# Titanocene-Catalysed Electron Transfer-Mediated Opening of Epoxides

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**Abstract:** The use of epoxides as substrates for radical reactions via electron transfer is described. The discussion of the evolution of stoichiometric reagents focuses on recent developments in the field of titanocene(III) reagents. Special attention is devoted to the emergence of catalytic conditions for this useful procedure that has led to the discovery of reagent-controlled radical reactions by variations of the cyclopentadienyl ligands.

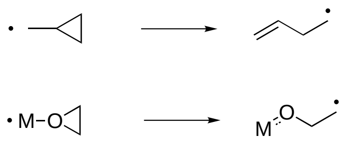
**Keywords:** electron transfer, enantioselectivity, epoxides, diastereoselectivity, radical reactions, titanium

## 1 Introduction

Over the past three decades, radicals have been increasingly utilised as reactive intermediates in organic synthesis.[1] Their ease of generation, high functional group tolerance and predictable behaviour in many transformations has led to numerous developments of novel methods for the efficient formation of C–C bonds. Most of these reactions constitute typical free radical reactions where the usual selectivities are substrate-controlled.[2] Reagent-controlled radical transformations have emerged more recently.[3] In this context, epoxides that can be readily prepared by a number of methods[4] are a very interesting class of radical precursors. They can easily bind to radical-generating Lewis acidic electron-transfer reagents and therefore allow the reagent-controlled formation of radicals and reagent-controlled ensuing radical reactions. Until now titanocene complexes have proven to be the most promising reagents in this context.[5] This chapter will present current results in this field and focus on the recently developed catalytic reaction conditions.

## 2 Stoichiometric Opening of Epoxides via Electron Transfer

Due to their high reactivity, epoxides have been used in a plethora of synthetic applications, most noticeably nucleophilic substitutions. The strained three-membered ring can, however, also be successfully employed as an electron acceptor in reductive openings by low-valent metal complexes. The general idea of this type of transformation has been outlined by Nugent and RajanBabu and is shown in Scheme 1.[5] The overall transformation can therefore be regarded as an analogue of the well-established opening of cyclopropylcarbinyl radicals to butenyl radicals.[6]



Scheme 1. Opening of epoxides with low-valent metal complexes.

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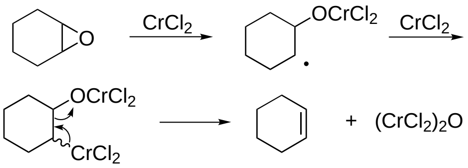
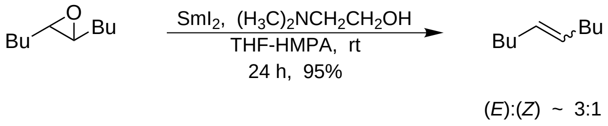
In the case of epoxides β-metaloxy radicals are formed. They constitute interesting intermediates for organic synthesis because they can either be further reduced to give β-metaloxy metal species or can be used for typical transformations of radicals.

The participation of β-metaloxy metal species in this context was first discussed by Kochi, Singleton, and Andrews in 1968[7] in their deoxygenation of styrene and cyclohexene oxide by chromium(II) reagents as shown in Scheme 2.



**Scheme 2.** Deoxygenation of cyclohexene oxide with chromium(II) chloride.

The proposed mechanism includes a reductive epoxide opening, trapping of the intermediate radical by a second equivalent of the chromium(II) reagent, and subsequent β-elimination of a chromium oxide species to yield the olefin. The highly potent electron-transfer reagent samarium diiodide has also been used for deoxygenations as shown in Scheme 3.[8]

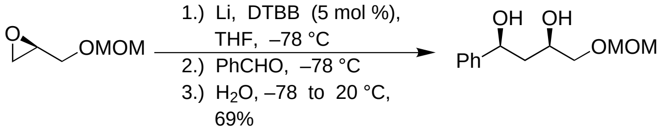


**Scheme 3.** Deoxygenation of epoxides with samarium diiodide.

The mixture of (*E*)- and (*Z*)-isomers obtained is considered as evidence for a radical ring opening mechanism because the initially formed intermediate is trapped with low stereoselectivity to yield two diastereomeric samariumoxy samarium species that eliminate to give the isomeric olefins. In order to exploit the carbanionic reactivity of the dimetallated intermediate in C–C and C–X bond forming reactions it is necessary to produce a temperature-stable organometallic compound. This goal was first achieved by Bartmann in 1986 by the use of radical anions of biphenyl.[9] Cohen[10] and Yus[11] have applied this methodology in the synthesis of more complex molecules. An example is shown in Scheme 4.

According to calculations by Houk and Cohen the first intermediate in these reactions is the radical anion of an epoxide.[12]

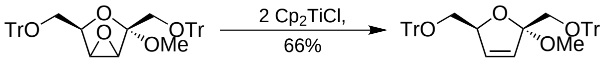
The β-metaloxy radical was first exploited for synthetic purposes in C–H and C–C bond forming reactions



**Scheme 4.** Opening of epoxides in the presence of aromatic radical anions.

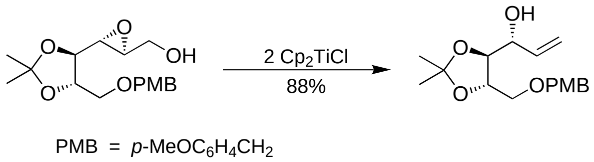
by Nugent and RajanBabu through the use of titanocene(III) chloride as electron-transfer reagent.[5] They established that the β-titaniumoxy radicals formed after electron transfer can be reduced by hydrogen atom donors, e.g., 1,4-cyclohexadiene or *tert*-butyl thiol, add to α,β-unsaturated carbonyl compounds, or react with olefins intramolecularly in *5-exo* cyclisations.

It should not be forgotten, however, that titanocene(III) complexes are also excellent reagents for the deoxygenation of epoxides as demonstrated independently by Schobert[13] and by Nugent and RajanBabu.[5d] An example of a reaction yielding a highly acid-sensitive product in reasonable yield is shown in Scheme 5.



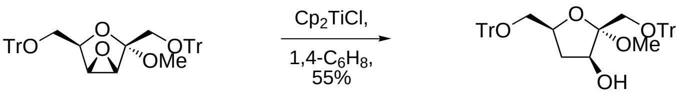
**Scheme 5.** Deoxygenation in the presence of titanocene chloride.

Another interesting application of the deoxygenation reaction is shown in Scheme 6. Sharpless epoxides are transformed to enantiomerically pure allylic alcohols.[14] It should be noted that the disadvantage of the loss of one-half of the substrate as in the kinetic resolutions of allylic alcohols according to the Sharpless protocol is not a problem when this titanocene based method is employed.



**Scheme 6.** Synthesis of enantiomerically pure allylic alcohols with titanocene chloride.

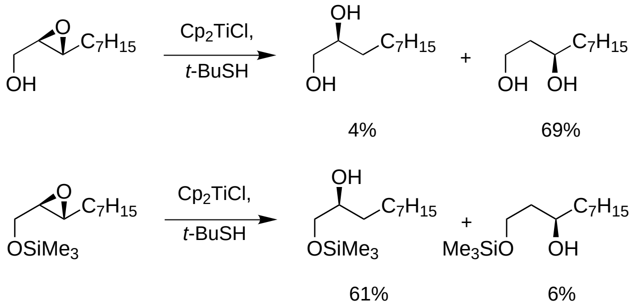
The transformations exploiting typical radical reactivity have been used in a number of synthetic applications that will be discussed before turning the focus to the development of the catalytic reaction conditions. The reductive opening of epoxides usual yields the less substituted alcohol *via* formation of the higher substituted radical. In analogy to Cohen's and Houk's calculations,[12] one could assume a titanocene(IV)-bound epoxide radical anion as intermediate although this is clearly speculative. The observed regioselectivity of epoxide opening could then be explained by the avoidance of substantial steric interactions between the ligands and the bulky substituent of the epoxide. Thus, the higher substituted β-titanoxy radical would be formed. This selectivity is complementary to the Bartmann opening.[9] Although one can also imagine a reversible epoxide opening to give the more stable radical, this typical Curtin–Hammet scenario[15] seems unlikely, because the selectivity of epoxide opening is independent of the radical trap employed. When the epoxide is 1,2-disubstituted, steric and electronic effects are responsible for the preferential formation of one product. In this context, benzyl radicals are always produced irrespective of the epoxide's substitution pattern. For these intermediates the more reactive *tert*-butyl thiol is the hydrogen atom donor of choice. Interestingly, useful regioselectivities can also be obtained when the additional stabilisation through conjugation is impossible. An example shown in Scheme 7.



**Scheme 7.** Reductive epoxide opening with titanocene chloride.

An explanation for the observed regioselectivity could be an additional destabilisation of the radical that is not formed during ring opening by the unfavourable inductive effect of the methoxy group.

Chelation of titanium can be favourably used for regioselective epoxide opening as shown in Scheme 8.[5d]

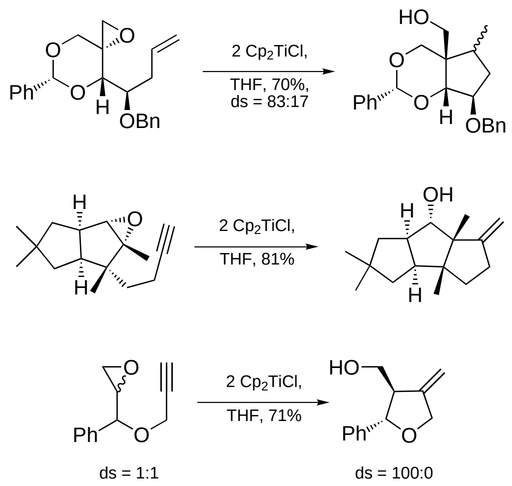


**Scheme 8.** Chelation as a means for controlling the regioselectivity of epoxide opening.

A possible – albeit still speculative – rationalisation for this useful selectivity is the formation of a less strained six-membered cyclic radical incorporating a titanocene(IV) unit.

More recently Doris et al. have described the reductive opening of α-keto epoxides.[16] In this manner β-hydroxy ketones can be obtained in high yield. The synthesis of enantiomerically pure compounds is easily realised. The titanocene(III) reagents are distinctly superior to samarium diiodide that is also known to induce this transformation.

Usually, the formation of C–C bonds is considered to be more important than the formation of C–H bonds. It is, therefore, not surprising that these reactions have attracted more attention. Of special importance in organic synthesis are *5-exo* cyclisations[17] and the titanocene-mediated reactions are a valuable tool for carrying out such transformations. Three examples are shown in Scheme 9.



**Scheme 9.** Titanocene-mediated *5-exo* cyclisations.

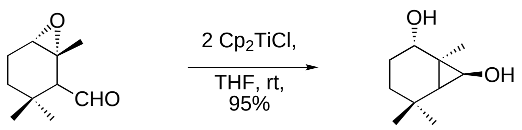
The observation of a stereoconvergent cyclisation by Roy et al.[18] as shown in the third example is of special interest from a synthetic point of view because it exploits the configurational lability of radicals in a favourable manner. The other examples, Nugent's and RajanBabu's cyclisation of a carbohydrate derived epoxide[5d] and Clive's quinane synthesis[19], amply demonstrate the usefulness of the titanocene-initiated epoxide opening.

The cyclisation of the radicals is not confined to carbon-carbon multiple bonds as radical traps. An intriguing cyclisation utilising aldehydes as radical acceptors has been reported by Fernández-Mateos et al.[20] The reaction shown in Scheme 10 constitutes a rare example of a highly efficient *3-exo* cyclisation.

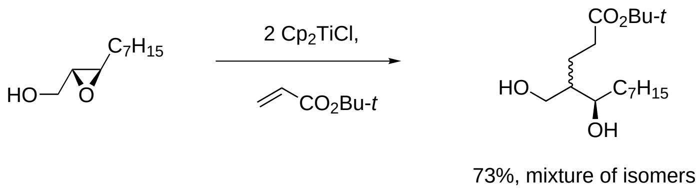
More recently *6-exo* and *7-exo* cyclisations have also been carried by the groups of Barrero and Takahashi.[21]

Although intermolecular additions to α,β-unsaturated carbonyl compounds have not been used as often, these transformations are also attractive from a synthetic point of view for the synthesis of δ-lactones or δ-hydroxy esters. An example is shown in Scheme 11.[5d]

Control of diastereoselectivity has so far remained difficult, however.



**Scheme 10.** Titanocene-mediated highly efficient *3-exo* cyclisation.



**Scheme 11.** Intermolecular addition to α,β-unsaturated carbonyl compounds.

## 3 Titanocene-Catalysed Epoxide Opening

### 3.1 Titanocene-Catalysed Reductive Epoxide Opening to Alcohols

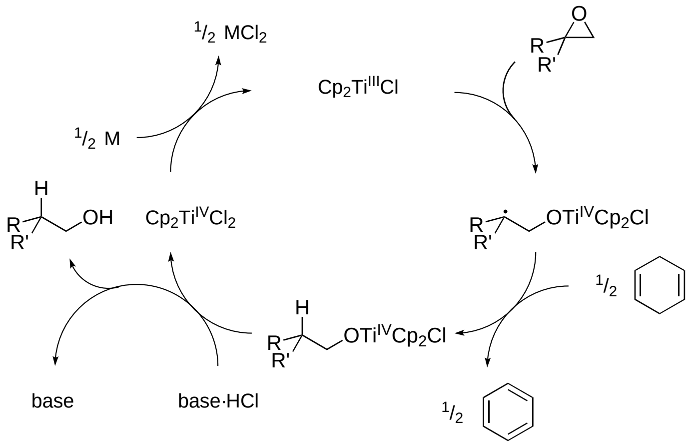
In the stoichiometric applications of titanocene complexes, no attempt to use ligands different from simple cyclopentadienyl has been reported as yet. In principle, the use of more complex titanocenes[22] is very interesting because then a simple means to employ reagent control in radical reactions would be at hand. Reagent control can be exercised either at the stage of radical generation, during the ensuing reaction of the generated radical, or in both stages. Intriguing goals in this context are enantioselective openings of *meso*-epoxides through electron transfer, ligand-controlled diastereoselective *5-exo* cyclisations, and diastereoselective addition reactions to α,β-unsaturated carbonyl compounds. Clearly, the stoichiometric use of titanocene complexes that have to be prepared in multiple-step syntheses is not attractive for these purposes.

Therefore, we decided to initiate a program directed towards the development of a titanocene-catalysed epoxide opening.[3c] Since titanocene dichloride is formed in the stoichiometric reaction after the protic quench, the requirement for a catalytic reaction, the regeneration of the redox active species *in situ*, constitutes the challenge to be met. This underlying question is depicted in Scheme 12

The solution of the similar problem of achieving catalytic turn-over[23] in McMurry couplings,[24] Nozaki–Hiyama reactions,[25] and pinacol couplings[26] had been reported by Fürstner and by Hirao. Key step in these reactions is the *in situ* silylation of titanium- and vanadium-oxo species with $Me_3SiCl$ and reduction of the metal halides by suitable metal powders, e.g., zinc and manganese dust, as shown in Scheme 13.

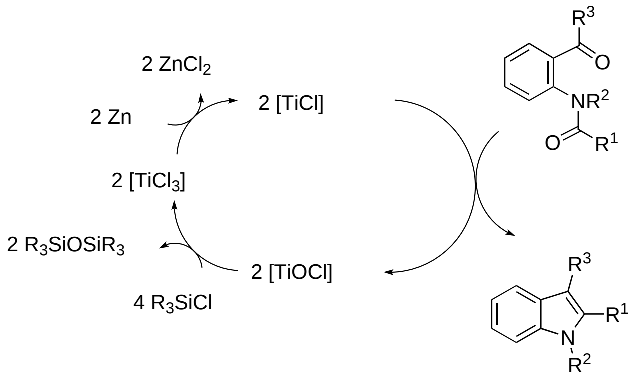
This method was later applied to samarium diiodide-initiated reactions[27] and to titanocene-catalysed pinacol couplings.[28] First examples of enantioselective reactions using $Me_3SiCl$ as mediator for catalysis have very recently been reported by Cozzi et al. as shown in Scheme 14.[29]

In the case of the epoxide openings, $Me_3SiCl$ is not an appropriate reagent for the cleavage of a titanium alkoxide because of the high oxophilicity of silicon. This

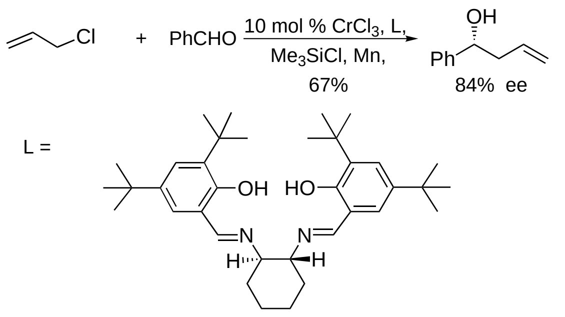


M = Mn, Zn, Mg

**Scheme 12.** Planned titanocene-catalysed reductive epoxide opening.



**Scheme 13.** Fürstner's McMurry reaction catalytic in titanium.

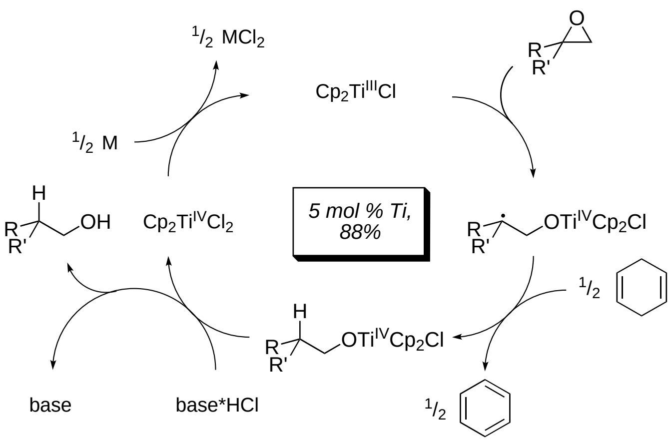


**Scheme 14.** Cozzi's catalytic enantioselective Nozaki–Hiyama reaction.

results in the formation of silylated chlorohydrins from the epoxide. Therefore, we decided to investigate buffered forms of hydrochloric acid as mediators for catalytic turnover. This concept relies on the stability of radicals under protic conditions. On closer examination of the intermediates in the stoichiometric reaction (Scheme 12) a number of characteristics of the acid to be employed are revealed:

1) The acid must not be strong enough to open epoxides via $S_N1$ or $S_N2$ reactions.
2) The acid must be strong enough to protonate alkoxides to enable turnover. The $pK_a$'s of typical alcohols in water are in the range of 15 – 18.
3) The acid must not oxidise the stoichiometric reductant or the titanocene(III) complex.
4) The base liberated must not complex and deactivate any titanium species in the proposed catalytic cycle.

With these conditions in mind, we decided to investigate amine hydrochlorides as mediators.[30] Since pyridine hydrochloride is known to open epoxides to the corresponding chlorohydrins[31] in chloroform, the employed acid must be weaker than pyridine hydrochloride but should be at least three orders of magnitude more acidic than typical alcohols to ensure quantitative protonation. Therefore, the acid should have a $pK_a$ of 6 – 12 in water. Amongst the acids investigated collidine and lutidine hydrochloride proved to be excellent mediators for achieving catalytic turnover in the presence of manganese dust as stoichiometric reductant.[32] Zinc dust, on the other hand, performed distinctly inferiorly. Presumably, the zinc dichloride formed during reduction of titanocene dichloride acted as a Lewis acid complexing and slowly opening the epoxide. Since the reaction is sensitive to moisture, we preferred collidine hydrochloride as acid because it is distinctly less hygroscopic than lutidine hydrochloride. Under the optimised conditions, the desired product was obtained in good yield. Compared to the stoichiometric conditions,[5] the amount of titanocene is reduced at the cost of employing stoichiometric amounts of collidine. A stoichiometric amount of the reductant is utilised in both cases. The resulting catalytic cycle is shown in Scheme 15.



R' = $CH_3$, R = $CH_2CH_2Ph$

base = 2,4,6-collidine,
1.5 equiv.

**Scheme 15.** Titanocene-catalysed reductive epoxide opening.

The catalytic system preserves the attractive features of the stoichiometric reaction, i.e., the high regioselectivity of epoxide opening and the exceptional functional group tolerance. Thus, electrons are transferred with high selectivity from manganese to titanium and not from manganese to the organic substrates. Amongst the groups tolerated are aromatic ketones, tosylates, halides, and aliphatic aldehydes.

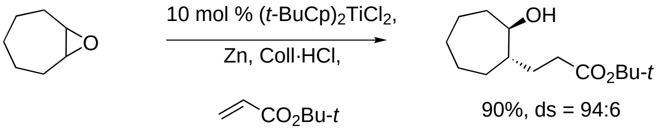
The opening of epoxy ketones that was recently reported by Doris et al. can also be carried out with catalytic amounts of titanocene dichloride.[16] Thus, the relatively sensitive β-hydroxy ketones are also readily tolerated under the catalytic conditions.

## 3.2 Titanocene-Catalysed Additions to α,β-Unsaturated Carbonyl Compounds

With an operating catalytic cycle for the reductive opening of epoxides in hand, we decided to investigate the preparatively more important formation of carbon-carbon bonds. The intermolecular addition reactions to α,β-unsaturated carbonyl compounds have been described in the stoichiometric reaction by Nugent and RajanBabu.[5] The general idea for the catalytic conditions is outlined in Scheme 16.

Similar to the reductive opening, titanocene-oxygen bonds have to be protonated. Here, a titanium enolate, that is generated after reductive trapping of an enol radical, has to protonated in addition to a simple titanocene alkoxide. As before, 2,4,6-collidine hydrochloride constitutes a suitable acid to achieve catalytic turnover. Zinc dust turned out to be the reductant of choice.[32c] The features of the stoichiometric reaction are preserved under our conditions. Acrylates and acrylonitriles are excellent radical acceptors in these reactions. Methyl vinyl ketone did not yield the desired addition product. Under the standard reaction conditions α-substituted acceptors are readily tolerated but β-substitution gives the products only in low yields.

The problem of diastereoselectivty of additions to cyclic radicals arising from the opening of bi- or tricyclic epoxides, e.g., cycloheptene oxide or norbornene oxide, has been addressed only recently.[33] In the former case reasonable selectivities can be obtained with titanocene dichloride (*trans:cis* = 76:24), but excellent selectivities are observed with bis(*tert*-butyl)-titanocene dichloride (*trans:cis* = 94:6) as shown in Scheme 17.



**Scheme 17.** Control of diastereoselectivity in intermolecular additions.

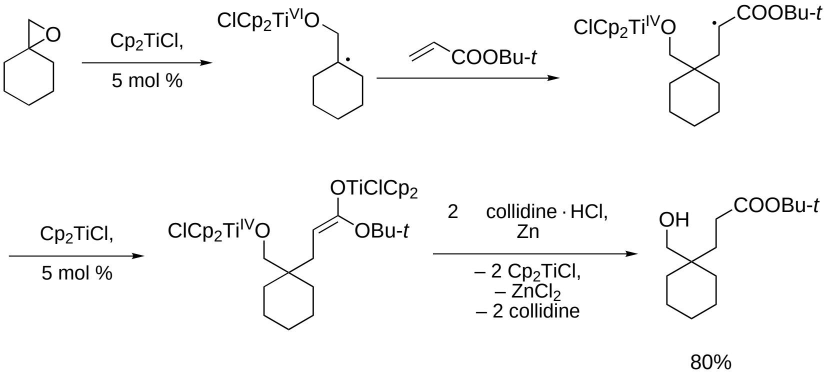
In the case of norbornene systems, complete *exo* selectivity was observed by Giese et al.[34] during radical additions carried out by the mercury method. In the titanocene-catalysed epoxide openings $Cp_2TiCl_2$ gives an *exo*:*endo* ratio of 4:1,[35] whereas $(t\text{-}BuCp)_2TiCl_2$ gives a 53:47 mixture.[36] Thus, the titanocene reagent control allows for a complete loss of the substrate-induced selectivity.

## 3.3 Titanocene-Catalysed *5-exo* Cyclisations

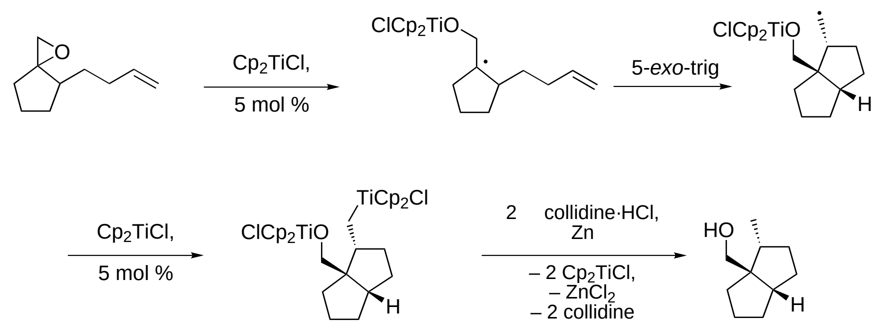
Probably the most important applications of radicals in organic chemistry are *5-exo* cyclisation reactions. Numerous applications of this exceptionally useful transformation and several elegant syntheses of natural products have been reported.[17] Although a general concept for a catalytic reagent-controlled cyclisation is still lacking, such a method would clearly be very useful for the design of novel transformations.

As a first step towards this goal, we managed to develop a titanocene-catalysed *5-exo* cyclisation of radicals derived from suitable unsaturated epoxides. The mechanism of the cyclisation is depicted in Scheme 18.[32]

Key step in achieving catalytic turnover is the protonation of titanium-oxygen and titanium-carbon bonds



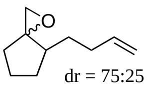
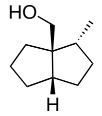
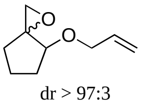
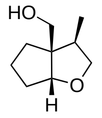
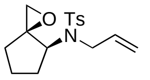
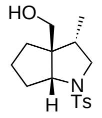
**Scheme 16.** Titanocene-catalysed addition to α,β-unsaturated carbonyl compounds.



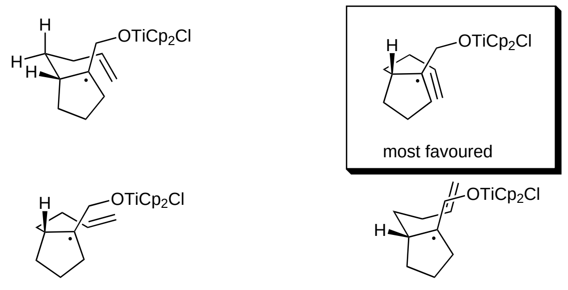
**Scheme 18.** Titanocene-catalysed *5-exo* cyclisation.

that is readily achieved by employing collidine hydrochloride as protic acid. An interesting feature of the cyclisation shown above is its diastereoconvergent nature. From a diastereomeric mixture of the epoxides the cyclisation product is obtained as essentially a single isomer. Unfortunately, this is not always the case as shown in Table 1.[37]

**Table 1.** Titanocene-catalysed formation of [3.3.0] systems. For reasons of clarity only the major isomer is shown.

| Substrate | Product | Yield, Selectivity |
|---|---|---|
|  dr = 75:25 |  | 66, >98:<2 |
|  dr > 97:3 |  | 68, 58:42 |
|  |  | 62, 86:14 |

Models explaining the observed selectivities can be obtained from a simple analysis of transition structures according to Spellmeyer's and Houk's work.[38] These authors have calculated the transition states for cyclisations of radicals like the ones shown in Scheme 19 but with a hydrogen atom being replaced by the $CH_2OTiCp_2Cl$ group.



**Scheme 19.** Transition state models for cyclisation in analogy to Spellmeyer and Houk.

The presence of this bulky group leads to a higher diastereoselectivity than in the unsubstituted case because interactions of the olefin with the titanocene group lead to the exclusive formation of one diastereomer, presumably through the most favoured transition structure shown in Scheme 19 where steric interactions should be minimised.

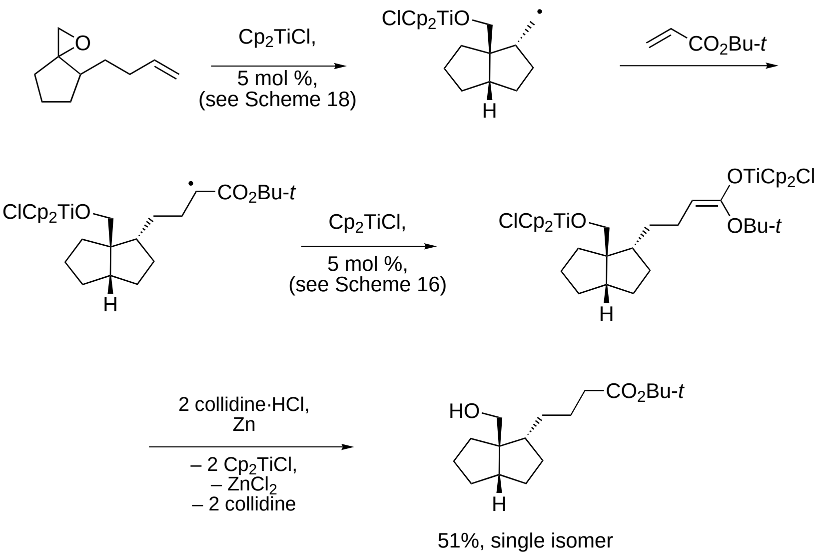
We are currently employing substituted titanocene complexes to obtain reagent-controlled cyclisations.

Interesting radical acceptors for cyclisation reactions are alkynes because the products contain double bonds that can be subjected to further transformations. In the case of terminal alkynes high yields of the desired products can be obtained as single isomers. With non-terminal alkynes as acceptors the olefinic isomers are generated as mixtures of (*E*)- and (*Z*)-isomers in high yields but with low selectivity.[37]

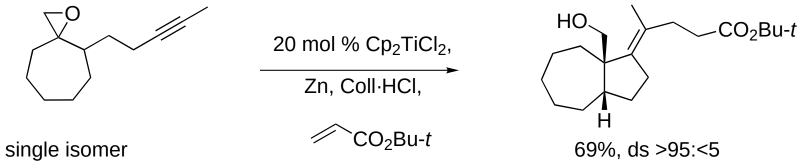
## 3.4 Titanocene-Catalysed Radical Tandem Reactions

A very attractive feature of radical chemistry is the generation of a novel radical after cyclisation or any other radical translocation. This feature allows the inclusion of a second carbon-carbon bond forming event and can, in principle, be extended even further. The resulting tandem reactions[39] can be extremely useful for the construction of complex molecules. Impressive early results have been reported by Stork in applications directed towards the synthesis of prostaglandins.[40] Our catalytic conditions also allow the realisation of tandem reactions. An example including a mechanistic proposal is shown in Scheme 20.

Key features of the catalytic cycle are the trapping of the radical generated after cyclisation by an α,β-unsaturated carbonyl compound, the reduction of the enol radical to give an enolate, and the following protonation of the titanocene alkoxide and enolate. The diastereoselectivity observed is essentially the same as in the simple cyclisation reaction. An important point is that the tandem reactions can be carried out with



**Scheme 20.** Titanocene-catalysed radical tandem reactions.



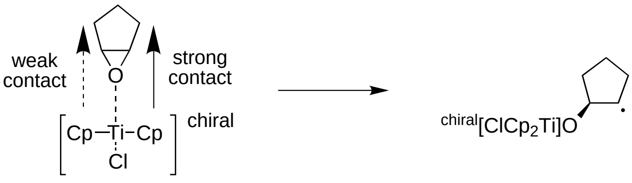
**Scheme 21.** Selective formation of a tetrasubstituted olefin *via* tandem radical reaction.

alkynes as radical acceptors. The trapping of the formed vinyl radical with α,β-unsaturated carbonyl compounds occurs with very high stereoselectivity as shown in Scheme 21.

Thus, our radical tandem reactions open a highly stereoselective access to tri- and tetrasubstituted alkenes that are otherwise difficult to prepare.

### 3.5 Catalytic Enantioselective Epoxide Opening

With the catalytic system described above, the enantioselective opening of *meso*-epoxides could also be pursued. Although many excellent examples of openings of *meso*-epoxides by $S_N2$ reactions have recently been reported, the reaction planned here is conceptually different.[41] In the $S_N2$ reaction the path of the incoming nucleophile has to be controlled. In the titanocene-catalysed reaction the intermediate radical has to be formed selectively. If an intermediate similar to the Bartmann opening[9] is to be postulated here, the selectivity-determining interaction should be that of the epoxide radical anion with a titanocene(IV) complex as shown in Scheme 22.



**Scheme 22.** Concept for enantioselective *meso*-epoxide opening *via* electron transfer.

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 admittedly very simplistic mechanistic rationale leads the way for the rational design of the cyclopentadienyl ligands. 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. Examination of the extensive literature on titanocene and cyclopentadienyl complexes[22] suggested ligands from terpenes as suitable for achieving this purpose. In *ansa*-metallocenes that have been used with great success recently, the chirality is centred around the metal.

Chirality transfer to the periphery of these complexes is not obvious in studies of molecular models and the crystallographic structures. Epoxide **1** was chosen as substrate as shown in Scheme 23 because it is readily accessible from (*Z*)-butenediol in two steps and the absolute stereochemistry of the opening product can be established by synthesis of authentic samples from malic acid.[42]

The results of the investigation of a number of titanocene complexes shown in Scheme 24 are summarised in Table 2.

**Table 2.** Reductive opening of epoxide **1** with various titanocene complexes.

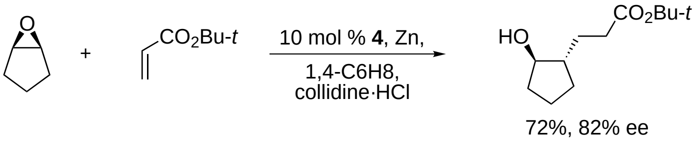
| Cat, mol % cat | yield [%] | (*R*):(*S*) |
|---|---|---|
| **2**, 10 | 55 | 78:22 |
| **3**, 10 | 45 – 51 | 60 – 76:40 – 24 |
| **4**, 10 | 76 | 3:97 |
| **5**, 10 | 72 | 3.5:96.5 |

Brintzinger's complex **2**[43] (10 mol %) performed poorly concerning the enantioselectivity of the epoxide opening (56%) as well as the yield of product (55%). The titanocene complex **3**[44] obtained from (1*R*,2*S*,5*R*)-menthol gave varying results due to its sensitivity to traces of moisture (ee = 20 – 52%). Clearly, the axially positioned cyclopentadienyl group is not ideal.

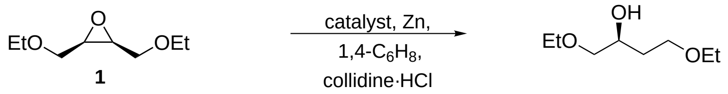
A satisfactory result was obtained with the ligand **4**[45] synthesised from *neo*-menthol containing an equatorial cyclopentadienyl group. The enantioselectivity of the opening achieved synthetically useful levels (97:3) and the isolated yields were reasonable. Complex **5**[44] with a ligand derived from phenylmenthone performed well. An enantioselectivity of 96.5:3.5 was observed. Phenylmenthol has already been extensively and successfully used as chiral auxiliary.[46]

These results suggest that both **4** and **5**, 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 **1**. The corresponding bis-*tert*-butyl ether epoxide constituted a more difficult example due to the increased steric demand of the bulky groups. With **4**, an enantioselectivity of 92.5:7.5 was obtained, whereas **5** gave the lower value of 87.5:12.5. An interesting and demanding problem is constituted by the opening of bicyclic *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. Complex **4** was the most selective catalyst giving reasonable enantioselectivity while preserving high diastereoselectivity as shown in Scheme 25. Titanocene **5** gave lower selectivities.

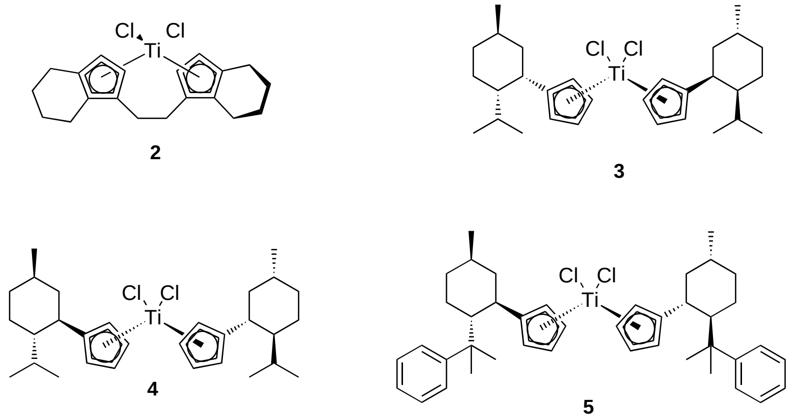
A comparison of the structures of **4** and **5** both in the crystalline form and in solution has been carried out.[47] The results obtained suggest that the structures are essentially the same in both states of aggregation and that crystal structure data can therefore be used for catalyst optimisation.



**Scheme 25.** Opening of cyclopentene oxide in the presence of **4**.



**Scheme 23.** Enantioselective test reaction for catalyst optimisation.



**Scheme 24.** Titanocene catalysts used for enantioselective opening of **1**.

## 4 Conclusion

The opening of epoxides via electron transfer has led to a number of synthetically useful reactions. So far, the stoichiometric reagents showing the most promising selectivities are the titanocene(III) reagents introduced by Nugent and RajanBabu.[5] The recent emergence of a reaction catalytic in titanium has increased the usefulness of this reaction even further.[31,36,41,45] The key step in the catalytic protocol is constituted by protonation of titanium-oxygen and titanium-carbon bonds. This novel approach has for the first time allowed the use of substituted titanocenes to influence the diastereoselectivity and enantioselectivity of radical reactions. It remains to be seen how general this approach of reagent control in radical chemistry is going to be.

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