least 2 equiv of titanocene dichloride. This is especially disadvantageous for complexes that have to be synthesized in a number of steps[107] and cannot be recycled.

B. Titanocene-Catalyzed Epoxide Openings

As outlined above and in the section on stoichiometric pinacol couplings, the main obstacle in investigating the influence of ligands different from simple cyclopentadienyl on the selectivities is the stoichiometric use of the titanocene complex. However, the improvement of reagent control in the regioselectivity of the opening of monosubstituted epoxides, the control of diastereoselectivity of cyclization reactions, and the enantioselective opening of *meso*-epoxides are synthetically important goals. Clearly a catalytic reaction would be suited to circumvent the limitation of using stoichiometric amounts of titanocene complexes to achieve reagent control. Of course, the aim must be to develop a catalytic system preserving the advantages of the stoichiometric reagent.

The planned catalytic cycle for the reductive opening in the presence of 1,4-cyclohexadiene as hydrogen-atom donor is outlined in Figure 6.[108]

As in the titanocene-catalyzed protic pinacol coupling, the resulting titanocene alkoxide has to be cleaved to yield titanocene dichloride and to liberate

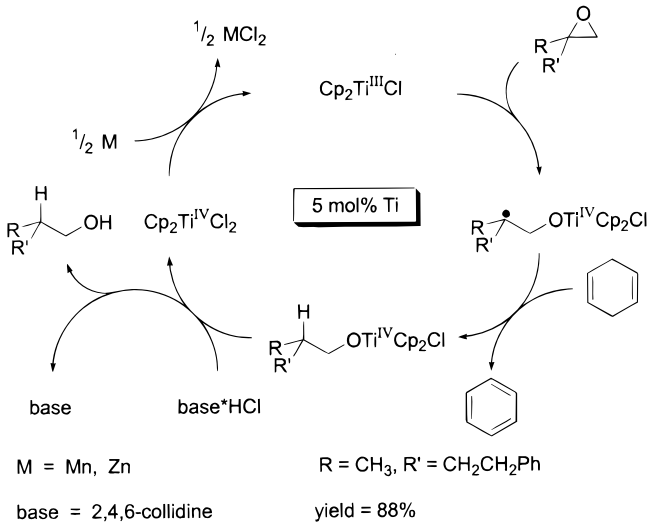


Figure 6. Titanocene-catalyzed reductive epoxide opening.

the product of the reaction, the alcohol. It is crucial for the success of the catalytic reaction that the epoxide is not opened via S_N2 or S_N1 under the reaction conditions either by the employed acid or the metal salt MCl_2 formed during reduction of Cp_2TiCl_2. As in the catalytic pinacol coupling, the base generated during protonation should not deactivate any titanium species by coordination and product inhibition must be avoided. Pyridine hydrochloride is known to open epoxides to the corresponding chlorohydrines as a mild protic acid in chloroform.[109] Thus, an acid with a higher pK_a in water than pyridine hydrochloride should be chosen. As outlined in section III.B.2, the acid should also be at least as strong as triethylamine hydrochloride in order to be able to quantitatively protonate alkoxides. 2,4,6-Collidine hydrochloride was a very useful acid to protonate titanocene alkoxides in combination with manganese as reductant as in the protic catalytic pinacol coupling. No significant amounts of byproducts could be detected in the crude reaction mixture. Zinc performed distinctly inferior as a stoichiometric reductant. Presumably the zinc chloride formed during reduction of the titanocene dichloride complexed the epoxide and liberated chlorohydrines via an S_N1 reaction. The catalytic system showed the same regioselectivity as the stoichiometric system. It should be noted, however, that in the case of 1-dodecene oxide this selectivity is somewhat higher in the catalytic transformation (94:6 vs 88:12). This could be due to the 1- and 2-dodecanol formed during the course of the reaction. According to the general reasoning described for the selectivity of epoxide opening, this should lead to increased regioselectivity of the reaction.

An important issue is the chemoselectivity of the catalytic epoxide opening. The stoichiometric reductive system has to be chosen carefully to ensure that electron transfer from the metal powder occurs exclusively to reduce titanocene dichloride. The high functional group tolerance of the stoichiometric reaction was preserved under the catalytic conditions. The mild acid 2,4,6-collidine hydrochloride is obviously not able to promote electron transfer from manganese to a variety of functional groups, e.g.,

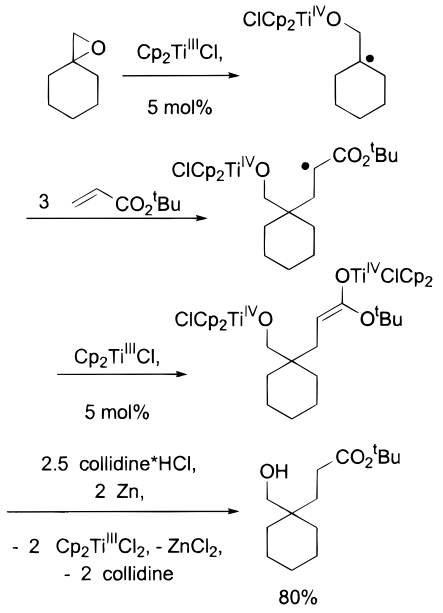


Figure 7. Titanocene-catalyzed intermolecular addition reactions.

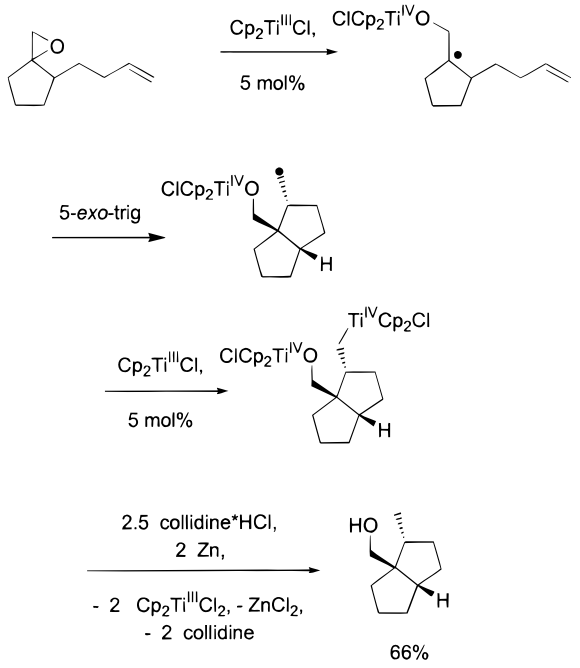


Figure 8. Titanocene-catalyzed cyclizations.

esters, nitriles, ketones, and even aliphatic aldehydes. Other easily reduced functional groups, e.g., bromides, chlorides, and tosylates, are also perfectly stable. Our stoichiometric reductive system is mild and could be useful in other catalytic radical reactions, also.

Preparatively more important than the catalytic reductive opening of epoxides are catalytic C−C bond forming reactions. Two important stoichiometric applications, cyclization reactions and intermolecular additions to α,β-unsaturated carbonyl compounds, have been reported to be successful using 2 equiv of titanocene by Nugent and RajanBabu.[98] We were successful in developing this methodology into a catalytic reaction. Intermolecular additions worked well under the conditions outlined in Figure 7.

The reaction exploits the stability of radicals and the instability of titanocene alkoxides and enolates under protic conditions. Once the enolate is formed, protonation liberates the reaction product with formation of titanocene dichloride. In situ reduction regenerates the redox-active titanocene(III) complex. The catalytic cycle is closed. Since the radicals formed after the intermolecular addition step can be trapped by the titanium(III) reagent or the stoichiometric reductant without concomitant elimination of titanium oxo species, no hydrogen donor, i.e., 1,4-cyclohexadiene, is necessary for the completion of the catalytic cycle. In intermolecular addition reactions, manganese as stoichiometric reductant was by no means ideal.[110] Conversions were low even after prolonged reaction times. This is in contrast to the reductive opening yielding simple alcohols. With the additional ester group present, the product can chelate the titanium catalyst and initiate product inhibition. This problem was solved simply by using zinc dust as the stoichiometric reductant or by adding zinc chloride to the reaction mixture. In this manner, the catalyst can be reactivated. The stronger Lewis acid zinc dichloride chelates the product and liberates the catalyst. The same effect, although less pronounced, could be achieved by addition of excess collidine. The stability of the intermediate radical under the reaction conditions is crucial for the success of the reaction. Under the optimized conditions, the reaction can be run with as little as 1 mol % of the catalyst.

For the use of titanocene complexes as catalysts in cyclization reactions, a similar concept lead to an efficient reaction.[111] (Figure 8)

As in the stoichiometric reaction, the radical formed after the cyclization step is trapped by a titanocene(III) reagent. To achieve catalytic turnover, both titanium−carbon and titanium−oxygen bonds have to be cleaved while the reaction product and titanocene dichloride are liberated. Protonation constitutes an ideal means to achieve these goals. 2,4,6-Collidine hydrochloride represented a suitable acid in these reactions. The products can be isolated in good yields. Generally, diastereoselectivities were in the usual range for radical cyclizations. It should be noted that the diastereoselctivity in the formation of the [3.3.0] system is somewhat higher (98:2 vs 90: 10) than in the stoichiometric system. As in the reductive opening, this seems to be due to the presence of the product alcohol. Current investigations in our group are focusing on the influence of the cyclopentadienyl ligands on the diastereoselectivity of the cyclization reaction to establish reagent control more firmly in this exiting area of radical chemistry.

C. Catalytic Enantioselective Epoxide Openings

With the catalytic system described in the section above, the goal of enantioselective reagent-controlled radical reactions by variation of the cyclopentadienyl ligand was within reach. A good point to start with is the enantioselective opening of *meso*-epoxides via electron transfer. Many excellent examples of catalytic enantioselective openings of *meso*-epoxides by

S_N2 reactions have recently been reported.[112] However, the S_N2 reactions are conceptually different from the approach described here, because in S_N2 reactions the path of the incoming nucleophile has to be controlled. In the titanocene-catalyzed reaction, the intermediate radical has to be formed selectively. If an intermediate similar to the Bartmann opening is postulated here,[93,97] the selectivity determining interaction should be that of the epoxide radical anion with a titanocene(IV) complex as depicted in Figure 9.

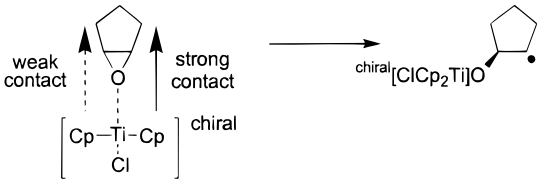
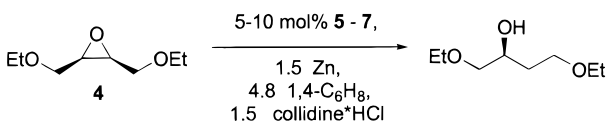


Figure 9. Plausible crucial intermediate in enantioselective epoxide openings.

According to the introductory remarks, reagent control is thus exercised in the radical forming step. Thus, two diastereomeric radicals are initially formed due to the chirality of the titanocene complex. The diastereoselectivity of the following reaction may also be controlled by the ligand sphere of titanium. After protic cleavage of the titanium−oxygen bond, enantiomeric products are formed. This mechanistic reasoning allowed for the rational design of the cyclopentadienyl ligands.[113] To achieve efficient differentiation in the steric interaction of the catalyst with the *meso*-epoxide, the ligand should be able to interact with the substrate in regions distant from the initial binding site, the epoxy group. Thus, efficient chirality transfer from the periphery of the titanocene complex to regions of the substrate distant from the binding site of the catalyst has to be achieved. Inspection of the extensive literature on titanocene and cyclopentadienyl complexes[107] suggested ligands from terpenes as suitable for achieving this purpose.[114] In *ansa*-metallocenes that have been used in enantioselective catalysis with great success recently,[115] the chirality is centered around the metal. Chirality transfer to the periphery of these complexes is not obvious in studies of molecular models and the crystalographic structures. Epoxide **4** was chosen as a test substrate as shown in eq 48 because it is readily accessible from (*Z*)-butene diol in two steps and the absolute stereochemistry of the opening product can be established by synthesis of authentic samples from malic acid.



(48)

The results of the investigation of a number of titanocene complexes shown in Figure 10 are summarized in Table 1.

Brintzinger's complex **2** shown in Figure 3 performed poorly concerning the enantioselectivity (56% ee) of the epoxide opening and the yield of product

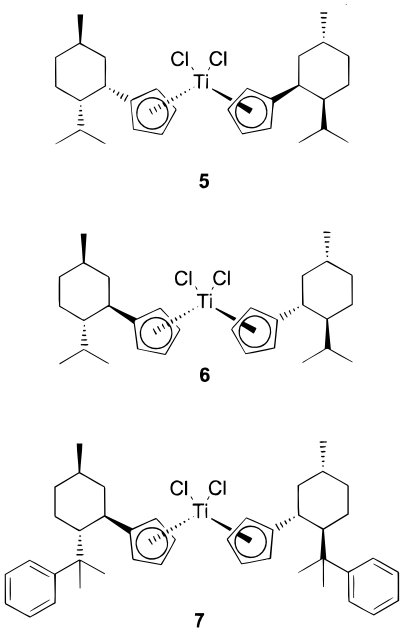


Figure 10. Titanocenes utilzed in enantioselective opening of *meso*-epoxides.

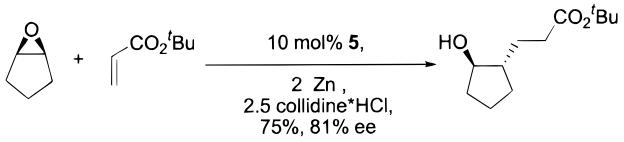
Table 1. Reductive Opening of Epoxide 3 with Various Titanocene Complexes

cat, mol % cat	yield [%]	(*R*):(*S*)
5, 10	51	76:24
6, 10	74	3:97
7, 5	65	3.5:96.5

(55%) in the presence of 10 mol % catalyst. The titanocene complex[114] **5** obtained from (1*R*,2*S*,5*R*) menthol via tosylation, S_N2 reaction with sodium cyclopentadienide, and metalation performed somewhat better, although the axially positioned cyclopentadienyl group is not ideal.

A satisfactory result was obtained with the ligand from *neo*-menthol **6** containing an equatorial cyclopentadienyl ligand.[116] The enantioselectivty of the opening reached synthetically useful levels (97:3), and the isolated yields were reasonable. Complex **7** with a ligand derived from phenyl menthone,[117] performed well giving an enantioselectivity of 96.5:3.5. Phenyl menthol[118] has already been extensively and successfully used as chiral auxiliary.[119] These results suggest that both **6** and **7**, after being reduced to the redox-active species, contain a chiral pocket well-suited for the steric differentiation of the enantiotopic groups of *meso*-epoxide **4**. The corresponding bis-*tert*-butyl ether epoxide constituted a more difficult example due to the increased steric demand of the bulky groups. Both catalysts performed distinctly worse. With **6**, an enantioselectivity of 92.5:7.5 was obtained, whereas **7** gave the lower value of 87.5:12.5.

An interesting and demanding problem is the opening of cyclic *meso*-epoxides, e.g., cyclopentene oxide, and trapping of the resulting radical with an acrylate, e.g., *tert*-butyl acrylate. Besides the enantioselectivity of epoxide opening, the diastereoselectivity of the C−C bond forming step has to be controlled.[120] Complex **6** was the most selective catalyst, giving higher enantioselectivity (81% ee) while preserving high diastereoselectivity (eq 49).



(49)

Titanocene catalyst **7** gave a lower enantioselectivity (86.5:13.5) with cyclopentene oxide as substrate. It should be noted that the diastereoselectivity of the addition reaction to *tert*-butyl acrylate (>97.5:<2.5) was substantially higher using **5**, **6**, and **7** than with Cp_2TiCl_2 as catalyst (86:14). Thus, the ligands derived from *neo*-menthol performed better than those derived from *neo*-phenyl menthol in all cases investigated. As for the opening of **4**, the Brintzinger complex **2** was not an efficient catalyst for the opening of cyclopentene oxide. Both chemical yield (24%) and enantioselectivity were low (29% ee). The diastereoselectivity of the addition to *tert*-butyl acrylate was rather low for this system (trans:cis = 90:10). The opening of cyclohexene and cycloheptene oxide with **7** as catalyst proceeded with somewhat higher enantioselectivity (91:9 in both cases). Diastereoselectivity of the addition reaction was lower than with cyclopentene oxide (81:19 for the cyclohexene oxide and 87:13 for cycloheptene oxide). In both cases this constituted an improvement compared to Cp_2TiCl_2 as catalyst (about 60:40 and 70:30, respectively). Thus, we have demonstrated that reagent control in the reductive opening of *meso*-epoxides can be exercised both at the stage of radical generation and at the subsequent transformations of the formed radicals. Although some of the initial results are promising, further investigations have to establish if reagent control in these reactions can be improved further to reach practically useful levels of stereoselection and catalytic activity in other simple cases and in natural product synthesis.

VI. Acknowledgment

We are indebted to our co-workers mentioned in the references for their creative and determined participation in the projects. A.G. thanks the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft for stipends and financial support of our work. The BASF AG is acknowledged for the generous gift of chemicals. Last but certainly not least, we thank Professor Brückner for his constant interest and support of our efforts during the last four years.

VII. References

(1) Gomberg, M. *Chem. Ber.* **1900**, *33*, 3150.
(2) (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon Press: Oxford, 1986. (b) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996. (c) Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; Wiley: New York, 1995. (d) Linker, T.; Schmittel, M. *Radikale und Radikalionen in der Organischen Synthese*; Wiley-VCH: Weinheim, 1998.
(3) (a) Giese, B. *Angew. Chem.* **1983**, *95*, 771; *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753. (b) Giese, B. *Angew. Chem.* **1985**, *97*, 555; *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 553. (c) Giese, B.; Dupuis, J. *Angew. Chem.* **1983**, *95*, 633; *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 622. (d) Dupuis, J.; Giese, B.; Rüegge, D.; Fischer, H.; Korth, H.-G.; Sustmann, R. *Angew. Chem.* **1984**, *96*, 887; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 896.
(4) For some leading references, see: (a) Bazukis, P.; Campos, O. O. S.; Bazukis, M. L. F. *J. Org. Chem.* **1976**, *41*, 3261. (b) Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448. (c) Curran, D. P.; Chen, M.-H. *Tetrahedron Lett.* **1985**, *26*, 4991. (d) Danishefsky, S. L.; Panek, J. S. *J. Am. Chem. Soc.* **1987**, *109*, 917. (e) Chen, Y.-J.; Lin, W.-Y. *Tetrahedron Lett.* **1992**, *33*, 1749.
(5) For a comprehensive account, see: Brocks, J. J.; Beckhaus, H.-D.; Beckwith, A. L. J.; Rüchardt, C. *J. Org. Chem.* **1998**, *63*, 1935 and references therein.
(6) See, for example: Francisco, S. J.; Montgomery, J. A., Jr. In *Energetics of Organic Free Radicals*; Simoes, J. A. M., Greenberg, A., Liebmann, J. F., Eds.; Blackie Academic & Professional: London, 1996.
(7) (a) Ojima, I. *Catalytic Asymmetric Synthesis*; VCH: Weinheim, 1993. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.
(8) Gansäuer, A. *Synlett* **1998**, 801.
(9) (a) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. (b) Smadja, W. *Synlett* **1994**, 1.
(10) For a review and recent examples, see: (a) Pattenden, G. *Chem. Soc. Rev.* **1988**, *17*, 361. (b) Busato, S.; Scheffold, R. *Helv. Chim. Acta* **1994**, *77*, 92. (c) Zhou, D. L.; Walder, P. Scheffold, R.; Walder, L. *Helv. Chim. Acta* **1992**, *75*, 995.
(11) For some recent work, see: (a) Branchaud, B. P.; Slade, R. M. *Tetrahedron Lett.* **1994**, *35*, 4071. (b) Slade, R. M.; Branchaud, B. P. *J. Org. Chem.* **1998**, *63*, 3544.
(12) For some recent references, see: (a) Ando, T.; Kamigaito, M.; Sawamoto, M. *Tetrahedron* **1997**, *53*, 15445. (b) Percec, V.; Barboiu, B.; Kim, H.-J. *J. Am. Chem. Soc.* **1998**, *120*, 305. (c) Simal, F.; Demonceau, A.; Noels, A. F. *Angew. Chem.* **1999**, *111*, 559; *Angew. Chem., Int. Ed.* **1999**, *38*, 538.
(13) (a) Andrus, M. B.; Argade, A. B.; Chen, X.; Pamment, M. G. *Tetrahedron Lett.* **1995**, *36*, 2945. (b) Andrus, M. B.; Asgari, D.; Scafani, J. A. *J. Org. Chem.* **1997**, *62*, 9365. (c) Kasuki T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, p 791.
(14) (a) Kaufman, M. D.; Grieco, P. A.; Bougie, D. W. *J. Am. Chem. Soc.* **1993**, *115*, 11648. (b) Breslow, R.; Zhang, X. J.; Huang, Y. *J. Am. Chem. Soc.* **1997**, *119*, 4535. (c) Meunier, B. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Vol. 2, p 173.
(15) For two examples, see: (a) Schultz, P. G.; Taylor, J. S.; Dervan, P. B. *J. Am. Chem. Soc.* **1982**, *104*, 6861. (b) Schultz, P. G.; Dervan, P. B. *J. Am. Chem. Soc.* **1983**, *105*, 7748.
(16) (a) Stubbe, J.; Kozarich, J. W. *Chem. Rev.* **1987**, *87*, 1107. (b) Claussen, C. A.; Long, E. C. *Chem Rev.* **1999**, *99*, 2797.
(17) (a) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (b) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. (c) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321.
(18) Renaud, P.; Gerster, M. *Angew. Chem.* **1998**, *110*, 2704; *Angew. Chem., Int. Ed.* **1998**, *37*, 2562.
(19) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163.
(20) Schumann, H.; Pachaly, B.; Schütze, B. C. *J. Organomet. Chem.* **1984**, *265*, 145.
(21) Nanni, D.; Curran, D. P. *Tetrahedron: Asymmetry* **1996**, *7*, 2417.
(22) (a) Blumenstein, M.; Schwartzkopf, K.; Metzger, J. *Angew. Chem.* **1997**, *109*, 245; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 235. (b) Schwartzkopf, K.; Blumenstein, M. Hayen, A.; Metzger, J. *Eur. J. Org. Chem.* **1998**, 177.
(23) Dakternieks, D.; Dunn, K.; Perchyonok, V. T.; Schiesser, C. H. *J. Chem. Soc., Chem. Commun.* **1999**, 1665.
(24) (a) Wu, J. H.; Radinov, R.; Porter, N. A. *J. Am. Chem. Soc.* **1995**, *117*, 11029. (b) Wu, J. H. Zhang, G.; Porter, N. A. *Tetrahedron Lett.* **1997**, *38*, 2067. (c) Porter, N. A.; Wu, J. H.; Zhang, G.; Reed, A. D. *J. Org. Chem.* **1997**, *62*, 6702. (d) Sibi, M. P.; Ji, J.; Wu, J. H.; Gürtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200. (e) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1997**, *62*, 3800.
(25) (a) Robertson, G. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, p 563. (b) Wirth, T. *Angew. Chem.* **1996**, *108*, 65; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 61.
(26) (a) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1991**, *56*, 4112. (b) Molander, G. A. Harris, C. R. *J. Org. Chem.* **1997**, *62*, 2944.
(27) (a) Kameyama, M.; Kamigata, N.; Kobayashi, M. *J. Org. Chem.* **1987**, *52*, 3312. (b) Kameyama, M.; Kamigata, N. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 648.
(28) Fittig, R. *Liebigs Ann.* **1859**, *110*, 23.
(29) (a) McMurry, J. E.; Rico, J. G.; Shih, Y. N. *Tetrahedron Lett.* **1989**, *30*, 1173. (b) McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 6942. (c) Nicolaou, K. C.; Yang, Z.; Sorensen, E. J.; Nakada, M. *J. Chem. Soc., Chem. Commun.* **1993**, 1024. (d) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630.
(30) For some early work and a recent review on the chemistry of low-valent titanium species, see: (a) Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041. (b) McMurry, J. E.; Fleming,

M. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708. (c) Fürstner, A.; Bogdanovic, B. *Angew. Chem.* **1996**, *108*, 2582; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2442.
(31) Raubenheimer, H. G.; Seebach, D. *Chimia* **1986**, *40*, 12.
(32) Clerici, A.; Clerici, L.; Porta, O. *Tetrahedron Lett.* **1996**, *37*, 3035.
(33) Handa, Y.; Inanaga, J. *Tetrahedron Lett.* **1987**, *28*, 5717.
(34) (a) Green, M. L. H.; Lucas, C. R. *J. Chem. Soc., Dalton Trans.* **1972**, 1000. (b) Coutts, R. S. P.; Wailes, P. C.; Martin, R. L. *J. Organomet. Chem.* **1973**, *47*, 375. (c) Sekutowski, D.; Jungst, R.; Stucky, G. D. *Inorg. Chem.* **1978**, *17*, 1848. (d) Stephan, D. W. *Organometallics* **1992**, *11*, 996.
(35) Barden, M. C.; Schwartz, J. *J. Am. Chem. Soc.* **1996**, *118*, 5484.
(36) Mukaiyama, T.; Kagayama, A.; Shiina, I. *Chem. Lett.* **1998**, 1107.
(37) Matsubara, S.; Hashimoto, Y.; Okano, T.; Utimoto, K. *Synlett* **1999**, 1411.
(38) (a) Pedersen, H. L.; Christensen, T. B.; Enemærke, R. J.; Daasbjerg, K.; Skrydstrup, T. *Eur. J. Org. Chem.* **1999**, 565. (b) Christensen, T. B.; Riber, D.; Daasbjerg, K.; Skrydstrup, T. *J. Chem. Soc., Chem. Commun.* **1999**, 2051.
(39) (a) Chiara, J. L.; Cabri, W.; Hanessian, S. *Tetrahedron Lett.* **1991**, *32*, 1125. (b) Uenishi, J.; Masuda, S.; Wakabayashi, S. *Tetrahedron Lett.* **1991**, *32*, 5097. (c) Kan, T.; Hosokawa, S.; Nara, S.; Oikawa, M.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 5532.
(40) Cotton, F. A.; Duraj, S. A.; Roth, W. J. *Inorg. Chem.* **1985**, *24*, 913.
(41) (a) Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 8014. (b) Konradi, A. W.; Kemp, S. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1994**, *116*, 1316.
(42) (a) Konradi, A. W.; Pedersen, S. F. *J. Org. Chem.* **1992**, *57*, 28. (b) Reetz, M. T.; Griebenow, N. *Liebigs Ann.* **1996**, 335. (c) Kammermeier, B.; Beck, G.; Holla, W.; Jacobi, D.; Napierski, B.; Jendralla, H. *Chem. Eur. J.* **1996**, *2*, 307.
(43) Reetz, M. T. *Angew. Chem.* **1984**, *96*, 542; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.
(44) Manzer, L. E. *Inorg. Chem.* **1977**, *16*, 525.
(45) (a) Roskamp, E. J.; Pederson, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 3152. (b) Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 6551.
(46) Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468.
(47) (a) Hirao, T.; Hasegawa, T.; Muguruma, Y., Ikeda, I. *J. Org. Chem.* **1996**, *61*, 366. (b) Hirao, T. *Synlett* **1999**, 175.
(48) Fürstner, A. *Chem. Eur. J.* **1998**, *4*, 567.
(49) (a) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2533. (b) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349. (c) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991.
(50) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *Angew. Chem.* **1999**, *111*, 3558; *Angew. Chem., Int. Ed.* **1999**, *38*, 3357.
(51) (a) Maury, O.; Villiers, C.; Ephritikhine, M. *New J. Chem.* **1997**, *21*, 137. (b) Villiers, C.; Ephritikhine, M. *Angew. Chem.* **1997**, *109*, 2477; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2380.
(52) Ephritikhine, M. *J. Chem. Soc., Chem. Commun.* **1998**, 2549.
(53) Nomura, R.; Matsuno, Endo, T. *J. Am. Chem. Soc.* **1996**, *118*, 11666.
(54) (a) Gansäuer, A. *J. Chem. Soc., Chem. Commun.* **1997**, 457. (b) Gansäuer, A.; Moschioni, M.; Bauer, D. *Eur. J. Org. Chem.* **1998**, 1923.
(55) So, J.-H.; Park, M. K.; Boudjok, P. *J. Org. Chem.* **1988**, *53*, 5871.
(56) Dunlap, M. S.; Nicholas, K. M. *Synth. Commun.* **1999**, *27*, 1097.
(57) (a) Wild, F. R. W. P.; Zsolnai, L.; Huttner, G.; Brintzinger, H. H. *J. Organomet. Chem.* **1982**, *232*, 233. (b) Collins, S.; Kuntz, B. A.; Taylor, N. J.; Ward, D. G. *J. Organomet. Chem.* **1988**, *342*, 21. (c) Jaquith; J. B.; Guan, J.; Wang, S.; Collins, S. *Organometallics* **1995**, *14*, 1079.
(58) Gansäuer, A. *Synlett* **1997**, 363.
(59) Gansäuer, A.; Moschioni, M. Unpublished results.
(60) Hirao, T.; Hatano, B.; Asahara, M.; Muguruma, Y.; Ogawa, A. *Tetrahedron Lett.* **1998**, *39*, 5247.
(61) Svatos, A.; Boland, W. *Synlett* **1998**, 549.
(62) Lipski, T. A.; Hilfiker, M. A.; Nelson, S. G. *J. Org. Chem.* **1997**, *62*, 4566.
(63) Bandini, M.; Cozzi, P. G.; Morganti, S.; Umani-Ronchi, A. *Tetrahedron Lett.* **1999**, *40*, 1997.
(64) Yamamoto, Y.; Hattori, R.; Itoh, K. *J. Chem. Soc., Chem. Commun.* **1999**, 825.
(65) (a) Hirao, T.; Asahara, M.; Muguruma, Y.; Ogawa, A. *J. Org. Chem.* **1998**, *63*, 2812. (b) Hirao, T.; Hatano, B.; Imamoto, Y.; Ogawa, A. *J. Org. Chem.* **1999**, *64*, 7665.
(66) Hatano, B.; Ogawa, A.; Hirao, T. *J. Org. Chem.* **1998**, *63*, 9421.
(67) For some recent references, see: (a) Li, C.-J. *Tetrahedron* **1996**, *52*, 5643. (b) Li, C.-J.; Chan, T. J. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997. (c) Li, C.-J.; Zhang, W.-C. *J. Am. Chem. Soc.* **1998**, *120*, 9102. (d) Zhang, W.-C.; Li, C.-J. *J. Org. Chem.* **1999**, *64*, 3230.
(68) *Handbook of Chemistry and Physics*, 78th ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, FL, 1997; pp **8**-45−**8**-55.
(69) (a) Gansäuer, A.; Bauer, D. *J. Org. Chem.* **1998**, *63*, 2070. (b) Gansäuer, A.; Bauer, D. *Eur. J. Org. Chem.* **1998**, 2673.
(70) (a) Girard, P.; Namy, J.-L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693. (b) For the first preparation of SmI_2 in THF see: Namy, J.-L.; Girard, P.; Kagan, H. B. *New J. Chem.* **1977**, *1*, 5.
(71) For some reviews on SmI_2, see: (a) Kagan, H. B.; Namy, J.-L. *Tetrahedron* **1986**, *42*, 6573. (b) Kagan, H. B. *New. J. Chem.* **1990**, *14*, 453. (c) Soderquist, J. A. *Aldrichim. Acta* **1991**, *24*, 15. (d) Skrydstrup, T. *Angew. Chem.* **1997**, *109*, 355; *Angew. Chem., Int. Ed.* **1997**, *36*, 345. (e) Krief, A.; Laval, A.-M. *Chem Rev.* **1999**, *99*, 745.
(72) Fukuzawa, S.-I.; Nakanishi, A.; Fujinama, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1986**, 624. (b) Fukuzawa, S.-I.; Nakanishi, A.; Fujinami, T., Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1669. (c) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5763. (d) Inanaga, J.; Ujikawa, O.; Handa, Y.; Otsubo, K.; Yamaguchi, M. *J. Alloys Compd.* **1993**, *192*, 197.
(73) (a) Fukuzawa, S.-I.; Iida, M.; Nakanishi, A.; Fujinami, T.; Sakai, S. J. *J. Chem. Soc., Chem. Commun.* **1987**, 920. (b) Kagan, H. B.; Namy. J.-L. In *Lanthanides: Chemistry and Use in Organic Synthesis*; Kobayashi, S., Ed.; Springer: Berlin, 1999.
(74) Otsubo, K.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 1487.
(75) Lloyd, R. V.; Causey, J. G. *J. Chem. Soc., Perkin Trans. 2* **1981**, 1143. (b) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 1656.
(76) (a) Kawatsura, M.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 6900. (b) Matsuda, F.; Kawatsura, M.; Hosaka, K.; Shirahama, H. *Chem. Eur. J.* **1999**, *5*, 3252.
(77) Enholm, E. J.; Trivellas, A. *Tetrahedron Lett.* **1989**, *30*, 1063.
(78) Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236.
(79) Kito, M.; Sakai, T.; Yamada, K.; Matsuda, F.; Shirahama, H. *Synlett* **1993**, 158.
(80) Weinges, K.; Schmidbauer, S. B.; Schick, H. *Chem. Ber.* **1994**, *127*, 1305.
(81) (a) Hon, Y.-S.; Lu, L.; Chu, K.-P. *Synth. Commun.* **1991**, *21*, 1981. (b) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1994**, *59*, 3186.
(82) Fukuzawa, S.-I.; Seki, K.; Tasuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482.
(83) Molander, G. A.; McWilliams, J. C.; Noll, B. C. *J. Am. Chem. Soc.* **1997**, *119*, 1265.
(84) Mikami, K.; Yamaoka, M. *Tetrahedron Lett.* **1998**, *39*, 4501.
(85) Corey, E. J.; Zheng, G. Z. *Tetrahedron Lett.* **1997**, *38*, 2045.
(86) Molander, G. A.; Chad, C. N. *J. Org. Chem.* **1998**, *63*, 9031.
(87) (a) Sturino, C. F.; Fallis, A. G. *J. Org. Chem.* **1994**, *59*, 6514. (b) Sturino, C. F.; Fallis, A. G. *J. Am. Chem. Soc.* **1994**, *116*, 7447.
(88) (a) Marco-Contelles, J.; Gallego, P.; Rodríguez-Fernández; M.; Khiar, N.; Destabel, C.; Bernabé, M.; Martínez-Grau, A.; Chiara, J. L. *J. Org. Chem.* **1997**, *62*, 7397. (b) Miyabe, H.; Torieda, M.; Inoue, K.; Tajiri, K.; Kigushi, T.; Naito, T. *J. Org. Chem.* **1998**, *63*, 4397.
(89) (a) Yamamoto, Y.; Matsumi, D.; Itoh, K. *J. Chem. Soc., Chem. Commun.* **1998**, 875. (b) Yamamoto, Y.; Matsumi, D.; Hattori, R.; Itoh, K. *J. Org. Chem.* **1999**, *64*, 3224.
(90) (a) Birch, A. J. *J. Proc. R. Soc. N.S.W.* **1950**, *83*, 245. (b) Hallsworth, A. S.; Henbest, H. B. *J. Chem. Soc.* **1957**, 4604. (c) Hallsworth, A. S.; Henbest, H. B. *J. Chem. Soc.* **1960**, 3571. (d) Brown, H. C.; Ikegami, S.; Kawakami, J. H. *J. Org. Chem.* **1970**, *35*, 3243. (e) Benkeser, R. A.; Rappa, A.; Wolsieffer, L. A. *J. Org. Chem.* **1986**, *51*, 3391.
(91) Kochi, J. K.; Singleton, D. M.; Andrews, L. J. *Tetrahedron* **1968**, *24*, 3503.
(92) Matsukawa, M.; Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 2101.
(93) Bartmann, E. *Angew. Chem.* **1986**, *98*, 629; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 855.
(94) Cohen, T.; Jeong, I.-H.; Mudryk, B.; Bhupathy, M.; Awad, M. M. A. *J. Org. Chem.* **1990**, *55*, 1528.
(95) Bachki, A.; Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1907. (b) Bachki, A.; Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2997.
(96) Kasuki T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, p 621.
(97) Dorigo, A. E.; Houk, K. N.; Cohen, T. *J. Am. Chem. Soc.* **1989**, *111*, 8976.
(98) (a) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561. (b) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1989**, *111*, 4525. (c) RajanBabu, T. V.; Nugent, W. A.; Beattie, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6408. (d) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986.
(99) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.
(100) Schobert, R. *Angew. Chem.* **1988**, *100*, 869; *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 855.
(101) Yadav, J. S.; Shekharam, T.; Gadgil, V. R. *J. Chem. Soc., Chem. Commun.* **1990**, 843.
(102) Giese, B.; Kopping, B.; Göbel, T.; Thoma, G.; Dickhaut, J.; Kulicke, K. J.; Trach, F. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1996; Vol. 48, p 301.
(103) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(104) (a) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 482. (b) Beckwith, A. L. J.; Lawrence, T.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 484. (c) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545. (d) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959. (e) RajanBabu, T. V.; Fukunaga, T. *J. Am. Chem. Soc.* **1989**, *111*, 296. (f) RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139.

(105) Giese, B.; Dupuis, J.; Groninger, K.; Hasskerl, T.; Nix, M.; Witzel, T. In *Substituent Effects in Radical Chemistry*; Viehe, H. G., Ed.; D. Reidel Publishing Co.: Dordrecht, 1986; p 283.

(106) Fernández-Mateos, A.; Martin de la Nava, E.; Pascual Coca, G.; Ramos Silvo, A.; Rubio González, R. *Org. Lett.* **1999**, *1*, 607.

(107) (a) Halterman, R. L. *Chem. Rev.* **1992**, *92*, 965. (b) Halterman, R. L. In *Metallocenes*; Togni, A., Halterman, R. L., Eds.; Wiley-VCH: Weinheim; 1998; Vol. 1, p 455.

(108) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem.* **1998**, *110*, 107; *Angew. Chem., Int. Ed.* **1998**, *37*, 101.

(109) Loreto, M. A.; Pellacani, L.; Tardella, P. A. *Synth. Commun.* **1981**, *11*, 287.

(110) Gansäuer, A.; Bluhm, H. *J. Chem. Soc., Chem. Commun.* **1998**, 2143.

(111) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849.

(112) (a) Nugent, W. A. *J. Am. Chem. Soc.* **1992**, *114*, 2768. (b) Paterson, I.; Berrisford, D. J. *Angew. Chem.* **1992**, *104*, 1204; *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1179. (c) Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897. (d) Leighton, J. L.; Jacobsen, E. N. *J. Org. Chem.* **1996**, *61*, 389. (e) Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420. (f) Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924. (g) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *46*, 14361. (h) Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 4783. (i) Shimizu, K. D.; Cole, B. M.; Krueger, C. A.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Angewandte Chemie* **1997**, *109*, 1782; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1704. (j) Nugent, W. A. *J. Am. Chem. Soc.* **1998**, *120*, 7139. (k) Sagawa, S.; Abe, H.; Hase, Y.; Inaba, T. *J. Org. Chem.* **1999**, *64*, 4962. (l) Wu, M. H., Hansen, K. B.; Jacobsen, E. N. *Angew. Chem.* **1999**, *111*, 2167; *Angew. Chem., Int. Ed.* **1999**, *38*, 2012.

(113) (a) Gansäuer, A.; Lauterbach, T.; Bluhm, H.; Noltemeyer, M. *Angew. Chem.* **1999**, *111*, 3112; *Angew. Chem., Int. Ed.* **1999**, *38*, 2909. (b) Gansäuer, A.; Bluhm, H.; Pierobon, M. Manuscript in preparation.

(114) (a) Cesarotti, E.; Kagan, H. B.; Goddard, R.; Krüger, C. *J. Organomet. Chem.* **1978**, *162*, 297. (b) Gansäuer, A.; Bluhm, H. Manuscript in preparation.

(115) (a) Hoveyda, A. H.; Morken, J. P. *Angew. Chem.* **1996**, *108*, 1378; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1262. (b) Hoveyda, A. H.; Morken, J. P. In *Metallocenes*; Togni, A., Halterman, R. L., Eds.; Wiley-VCH: Weinheim; 1998; Vol. 2, p 625.

(116) Halterman, R. L.; Vollhardt, K. P. C. *Organometallics* **1988**, *7*, 883.

(117) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.

(118) Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953.

(119) (a) Giese, B.; Heuck, K.; Lenhardt, H.; Lüning, U. *Chem. Ber.* **1984**, *117*, 2132. (b) Giese, B. *Angew. Chem.* **1989**, *101*, 993; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969.

CR9902648