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Reductive C–C Bond Formation after Epoxide Opening via Electron Transfer

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Abstract This review presents a description of the C–C bond-forming reactions that have emerged in the field of titanocene mediated or catalyzed epoxide opening over the last 5 years or so. The powerful tandem sequences for polycyclization will be especially emphasized.

Keywords Catalysis · Cyclizations · Electron transfer · Radicals · Tandem reactions

Abbreviations

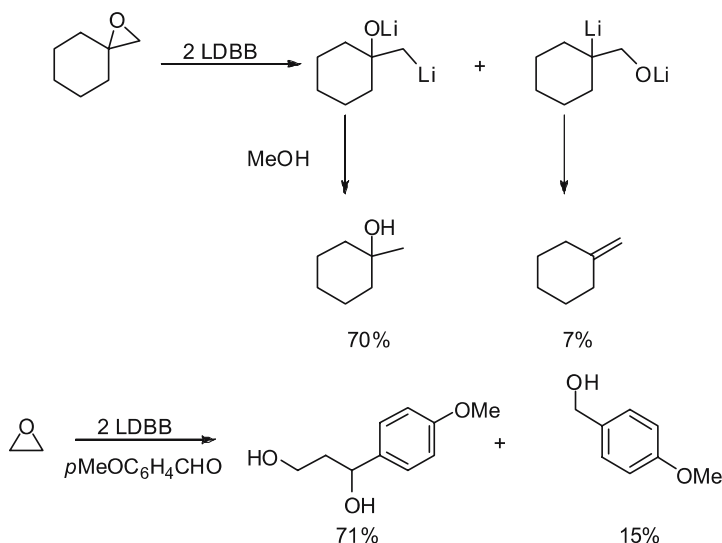
LDBB	lithium 4,4'-di- <i>tert</i> -butylbiphenylidene
THF	tetrahydrofuran
Tr	triphenylmethyl
TBS	<i>tert</i> -butyldimethyl silyl
PMB	<i>para</i> -methoxybenzyl
Coll	2,4,6-collidine (2,4,6-trimethylpyridine)
eq	equivalent(s)
ET	electron transfer
Ts	tosyl (<i>p</i> -CH ₃ C ₆ H ₄ SO ₂)
dr	diastereomeric ratio
RT	room temperature
MCPBA	<i>meta</i> -chloroperoxybenzoic acid
Py	pyridine
DMAP	4-dimethylaminopyridine
AIBN	Azo-bis-isobutyronitrile

1**Introduction**

Epoxides are amongst the most frequently employed substrates in organic synthesis. This is due to the ease of their preparation from readily available precursors, for example olefins and carbonyl compounds, and their high reactivity [1–4, 6]. The latter point arises from the strain inherent in the three-membered ring that is released during ring opening. Epoxides, especially when prepared in high enantiomeric excess, have been very useful in S_N2 reactions in this respect [7–9]. An alternative approach to exploiting the high reactivity of the strained epoxide is constituted by ring-opening reactions utilizing electron transfer reagents. In these reactions “Cp₂TiCl” has, to date, emerged as the most powerful reagent. Gratifyingly, the regioselectivity of ring opening is complementary to the S_N2-type reactions. After epoxide opening β -titanoxy radicals are obtained that can be used in many typical but also in quite unusual radical reactions. Moreover, many often highly functionalized products can be obtained in a straightforward manner. These developments will be reviewed in this article.

1.1**Epoxide Opening by Single Electron Transfer: Birch Conditions and Radical Anions**

Before turning to epoxide opening with low valent metal complexes, the reduction of epoxides under Birch conditions [10–13] will be discussed very briefly for historical reasons. The initially formed radical is reduced further to give carbanionic species, that do not display the reactivity of radicals. No C–C bond-forming reactions have initially been reported.



Scheme 1 Epoxide opening with arene radical anions under ET conditions

Bartmann [14], Cohen and Houk [15, 16] and Yus [17, 18] have employed aromatic radical anions as more convenient reducing agents to generate the same functionalized organolithium reagents. The typical electrophiles, such as aldehydes, and reactive alkylating agents were employed in C–C bond-forming reactions. Examples are shown in Scheme 1.

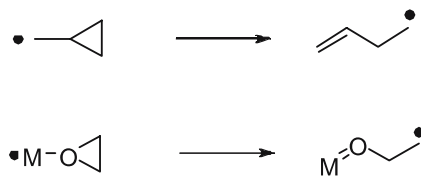
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Epoxide Opening by Low Valent Metal Complexes: General Considerations and Mechanism of Epoxide Opening

2.1

General Considerations

With respect to the utilization of epoxide-derived radicals for organic synthesis the use of low valent metal complexes is highly promising. In principle, the advantages of Lewis-acid catalysis [19] and radical chemistry [20–23] can be combined by this approach. This is achieved by activating the epoxide towards ET by complexation with the metal and at the same time controlling the regioselectivity of epoxide opening through the metal and its ligands. The much stronger epoxide activation necessary for S_N-type reactions can be avoided by fine-tuning the acidity of the metal center [24]. Perhaps even more importantly, the ensuing radical reactions can be controlled by the metal complex and its ligands.



Scheme 2 Opening of the cyclopropylcarbinyl radical and epoxide opening by low valent metal complexes

To the best of our knowledge the first successful realization of this concept was achieved by Kochi in 1968, who described the deoxygenation of epoxides with Cr(II) reagents. However, no further attempts were undertaken to form C – C bonds with the pivotal β -metaloxy radicals [25].

Nugent and RajanBabu introduced titanocene (III) chloride “Cp₂TiCl” as an excellent reagent for the reductive opening of epoxides in 1988. They were also the first to outline the analogy of epoxide opening through ET with the well-established opening of a cyclopropylcarbinyl radical [26–29] (Scheme 2). As yet, “Cp₂TiCl” and substituted titanocenes have remained the most powerful reagent for this type of reaction and have recently attracted considerable interest [30–35].

The structure of the reagent, the mechanism of epoxide opening, deoxygenations, dimerizations and intermolecular additions will be discussed first before covering the preparatively much more important cyclization reactions [36].

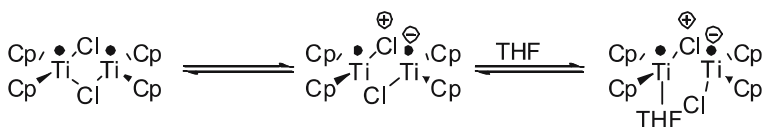
2.2

Structure of the Reagent and Mechanism of Epoxide Opening

Before entering the discussion of the synthetic results, a brief description of the structure of “Cp₂TiCl” and the mechanism of epoxide opening is given. These results serve as a guide for choosing a suitable catalyst for a given application.

Usually zinc or manganese reduced solutions of the respective titanocene dichlorides are used in the practical reactions. Daasbjerg and his group have demonstrated that in the case of Cp₂TiCl₂ this reduced solution contains mainly the chlorine-bridged dimer (Cp₂TiCl)₂ and a small amount of the monomer Cp₂TiCl. No bimetallic complexes are involved [37–41]. For the sake of simplicity we denote this mixture of compounds as “Cp₂TiCl”. Surprisingly the dimer, presumably in its half-open form, constitutes the more reactive species (Scheme 3) [42, 43].

Substitution of the Cp ligands reduces the tendency to dimerize. Introduction of a cyclohexyl group is sufficient for rendering the monomer the only detectable species by CV. The substituted titanocene chlorides open epoxides slower than “Cp₂TiCl”. However, the resulting β -metaloxy radicals are more



Scheme 3 Structure of “Cp₂TiCl” in solution

persistent. This can be advantageous for the use of substituted titanocenes in slow radical reactions [42, 43].

Epoxides are usually opened to give the higher substituted radicals, especially with substituted titanocenes. Chelation can be important when hydroxy groups are involved [26–29, 42, 43].

3

Formation of C–C Double Bonds by Epoxide Deoxygenation and Epoxide Dimerization

Olefins can be prepared by the deoxygenation of epoxides usually in good to excellent yields. However, the reaction is of synthetic use only if the epoxides employed as starting materials are prepared from other functional groups than olefins or if they can be isolated or readily accessed from natural sources. The issue of regioselectivity of deoxygenation is critical, however.

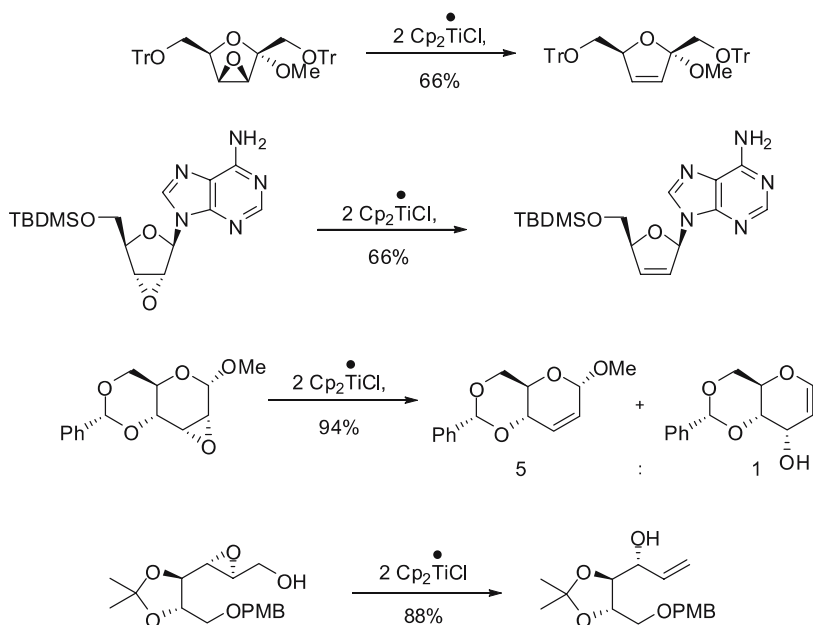
Nugent and RajanBabu described that with “Cp₂TiCl”, that had been isolated and purified prior to use, an (*E*) to (*Z*) ratio of 3–4 : 1 of 5-decenes was observed from either *cis*- or *trans*-5-decene oxide [28, 29]. Therefore, it seems clear that a common long-lived β-titanoxy radical intermediate was formed from both epoxides. After further reduction and elimination the formation of the mixture of olefin diastereoisomers was observed.

Examples for straightforward epoxide preparation from natural sources can be found in carbohydrate chemistry [28, 29]. Deoxygenations of such compounds are shown in Scheme 4.

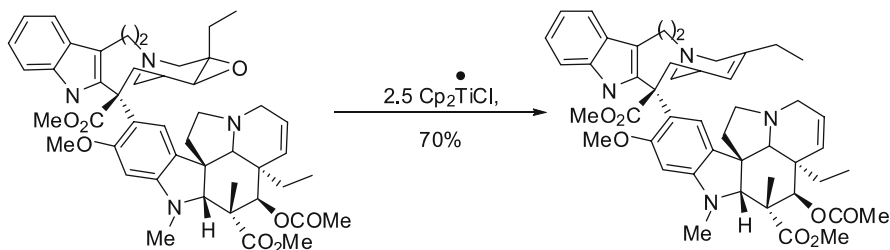
The first example amply demonstrates the exceptional chemoselectivity of the “Cp₂TiCl” reagent. The dihydrofuran product is already decomposed by traces of acid.

A limitation of epoxide deoxygenation with functionalized substrates became apparent in the second case where a mixture of olefins was isolated. Thus, the regioselectivity of epoxide opening and elimination of the titanium oxygen species was too low for practical use.

An effective deoxygenation using enantiomerically pure epoxides from primary allylic alcohols (“Sharpless epoxides”) [44] to give enantiomerically pure secondary allylic alcohols was described by Yadav [45]. This approach circumvented a kinetic resolution of secondary allylic alcohols that implies a maximum yield of 50% (Scheme 5).



Scheme 4 Epoxide deoxygenation reactions



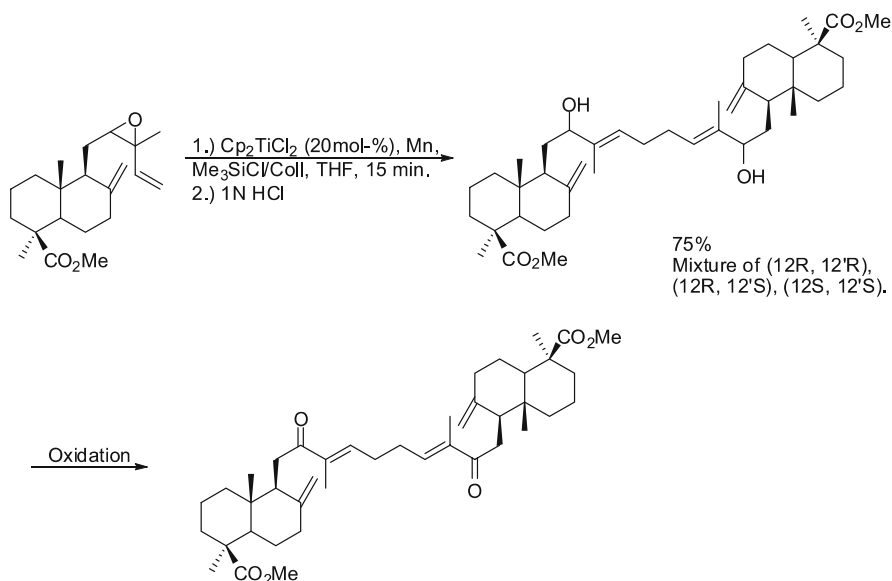
Scheme 5 Doris' deoxygenation en route to leurosine

Two deoxygenations of naturally occurring compounds have been reported. Anhydrovinblastine, an important intermediate for the anticancer drug navelbine, was prepared by Doris and coworkers from leurosine, an abundant alkaloid from the Madagascan periwinkle *Catharantus roseus*, in 70% yield by using Cp_2TiCl (Scheme 5) [46].

Stereospecific deoxygenations in the cryptophycin family of natural products from *Nostocaceae* were reported by Moore [47]. The products were important in the elucidation of the natural product's structure and for the preparation of novel cryptophycin derivatives.

Another interesting example of a reaction without additional organic radical trap has very recently been reported by Barrero and his group [48].

Vinylepoxides were used for the generation of β -titanoxy allylradicals. These species are too stable to be readily reduced by a second equivalent of “Cp₂TiCl” and can therefore dimerize to yield 1,5-dienes. While the diastereoselectivity is low in simple cases, the usefulness of the method is amply demonstrated by a very short and straightforward access to analogues of the natural onoceranes as shown in Scheme 6.



Scheme 6 Barrero's dimerization of vinylepoxides for the preparation of homoonocerans

4

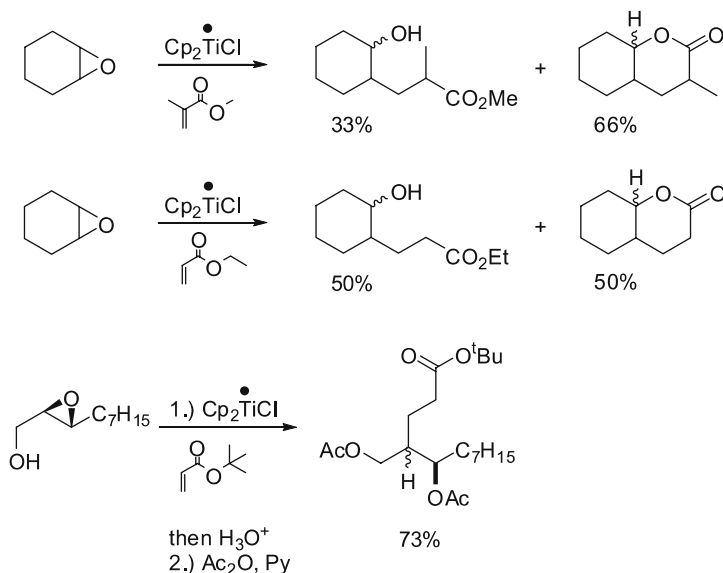
Formation of C–C Bonds by Intermolecular Addition

4.1

Stoichiometric Reactions

Epoxide-derived radicals are generated under very mild reaction conditions and are therefore valuable for intermolecular C–C bond-forming reactions [27, 29]. The resulting products, δ -hydroxyketones, δ -hydroxyesters or δ -lactones constitute important synthetic intermediates. The first examples were reported by Nugent and RajanBabu who used a variety of epoxides, such as cyclohexene oxide and a “Sharpless” epoxide (Scheme 7).

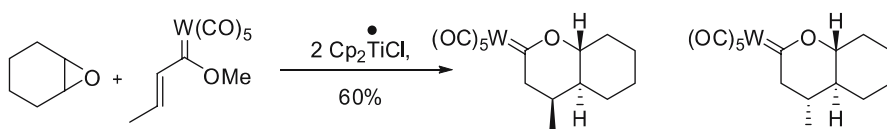
Similar examples of the latter reactions were also reported by Chakraborty [49]. Analogous transformations cannot be achieved with organometallic



Scheme 7 Stoichiometric intermolecular addition reactions

reagents, for example cuprates, because of competing β -elimination pathways.

The outstanding chemoselectivity of “ Cp_2TiCl ” was amply demonstrated by Merlic [50, 51] and by Dötz [52] who employed α , β -unsaturated tungsten and chromium carbenes as radical traps for C – C bond formation. In the latter contribution the very acid sensitive glycol epoxides were used with good success. An example is shown in Scheme 8.



Scheme 8 Addition reactions with tungsten carbenes

Little used organic acceptors for these reactions, also [53, 54]. The use of a glycol as the radical source together with a functionalized enone as the radical acceptor is remarkable. Enones are swiftly reduced by “ Cp_2TiCl ” [55] and thus epoxide activation must be considered as even more efficient. The product of the addition constitutes a valuable intermediate en route to derivatives of thrsiferiol.

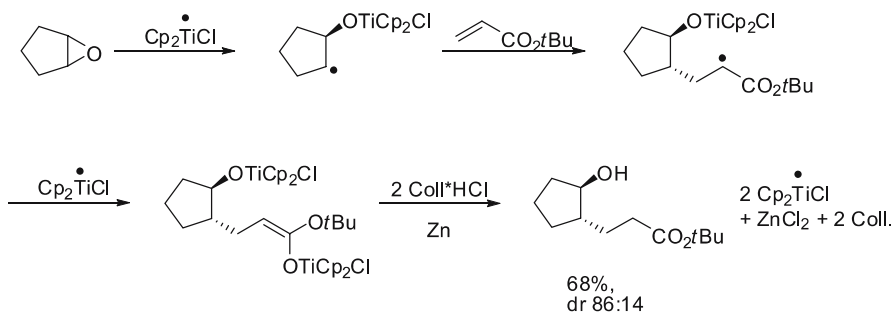
Malacria has reported the use of epoxysilanes for intermolecular addition reactions to acrylates, acrylonitrile and vinylsulfones [56].

4.2

Catalytic Reactions

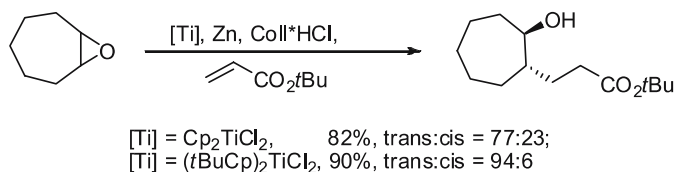
In stoichiometric applications of titanocene complexes, no attempt to use ligands other than unsubstituted cyclopentadienyl have been reported. The use of more complex titanocenes [57, 58] in catalytic reactions is, however, very promising for controlling the regio- and stereochemical course of the reaction.

Catalytic turn-over [59, 60] in McMurry couplings [61], Nozaki–Hiyama reactions [62, 63], and pinacol couplings [64, 65] has been reported by Fürstner and by Hirao by *in situ* silylation of titanium, chromium and vanadium oxo species with Me_3SiCl . In the epoxide-opening reactions, protonation can be employed for mediating catalytic turn-over instead of silylation because the intermediate radicals are stable toward protic conditions. The amount of “ Cp_2TiCl ” needed for achieving isolated yields similar to the stoichiometric process can be reduced to 1–10 mol % by using 2,4,6-collidine hydrochloride or 2,6-lutidine hydrochloride as the acid and Zn or Mn dust as the reductant (Scheme 9) [66, 67].



Scheme 9 Catalytic intermolecular addition (5 mol % [Ti])

These conditions were well suited for the preparation of δ -hydroxyesters, lactones, and δ -hydroxynitriles. Moreover, the usefulness of substituted titanocenes for enantio- and diastereoselective preparation of these products has been demonstrated as shown in Scheme 10 [68–72].



Scheme 10 Control of diastereoselectivity of the addition reaction

4.3

Polymerizations

Over the past decade there has been intense interest in living radical polymerizations. In these reactions molecular weight (M_n) and polydispersity (M_w/M_n) can be controlled by the reversible termination of the growing chains. Asandei and his group have demonstrated that the “ Cp_2TiCl ”-catalyzed epoxide opening can be successfully used in the initiation of a radical polymerization. The correlation between the epoxide and ligand structure in the initiation and catalysis of living radical polymerizations has been studied. Moreover, graft polymers can be readily accessed [73–76].

5

Cyclizations

The most frequently employed reactions in radical chemistry are cyclizations [36]. The preparation of 5-membered rings by 5-exo cyclizations has proven to be especially powerful. The kinetically disfavored 6-endo cyclizations and the significantly slower 6-exo cyclizations have attracted less attention, even though important applications have been reported.

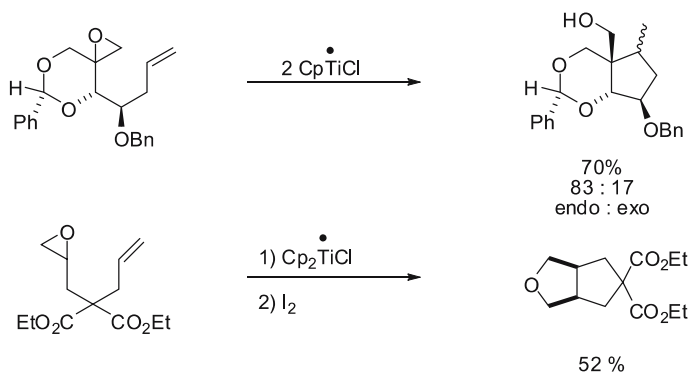
5.1

5-exo, 6-exo and 6-endo Cyclizations

5.1.1

Evolution of the Reaction and Initial Examples

In the case of titanocene mediated or catalyzed epoxide opening 5-exo cyclizations were also investigated first. Nugent and RajanBabu reported



Scheme 11 Stoichiometric cyclizations

alkenes and alkynes as radical traps and demonstrated that alkyl radicals (originating from cyclizations with alkenes) were reduced by a second equivalent of “ Cp_2TiCl ” whereas vinyl radicals (obtained from alkynes) reacted by H-atom abstraction from THF. Moreover, THF derivatives could be obtained by oxidative trapping of the alkyltitanium species with iodine and ensuing nucleophilic substitution [26, 29].

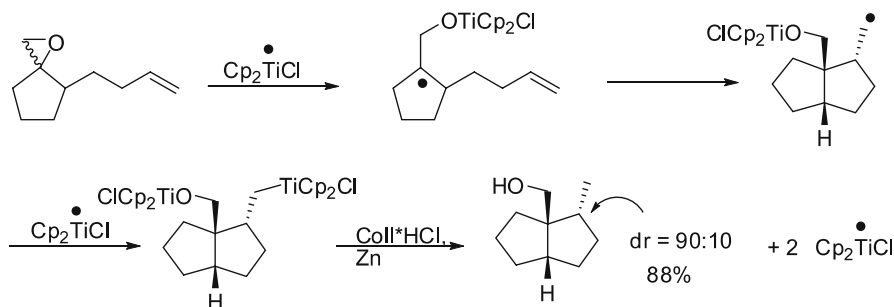
As in the case of the intermolecular additions the cyclizations are tolerant to a wide range of functional groups. The mechanism of the cyclizations and two examples of the synthesis of more complex products are shown in Scheme 11.

5.1.2

Catalytic Conditions

To improve the utility of Nugent’s and RajanBabu’s conditions even further, catalytic conditions for cyclizations have been developed. They address the issue of reagent control of the cyclization and the mode of its termination. The formation of an alkyl titanocene species after reductive trapping allows two distinctive pathways for the regeneration of the catalyst.

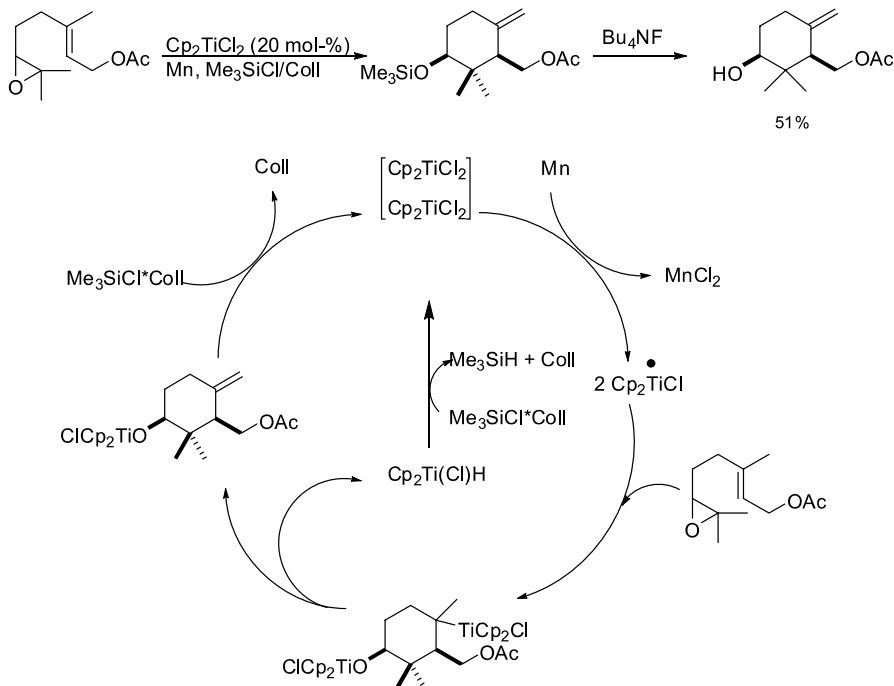
Probably the most straightforward approach is constituted by protonation of the Ti–C bond. This was first realized by using collidine hydrochloride as the acid (Scheme 12). These conditions have proven especially useful in unusual cyclizations as discussed later [66, 67].



Scheme 12 Catalytic cyclizations employing Coll*HCl as mediator

In the organometallic literature it is well documented that alkyltitanium species can undergo β -hydride eliminations swiftly [77, 78]. This was exploited by the group of Oltra and Cuerva for the termination of the cyclization by employing Me_3SiCl and collidine for regenerating the redox-active catalyst by silylation of the Ti–O bond [79, 80]. Ti–C bonds are not affected and thus the alkyl titanocenes decompose via a β -hydride elimination with the most accessible hydrogen atoms to yield mainly exocyclic olefins (if applicable).

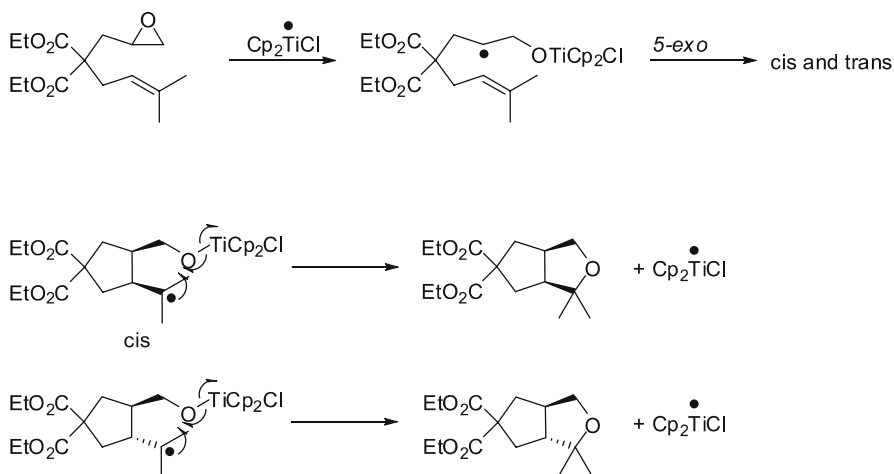
This regioselectivity of the termination of the cyclization is complementary to cationic reactions and therefore synthetically highly attractive. From “ Cp_2TiClH ”, Cp_2TiCl_2 is regenerated with Me_3SiCl through an exchange of hydride for chloride. An example of a 6-endo cyclization using this methodology is shown in Scheme 13.



Scheme 13 Catalytic cyclization terminated by β -hydride elimination

Another method for conducting cyclizations catalytic in “ Cp_2TiCl ” is shown in Scheme 14. It relies on the thermodynamically favorable ring closure of THF from δ -titanoxy radicals [81,82]. This step is mechanistically related to the “oxygen rebound” steps of oxidation reactions. While the scope of this transformation remains to be established, the presence of substituted THF-derivatives in many natural products renders the method potentially attractive.

A protocol relying on the use of BEt_3 together with lutidine hydrochloride has been described by Takahashi for the regeneration of “ Cp_2TiCl ” from cyclizations involving β -hydride elimination as the terminating step [83].



Scheme 14 Catalytic cyclization terminated by THF-formation

5.1.2.1

Synthetic Applications

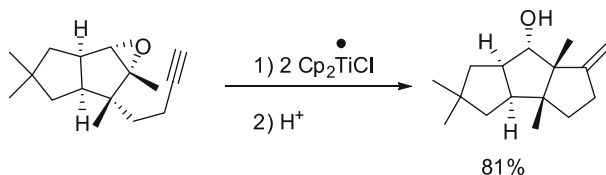
The stoichiometric and catalytic protocols have been employed in a number of synthetic applications involving formations of one or more rings that will be discussed next. The functional group tolerance and short approaches to complex structure are especially relevant.

5.1.2.2

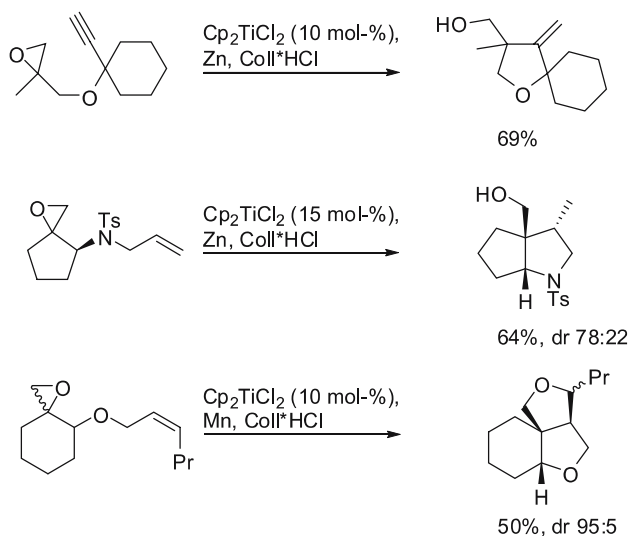
“Simple” Cyclizations

By simple cyclizations we imply reactions where only one ring is formed and for the sake of clarity these cases will be presented separately. The first example of such transformations in natural product synthesis was reported by Clive et al. in the synthesis of (\pm)-ceratopicanol as shown in Scheme 15 [84, 85].

Roy and his group have synthesized a number of THF derivatives from suitable ethers of “Sharpless epoxides” [86, 87]. The example shown

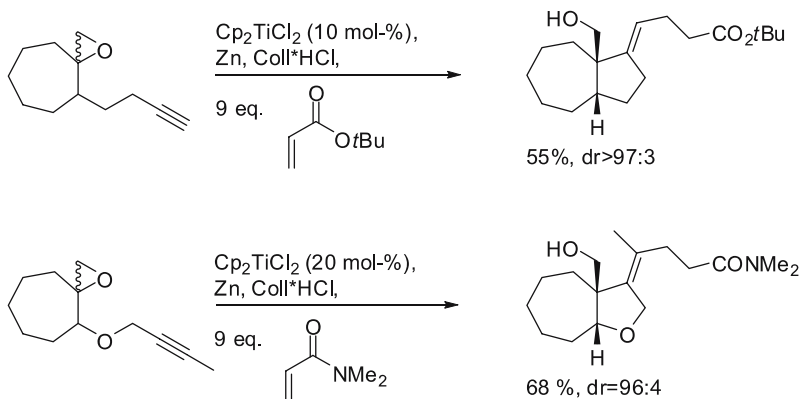


Scheme 15 Clive's cyclization en route to ceratopicanol

**Scheme 18** Catalytic synthesis of heterocycles

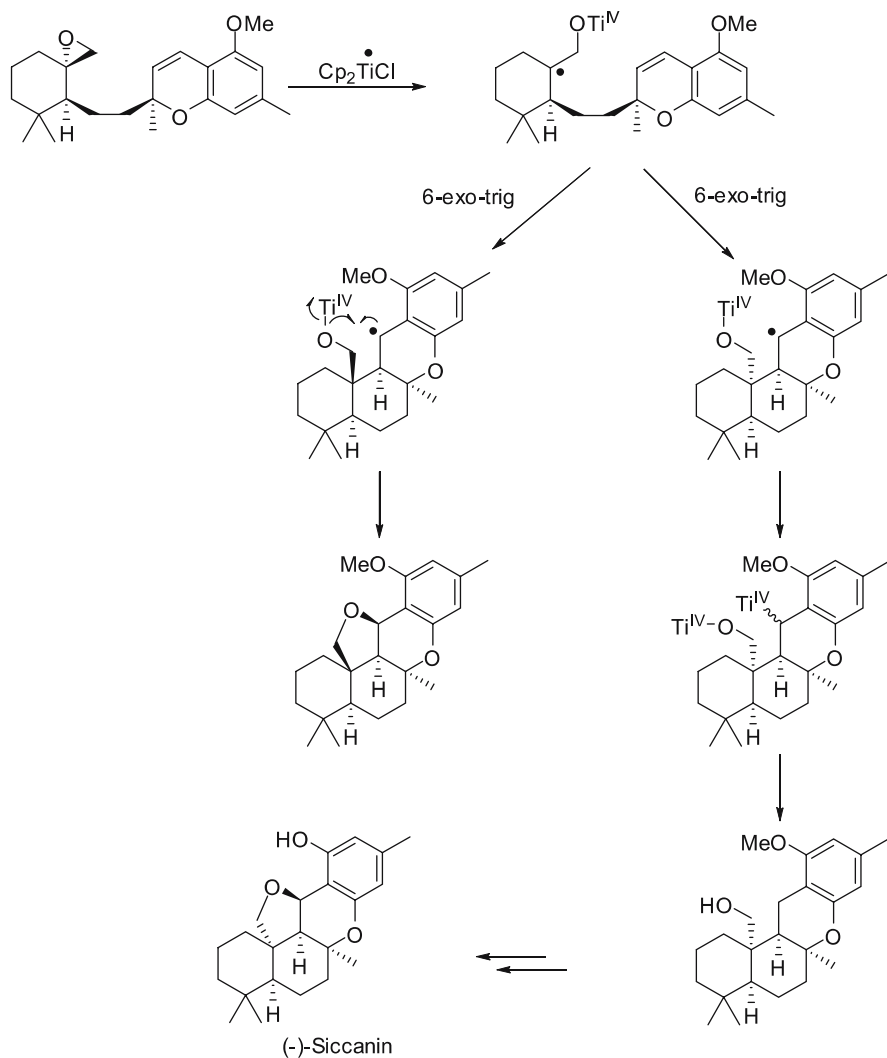
disubstituted or trisubstituted olefins resulted in the formation of polycyclic THF derivatives (Scheme 18) [92, 93].

Barrero, Ultra and coworkers reported on the use of epoxygeranyl acetate in titanocene-mediated cyclizations and found that the termination of the reaction took place via a β -hydride elimination after trapping of the radical by the second equivalent of “ Cp_2TiCl ” [94, 95]. This finding together with Takahashi’s tandem cyclization [96] (see below) marks the first example of extremely interesting developments in epoxypolyene cyclizations via radicals that are discussed separately in the following section.

**Scheme 19** Catalytic cyclization-addition sequence

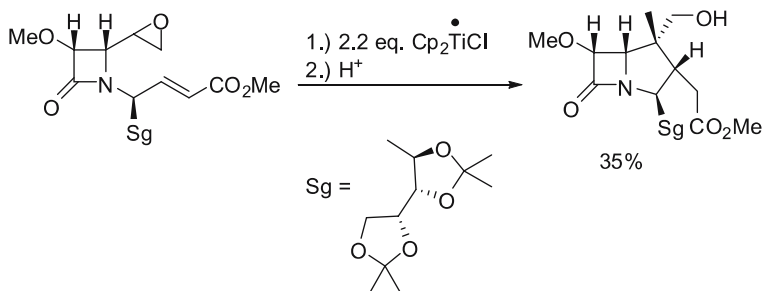
The protic catalytic conditions are also compatible with trapping of the radicals formed after cyclization with acrylates or acrylonitriles prior to their reduction with “ Cp_2TiCl ”. In this manner highly substituted alkenes for the potential preparation of modified steroids can be accessed (Scheme 19) [97].

Trost and his group reported a 6-endo cyclization en route to (–)-siccanin (Scheme 20). The minor diastereoisomer of the radical formed during cyclization yielded a THF derivative directly [98, 99].



Scheme 20 Trost's approach to siccanin

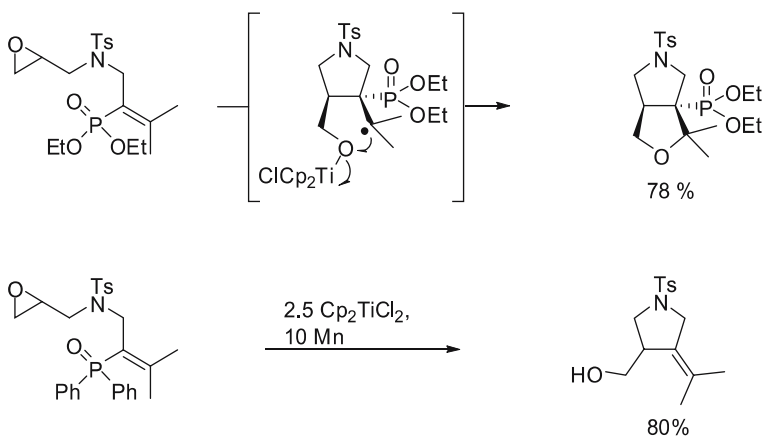
The exceptional mildness of Nugent's and RajanBabu's system was demonstrated by Grande et al. in a synthesis of polyfunctionalized carbacephems as shown in Scheme 21. The sensitive β -lactam and the other functional groups are readily tolerated by " Cp_2TiCl " [100].



Scheme 21 Grande's synthesis of novel β -lactams

Ziegler and Saprong described a stoichiometric cyclization onto an alkyne for the synthesis of the carbocyclic core of "entecavir" from diacetone glucose. Inverse addition was required to minimize deoxygenation. The highly diastereoselective reaction is tolerant to silyl ethers [101].

Malacria and coworkers reported a vinylation sequence of epoxides by employing vinyl phosphine oxides as a radical trap. The overall sequence relies on the facile elimination of phosphinoyl radicals. With vinyl phosphonates the THF derivatives were obtained (Scheme 22). The reaction works equally well under stoichiometric or catalytic conditions [102, 103].



Scheme 22 Malacria's vinylation reaction and THF-synthesis

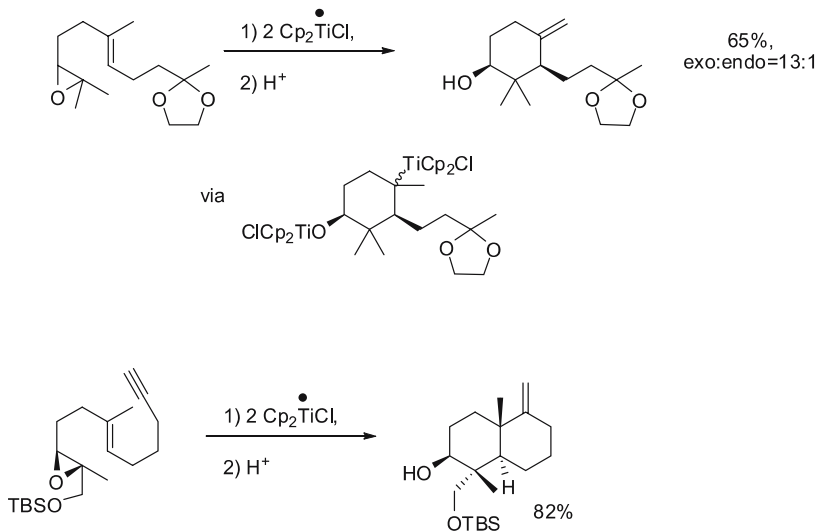
RajanBabu et al. have described an addition-elimination sequence employing vinyl stannanes for the preparation of homoallylic alcohols containing 5-membered rings [104].

Chakraborty has described the highly diastereoselective. Barrero and his group developed an approach to functionalized six-membered rings with exocyclic olefins from α -oxygenated derivatives of geraniol. The diastereoselectivity observed is reasonable and thus the method holds promise for natural product synthesis [105].

5.1.2.3

Tandem and Transannular Cyclizations

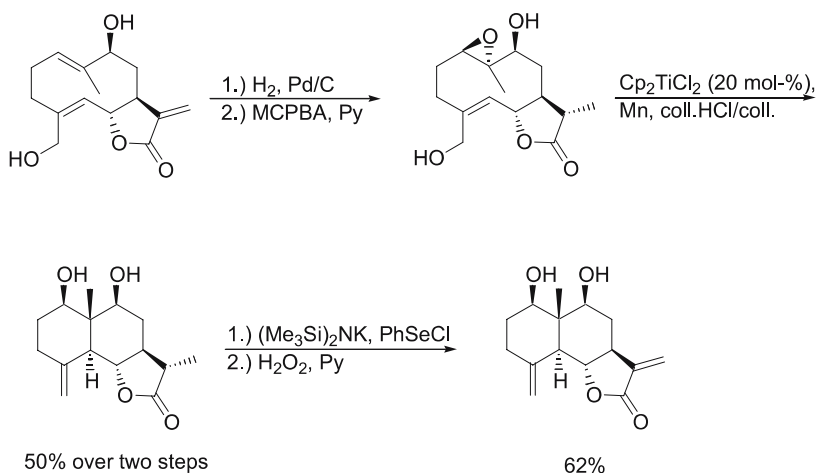
Tandem cyclizations are ideally suited for the efficient preparation of polycyclic compounds from simple starting materials, especially with radicals as reactive intermediates [106–108]. The first reports employing “ Cp_2TiCl ” as a reagent in epoxy polyene cyclizations appeared in 2001 from the group of Takahashi [96] for the synthesis of (\pm)-smenospondiol and from Barrero’s group [94, 95]. While Takahashi employed alkynes for obtaining exocyclic olefins, Barrero used olefins as described above (Scheme 23). Both approaches yielded the desired compounds efficiently. However, it seems that the use of olefins is more general, as the “natural” substrates of the epoxy-polyene cyclizations can be used.



Scheme 23 Epoxy polyene cyclizations via radicals

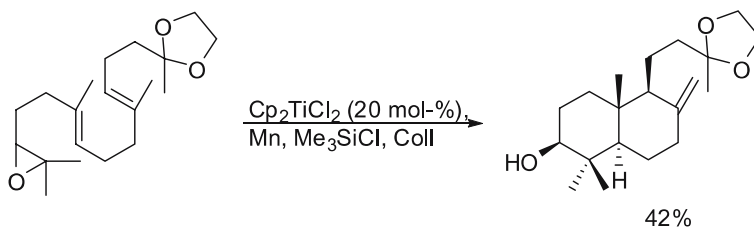
Oltra and Cuerva have reported a unified strategy for the synthesis of the eudesmanolides that relies on the collidine-chlorotrimethylsilane reagent

combination for catalyst regeneration (Scheme 24) [77]. The desired products could be obtained by transannular cyclizations from either the alcohols or even the hydrocarbons. This amply demonstrates the flexibility of their catalytic protocol. It should be noted that by this elegant semisynthetic approach the side-products of biosynthesis can be efficiently obtained.



Scheme 24 Oltra's and Cuerva's transannular cyclizations

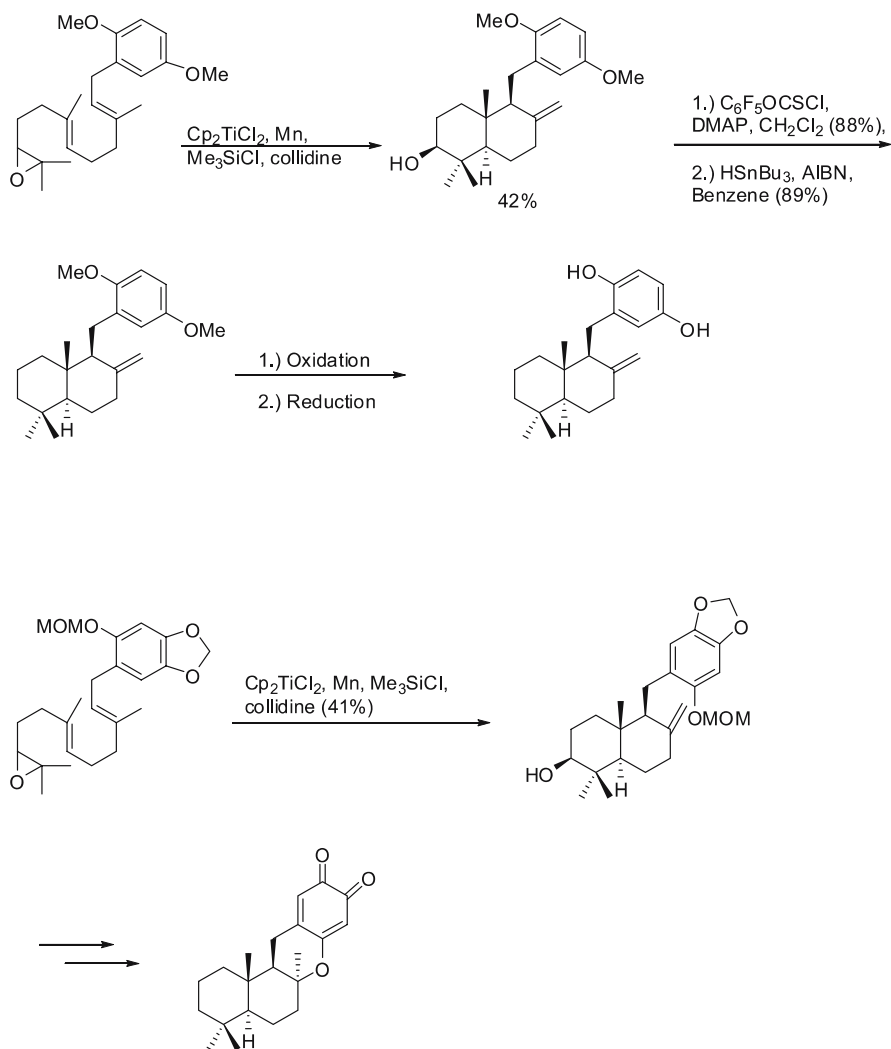
Later the same group reported the application of their method in the synthesis of a number of natural products from simple starting materials such as epoxygeranyl acetate, ketals of epoxygeranylacetone or the epoxy acetate of geranyl geraniol as shown in Scheme 25. Even oxidosqualene can serve as a useful substrate for this reaction. These findings raise the intriguing possibility of biological epoxypolyene cyclizations via radicals [78].



Scheme 25 Oltra's and Cuerva's catalytic epoxy polyene cyclizations

The method was later extended to the synthesis of a number of meroterpenoids from epoxygeranyl carbonates or acetates in a two-step approach combining titanocene catalysis with Stille reactions (carbonates) [108, 109] or copper-catalyzed allylic substitutions (acetates) [110–112]. The cyclizations

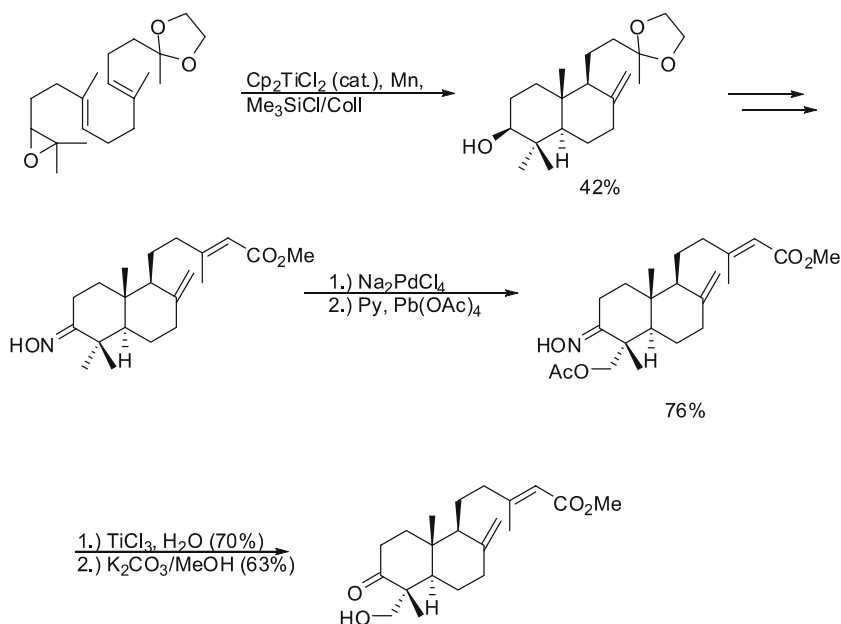
via radicals are superior to cationic reactions as no special groups are needed to control the termination of the sequence and functional group tolerance is much higher. Two examples are shown in Scheme 26.



Scheme 26 Tandem cyclization approach to puupehedione

By combining the benefits of Pd(II) and Ti(III) chemistry, syntheses of γ -dioxxygenated terpenoids, such as rostratone could be readily accessed (Scheme 27) [113].

A simple approach to sclareol oxide has also been reported [114].



Scheme 27 Approach to dioxxygenated terpenoids employing Ti and Pd chemistry

5.2

Unusual Radical Traps and Unusual Ring Sizes

The above-mentioned important and impressive applications of titanocene mediated and catalyzed epoxide opening have been achieved by using the already classical 5-exo, 6-exo and 6-endo cyclizations with alkenes or alkynes as radical acceptors. Besides these achievements, the high chemoselectivity of radical generation and slow reduction of the intermediate radicals by “ Cp_2TiCl ” has resulted in some remarkable novel methodology.

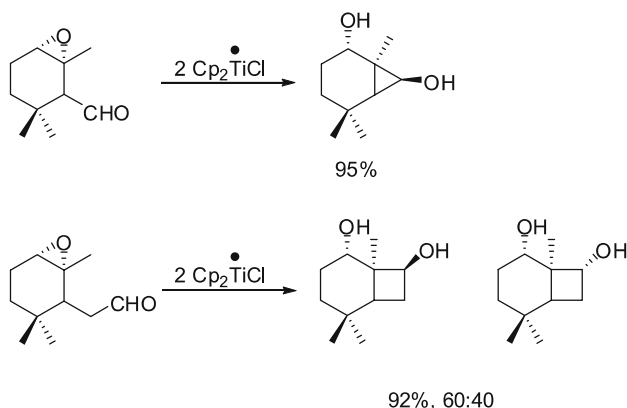
5.2.1

Unusual Radical Traps

The nucleophilic radicals generated after epoxide opening are slowly reduced by “ Cp_2TiCl ” and are therefore relatively persistent. Thus, many addition reactions to functional groups that are too slow for maintaining radical chain reactions can be realized. This is especially so when electrophilic radicals that are swiftly reduced by “ Cp_2TiCl ” are generated during the cyclization.

In this context Fernandez-Mateós and his group reported efficient cyclizations with aldehydes and ketones as radical traps [115]. The authors propose a reduction of the intermediate alkoxy radicals by a second equivalent of

" Cp_2TiCl ". Hydrogen atom abstraction from THF seems possible, also. Most remarkably, the reaction can be employed in the efficient synthesis of cyclopropanols and cyclobutanols as shown in Scheme 28.



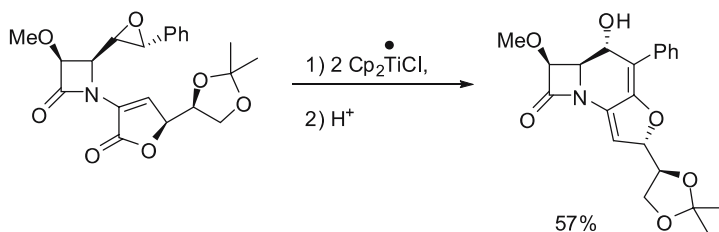
Scheme 28 Fernandez-Mateos cyclizations with aldehydes as radical traps

In general, aldehydes constitute the more efficient radical acceptors. Surprisingly, when enones were employed as radical acceptors 1,2-addition to the carbonyl group was in some cases preferred over the conjugate 1,4-addition [116].

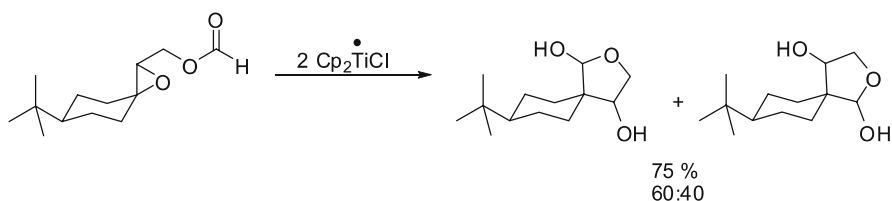
The radical addition to a ketone has been used as a key step in the preparation of (*E*)-*endo*-begamoten-12-oic acids [115] and for the synthesis of carbacephams [118, 119].

Esters are commonly regarded as unreactive toward addition of alkyl radicals [120]. Recently, two studies have demonstrated that this may not be true. In the first, somewhat special, example, the addition of a benzylic radical to the carbonyl group of butenolides was observed during the preparation of potential novel β -lactam antibiotics (Scheme 29) [118].

In a more general study it has been reported that epoxy formates can be employed for the preparation of hydroxy lactols as shown in Scheme 30. Other esters failed to give the desired products, though [121].

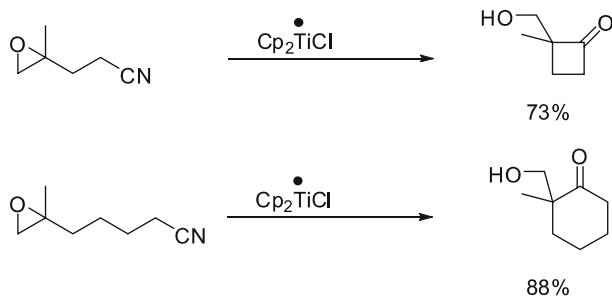


Scheme 29 Grande's cyclization onto the carbonyl group of a butenolide



Scheme 30 Fernandez-Mateos' cyclizations with a formate

Fernandez-Mateos recently demonstrated that nitriles constitute excellent radical traps in titanocene-mediated epoxide openings, even though these cyclizations are considered as being quite slow. As shown in Scheme 31 cyclobutanones, cyclopentanones, and cyclohexanones can be prepared in high yields [122].



Scheme 31 Fernandez-Mateos' cyclizations with nitriles

5.2.2

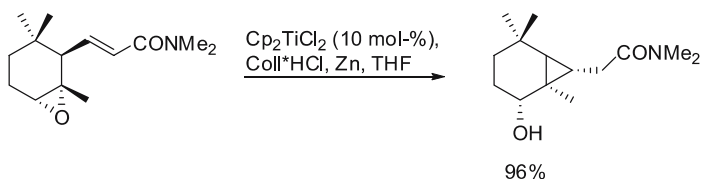
Unusual Ring Sizes

Difficulties encountered in the preparation of three- and four-membered rings via radical cyclization are due to the strain of these compounds. Thus, ring opening usually proceeds much faster than ring closure.

The catalytic conditions are well suited for the preparation of cyclopropanes provided that α, β -unsaturated carbonyl compounds are employed as radical acceptors (formation of electrophilic radicals after cyclization) as shown in Scheme 32 [123].

It has been demonstrated that in these cases cyclopropane formation is reversible and thermodynamically favorable [124]. Recently, a single example of the stoichiometric version of this reaction has been independently reported by Fernandez-Mateos [116].

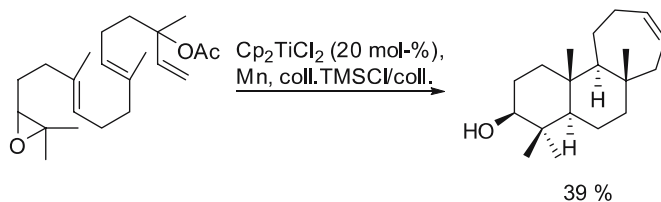
The preparation of cyclobutanes via the catalytic conditions can be extremely efficient provided that the radical formed after epoxide opening is sterically shielded and cyclization promoted by the Thorpe–Ingold effect. It



Scheme 32 Catalytic 3-exo cyclization

remains to be seen if the catalysts can be optimized to avoid these noticeable limitations.

Employing their catalytic system, the group of Oltra and Cuerva demonstrated that 7-endo cyclizations can be performed in surprisingly high yields. Moreover, 7-endo-cyclizations were used by the same group in elegant catalytic cyclization cascades for the preparation of a number of natural products as shown in Scheme 33 [125]. Barreo et al. reported similar methodology [105].



Scheme 33 Oltra's and Cuerva's tandem sequence featuring a 7-endo cyclization

Finally, Roy and his group reported the first examples of stoichiometric 8-endo cyclizations for the preparation of aromatic ethers [126].

6 Conclusion

Since the seminal contributions by Nugent and RajanBabu the field of reductive C–C bond formation after epoxide opening via electron transfer has developed at a rapid pace. Novel catalytic methodology, enantio- and stereoselective synthesis and numerous applications in the preparation of biologically active substances and natural products have evolved. In brief, a large repertoire of useful and original reactions is available. These reactions are waiting to be applied in a complex context!

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