TRABAJO DE FIN DE GRADO EN INGENIERÍA QUÍMICA INDUSTRIAL

TITANOCENE MONOCHLORIDE (Cp_2TiCl): A FORMIDABLE TOOL IN CONTEMPORARY RADICAL AND ORGANOMETALLIC CHEMISTRY

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ABSTRACT

The vast range of reactions mediated by titanocene monochloride (Cp_2TiCl) in organic synthetic chemistry is reviewed. The power of Cp_2TiCl in organic chemistry is demonstrated by its ability to promote and/or catalyse several efficient transformations under mild reaction conditions in the presence of several functional groups, in an environmentally friendly manner and using simple experimental procedures.

KEYWORDS

titanocene monochloride (Cp_2TiCl), radical and organometallic chemistry.

CONTENTS

1. INTRODUCTION

Over the last 25 years radical reactions have been increasingly used in organic synthetic chemistry due to their mild reaction conditions, their high functional group tolerance and a broad accessibility to useful structures, often obtained through sequential transformations.[1] In this context, titanocene monochloride (Cp_2TiCl), a reagent whose central metal is titanium(III), the seventh most abundant metal on Earth[2], being a mild single-electron transfer (SET) reagent, has become into a formidable tool in organic synthesis.[3, 1e] Although Cp_2TiCl was synthesized for first time by Wilkinson in the 50s[4], after the seminal works of Nugent and Rajanbabu were describing it as a SET reagent and its initial applications in radical organic chemistry. In fact, Cp_2TiCl has been shown to promote and/or catalyse several efficient transformations in organic chemistry, under mild reaction conditions which are compatible with several functional groups, and use simple experimental procedures.

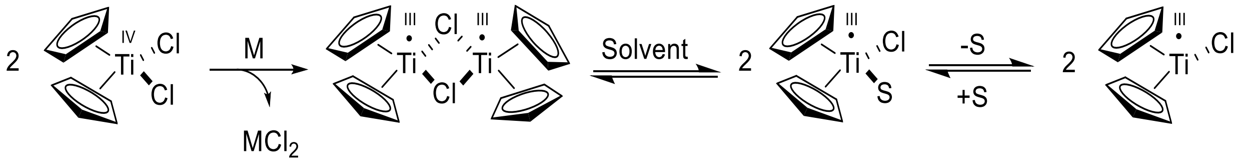
In this review we summarize the principal applications of Cp_2TiCl in organic synthesis with emphasis on the research from recent years. The review is subdivided into two main sections:

1) Preparation of Cp_2TiCl from commercial Cp_2TiCl_2 and the catalytic cycles for its regeneration

2) And the principal reactions mediated by Cp_2TiCl in organic chemistry.

2. PREPARATION OF TITANOCENE MONOCHLORIDE FROM COMMERCIAL Cp_2TiCl_2 AND CATALYTIC CYCLES TO REGENERATE Cp_2TiCl_2

The Cp_2TiCl complex can be easily prepared from commercial Cp_2TiCl_2 (Scheme 1) by using reductants such as elemental Al,[5] Zn[6] or Mn.[7] The solid structures of Cp_2TiCl can be dramatically different depending on the preparation. By reduction of Cp_2TiCl_2 with Zn or Mn, the dimeric species $[(Cp_2TiCl)_2]$ can be obtained and even isolated as a green crystalline powder.[8] The nature of these reducing agents in solution was studied by Skrydstrup *et al.*[9] who indicated the existence of an equilibrium between mononuclear and dinuclear species. Titanocene monochloride (Cp_2TiCl) can also be isolated[10] or prepared[11] by electrochemical reduction of Cp_2TiCl_2.

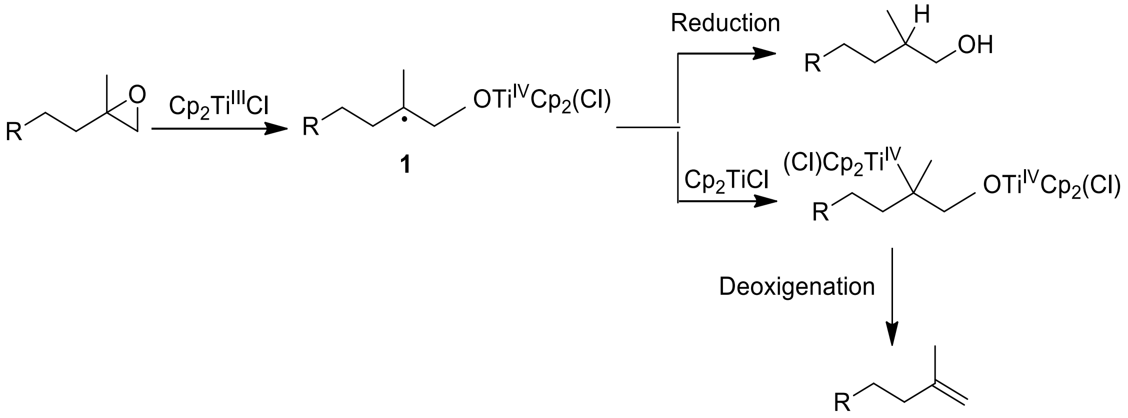


M= Mn, Zn

Scheme 1. Equilibrium of species in the preparation of Cp_2TiCl from Cp_2TiCl_2.

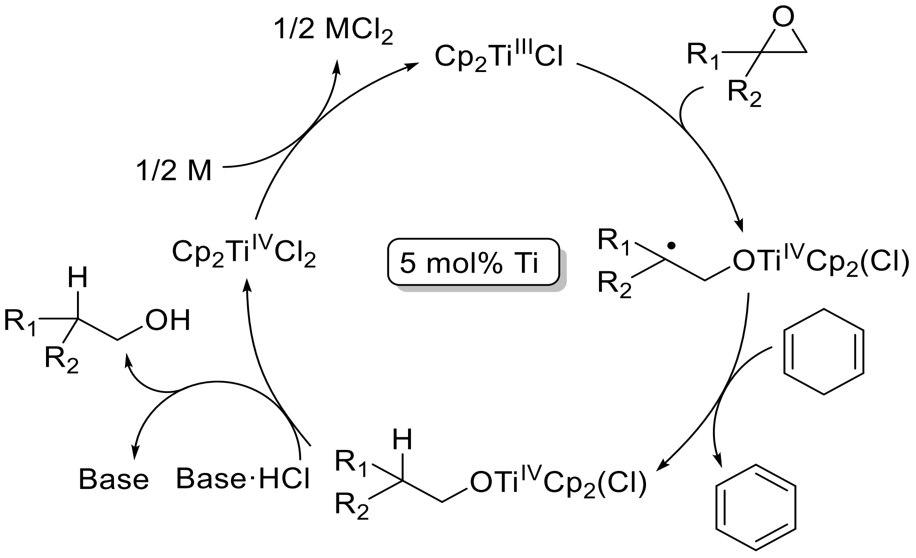
These Ti(III) structures have an unpaired d electron, giving them a soft-electron reducing character (E°= -0.8 vs Fc+/Fc).[12] Furthermore, Cp_2TiCl has a vacant site, allowing hetero atoms with free valence electrons to conduct electron transfers through an inner-sphere mechanism. [13]

Between 1988 and 1994 Nugent and Rajanbabu[14, 3a] discovered that titanocene(III) complexes were useful stoichiometric reagents for the reductive opening of epoxides with or without deoxygenation (Scheme 2).



Scheme 2. Stoichiometric opening of epoxides with Cp_2TiCl.

The β-titanoxyl radical **1** can also react with olefins conjugated with electron deficient groups such as nitriles or esters to create new C-C bonds.[3a] At this stage, the main drawback of Cp_2TiCl as a new tool in organic synthesis was the need to be used in stoichiometric amounts, and therefore the discovery of catalytic procedures to regenerate Cp_2TiCl_2 was desirable. In this sense, in a preliminary work Zhang *et al*.[15] introduced the combination of Cp_2TiCl_2 (cat.) and i-BuMgBr for pinacol coupling. However, the quantum lap in the development of this reagent was the description by Gansäuer *et al*.[16] (Scheme 3) of the way to use Cp_2TiCl in catalytic amounts for the reductive opening of epoxides with or without deoxygenation and to create new C-C bonds.



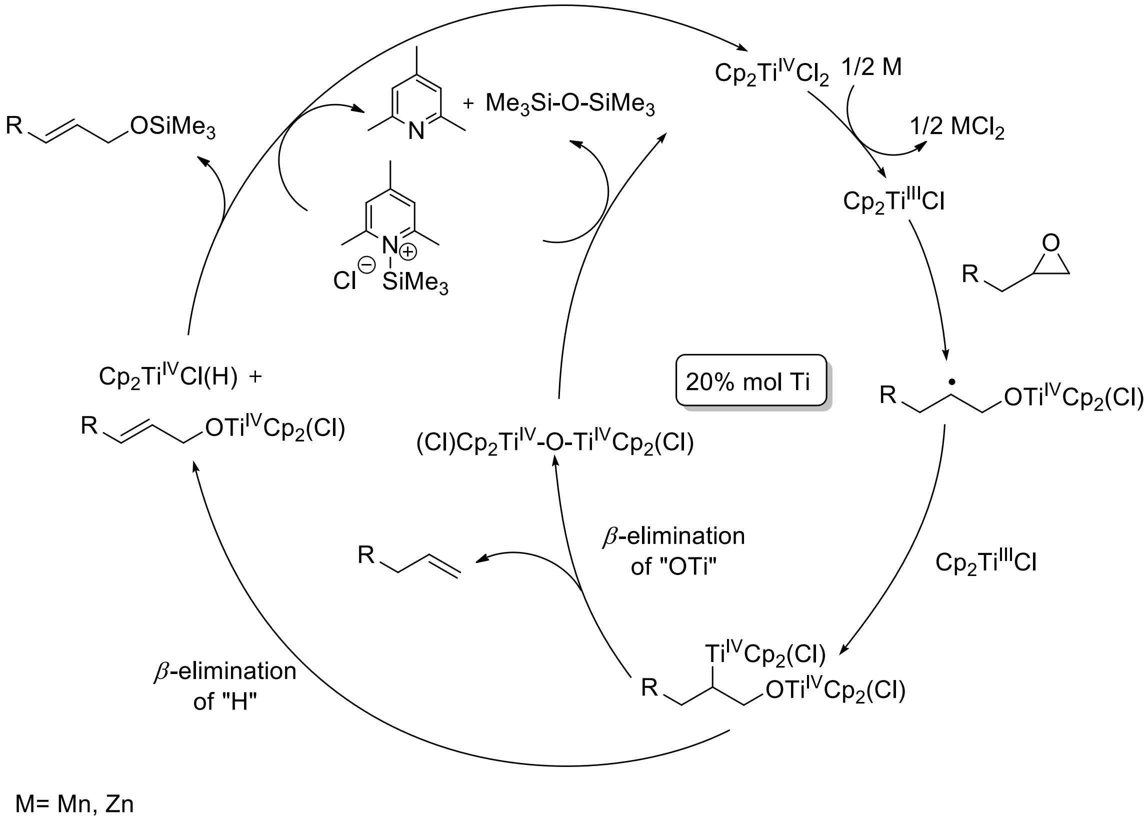
M = Mn, Zn
$R_1 = CH_3$, $R_2 = CH_2CH_2Ph$

Base = 2,4,6-collidine
Yield = 88%

Scheme 3. Epoxide opening with catalytic Cp_2TiCl.

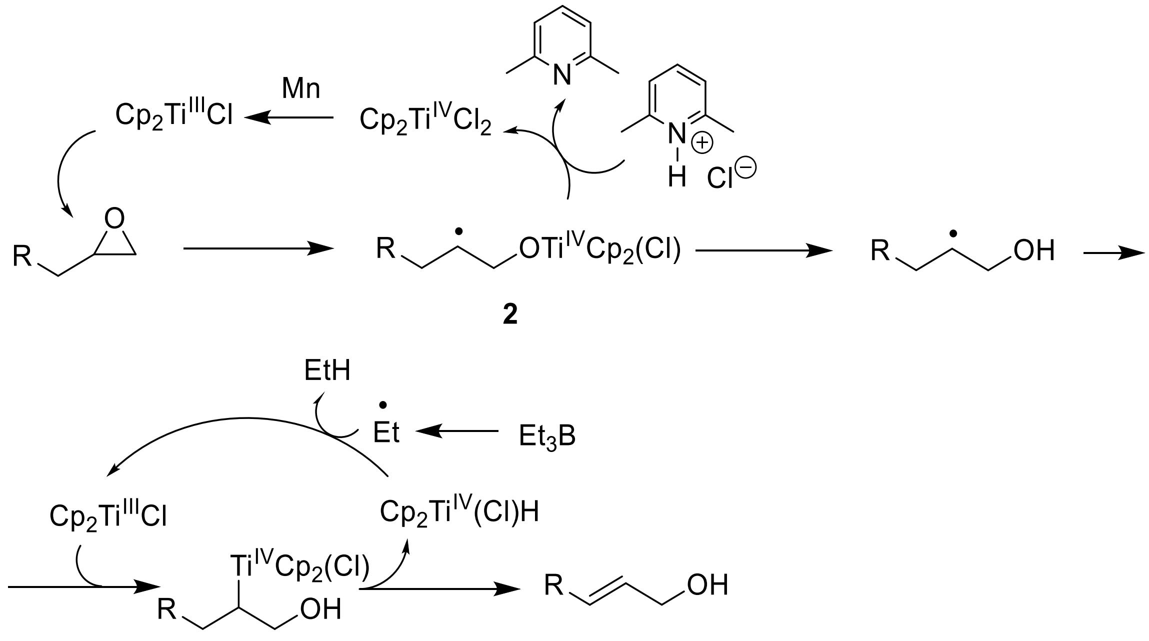
In this catalytic cycle hydrochloride-substituted pyridins (collidine hydrochloride) were used as a useful acid to protonate either a Ti-O or a Ti-C bond in order to regenerate Cp_2TiCl_2. However, this catalytic cycle was not capable to regenerate Cp_2TiCl_2 from $Cp_2Ti(Cl)H$, acetoxy-titanium derivatives or derivatives with "Ti^{IV}-O-Ti^{IV}" bonds. These latter derivatives of titanium are formed when the reaction does not finish under reducing conditions.

A second catalytic procedure was developed by Oltra *et al*.[17] who used 2,4,6-trimethyl-1-trimethylsilylpyridinium chloride [Coll/TMSCl] to regenerate Cp_2TiCl_2 from $Cp_2Ti(Cl)H$ and alcoxy-titanium derivatives (Scheme 4). In this process the homolytic opening of the epoxide generates a radical which can be trapped by a second $Cp_2Ti^{III}Cl$, leading to the formation of a C-Ti bond. Depending on the nature of the molecule it can follow two different paths, β-elimination of "OTi" and/or β-elimination of "H". In both cases the alcoxy-titanium derivatives and Cp_2TiClH would be transformed into Cp_2TiCl_2 by [Coll/TMSCl]. The new catalytic cycle allowed the preparation of alkenes and allylic alcohols from epoxides using catalytic amounts of Cp_2TiCl. This novel reagent combination subsequently played an important role in many of the chemical transformations catalysed by titanocene monochloride (Cp_2TiCl).



Scheme 4. Catalytic Cp_2TiCl epoxide opening using TMSCl/2,4,6-collidine as regenerator.

Takahashi *et al.*[18] combined 2,6-lutidine/HCl and Et_3B as mediators to regenerate Cp_2TiCl_2 from organotitanium(IV) species. 2,6-lutidine.HCl is thought to produce Cp2TiCl2 from titanium alkoxide **2**, whilst Et_3B promotes the conversion of $Cp_2Ti(Cl)H$ into Cp_2TiCl (Scheme 5). However, this catalytic cycle has not been widely used, possibly because the reaction shows lower levels of diastereoselectivity.



Scheme 5. Catalytic Cp_2TiCl epoxide opening using Et_3B/2,6-lutidine hydrochloride as regenerator.

Following the discovery of these catalytic cycles, Cp_2TiCl emerged as a powerful tool in organic chemistry. In fact, this SET reagent is capable of promoting and/or catalyzing transformations such as radical opening reactions, radical cascade cyclizations, coupling reactions, THF-ring formation reactions, H-atom transfer (HAT) to alkenes, alkynes and ketones, Barbier-type reactions, umpolung reactions, deoxygenation reactions and polymerization reactions (see section 3). In general, these transformations, that allow the preparation of interesting structures, occur under mild conditions compatible with several functional groups, are environmentally friendly and use simple experimental procedures. These reactions are explained in more detail in the next section.

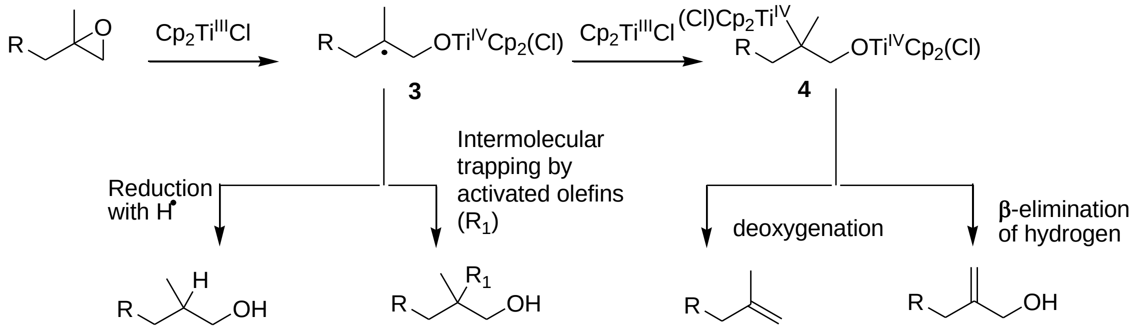
3. PRINCIPAL TRANSFORMATION MEDIATED BY Cp_2TiCl

In all reported procedures presented in this section the active species is written as $Cp_2Ti^{III}Cl$, either in catalytic or stoichiometric amounts, and is prepared in situ by reduction of Cp_2TiCl_2 with Zn or Mn dust.

3.1. Radical opening reactions

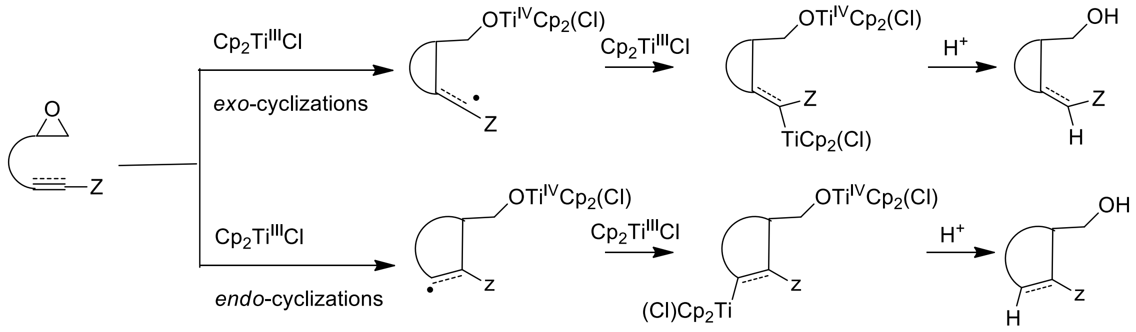
3.1.1. Radical opening of epoxides

Rajanbabu and Nugent[3a, 14] described how Cp_2TiCl promotes the regioselective homolytic ring opening of epoxides to generate the β-titanoxy radical **3** (Scheme 6). This radical reacts with a second molecule of Cp_2TiCl to generate the alkyltitanium complex **4** (Scheme 6). A number of interesting organic reactions starting from **3** or **4** have been developed. Complex **4** has been used to generate olefins[14d] [12d] by the elimination of $(Cp_2TiCl)_2O$ and to prepare allylic alcohols[19] by β-elimination of $Cp_2Ti(Cl)H$. Alternatively to the deoxygenation protocol, the radical intermediate **3** can be reduced, when it is trapped by an H-atom donor such as 1,4-cyclohexadiene or t BuSH, to afford alcohols[3a] with the opposite regiochemistry to that expected from the reduction with metal hydrides. More recently, Oltra *et al.*[20, 17b] reported that water can act as an efficient hydrogen-atom source in radical reductions mediated by Cp_2TiCl, avoiding the use of the conventional hydrogen atom sources used in radical chemistry such as 1,4-CHD, Bu_3SnH or 2-methylpropan-2-thiol, that are toxic, expensive and/or foul smelling. This novel procedure of reduction of radicals by hydrogen-atom transfer from water is explained in more detail in section 3.6.1. In the presence of activated olefins, radical **3** can also react with unsaturated groups to create new carbon-carbon bonds.[3a]



Scheme 6. Cp_2TiCl epoxide opening in synthetic organic chemistry.

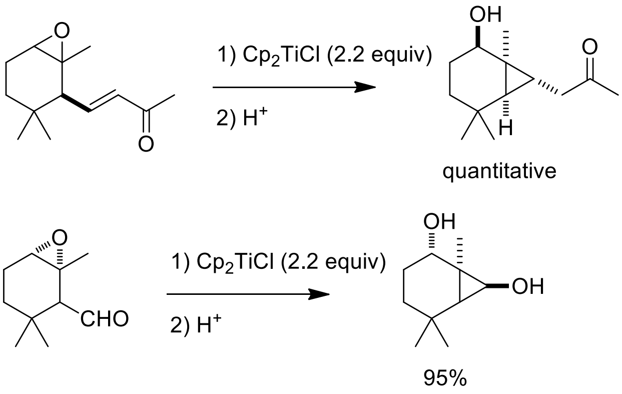
These protocols have been used by different authors to develop new cyclizations of unsaturated epoxides. Specifically, epoxyalkenes and epoxyalkynes,[14, 21] epoxyaldehides,[22] epoxynitriles,[22] epoxyketones,[22] epoxyesters[23] and epoxyamides[23] have been used as substrates in Cp_2TiCl-mediated cyclization reactions. In all these cases, the proposed mechanism for cyclization involved alkytitanium(III) species, formed by the trapping of the carbon-centered radical resulting from the cyclization step by a second molecule of Cp_2TiCl (Scheme 7).



Z= funtional group ester, nitrile, ketone and aldehyde

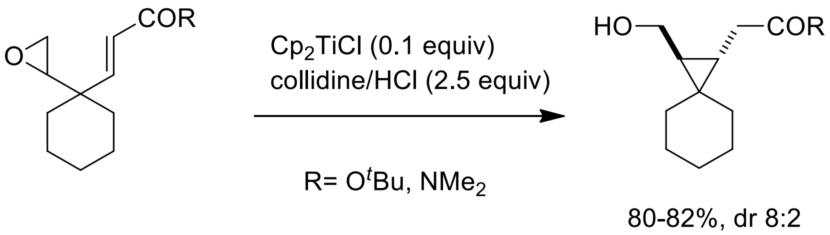
Scheme 7. Cp_2TiCl promoted cyclizations of remotely functionalized epoxides.

Fernández-Mateos *et al.*[22] developed a 3-exo cyclization using epoxyaldehydes and epoxyketones as starting materials (Scheme 8).



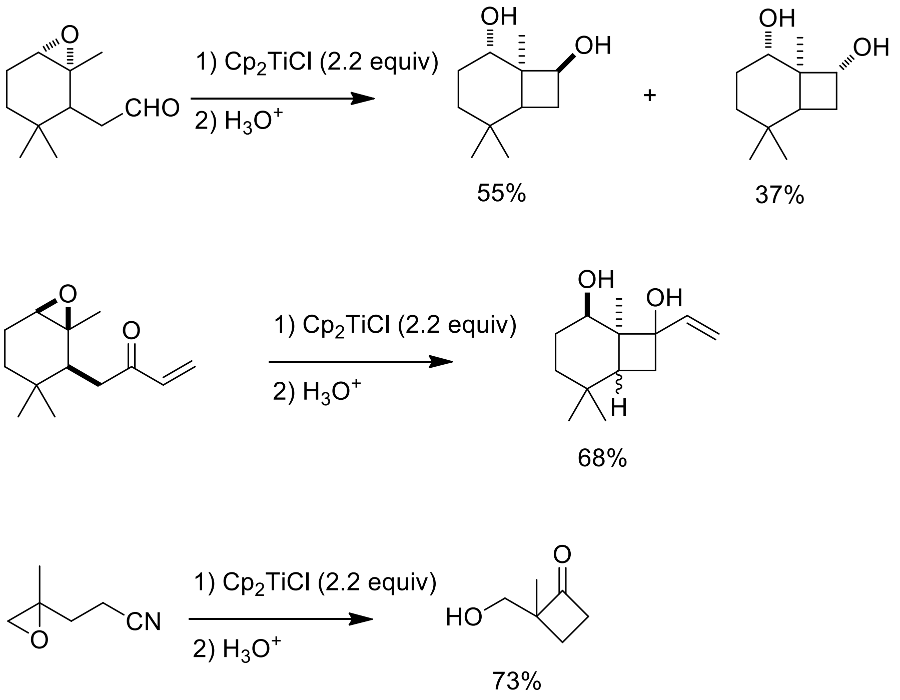
Scheme 8. Cp_2TiCl epoxide opening leading to cyclopropanes through 3-exo cyclizacions.

Later, a more versatile and efficient 3-exo cyclization reaction was developed by Gansäuer *et al.*[23] who, using unsaturated epoxides (Scheme 9), established that these cyclizations are thermodynamically favourable and that the efficiency of the reaction depends on the ease with which the cyclopropyl radical is trapped by another molecule of Cp_2TiCl.



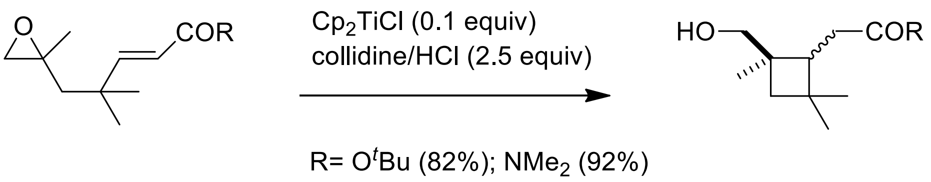
Scheme 9. Catalytic Cp_2TiCl epoxide opening in 3-exo cyclizacions.

An efficient 4-exo cyclization was developed by Fernández-Mateos *et al.*[22] using epoxyaldehides, epoxynitriles, and conjugated epoxyketones (Scheme 10).



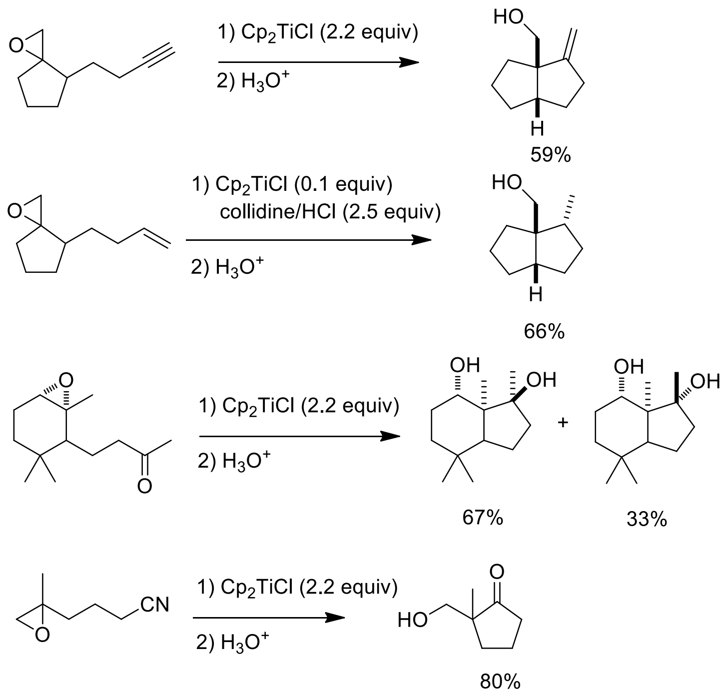
Scheme 10. Cp_2TiCl epoxide opening leading to cyclobutanes through 4-exo cyclizacions.

Gansäuer *et al.*[24] reported a combined computational and experimental study of the development of the first general titanocene catalyzed synthesis of substituted cyclobutanes via 4-exo cyclizations of unsaturated epoxydes (Scheme 11).



Scheme 11. Catalytic Cp_2TiCl epoxide opening in 4-exo cyclizacions.

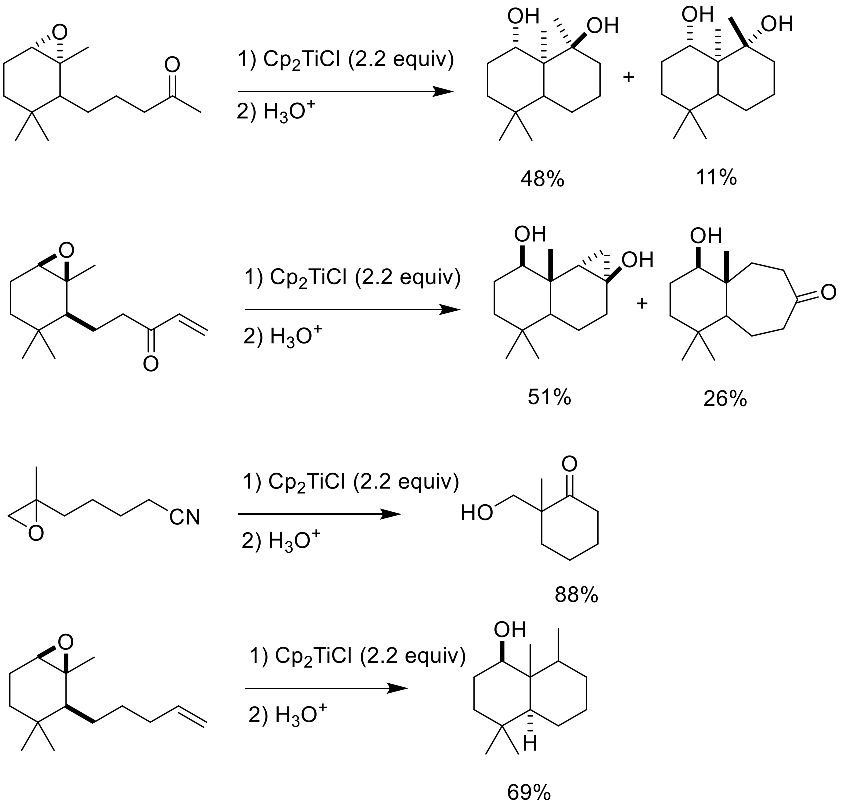
Versatile 5-exo cyclizations were developed by Nugent and Rajanbabu,[14] Gansäuer *et al.*[21] and Fernández-Mateos *et al.*[22] using epoxyalkenes, epoxyalkynes, epoxyketones and epoxynitriles (Scheme 12).



Scheme 12. Cp_2TiCl mediated epoxide opening in 5-exo cyclizacions.

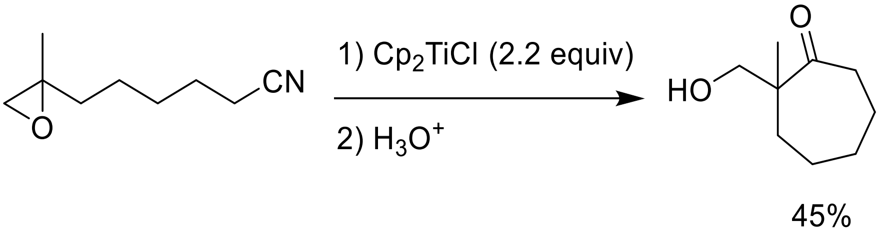
This cyclization, was also used by Gansäuer *et al.*[21b, 23] for the synthesis of tetrahydrofurans and pyrrolidines.

An important 6-exo cyclization using epoxyalkenes,[25] conjugated epoxyketones[25] and epoxynitriles[22b] was developed by Fernández-Mateos *et al.* (Scheme 13).



Scheme 13. Stoichiometric Cp_2TiCl epoxide opening in 6-exo cyclizacions.

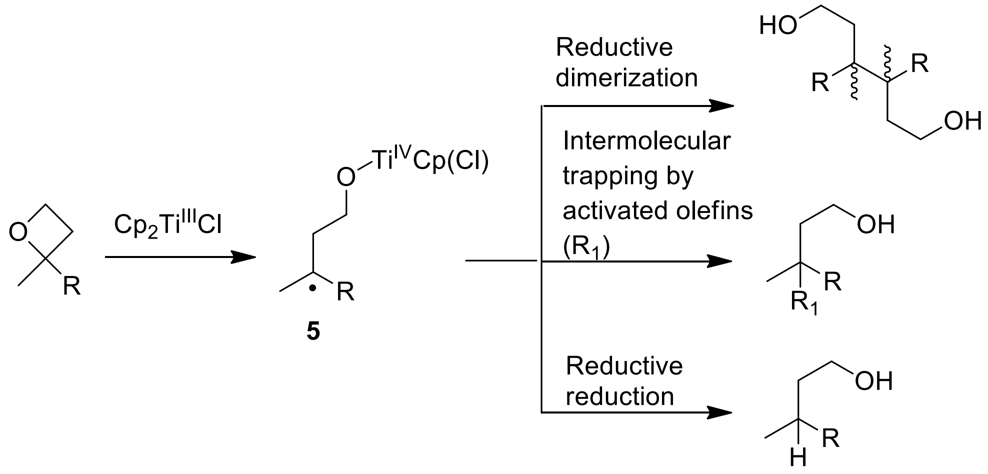
Finally, 7-exo cyclizations have been developed using epoxynitriles[22] and epoxyketones[25] (Schemes 13 and 14).



Scheme 14. Stoichiometric Cp_2TiCl epoxide opening in 7-exo cyclizacions.

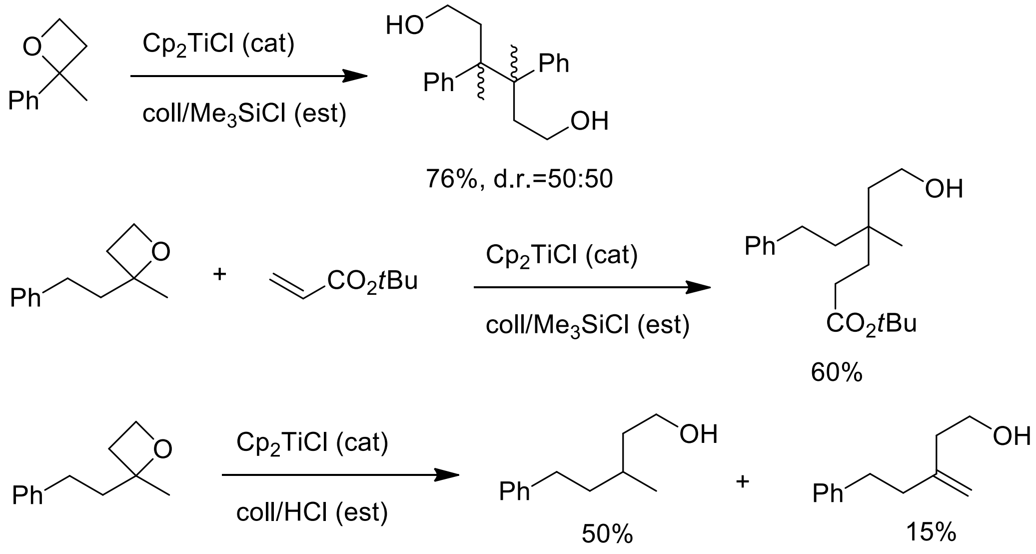
3.1.2. Radical opening of oxetanes

In 2008, Gansäuer *et al.*[26] reported the first opening of oxetanes and proposed a mechanism for this process through a combined synthetic and theoretical study. The computational study suggested that higher activation and reaction energies than those for the related epoxide opening reaction. Another significant difference is that the resulting γ-titanoxy radicals **5** are not shielded by the metal and its ligands, and therefore, behave like typical free radicals (which can undergo dimerization reactions, reductions and additions to acrylates) (Scheme 15).



Scheme 15. Cp_2TiCl oxetane opening in synthetic organic chemistry.

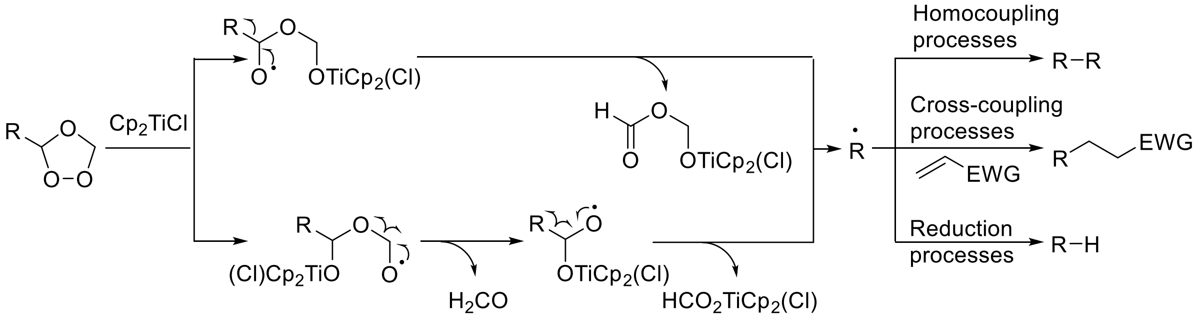
This protocol constitutes a smooth way of preparation of a potentially interesting class of functionalized radicals that can be used in typical reactions of free radicals (Scheme 16).



Scheme 16. Catalytic Cp_2TiCl oxetane opening.

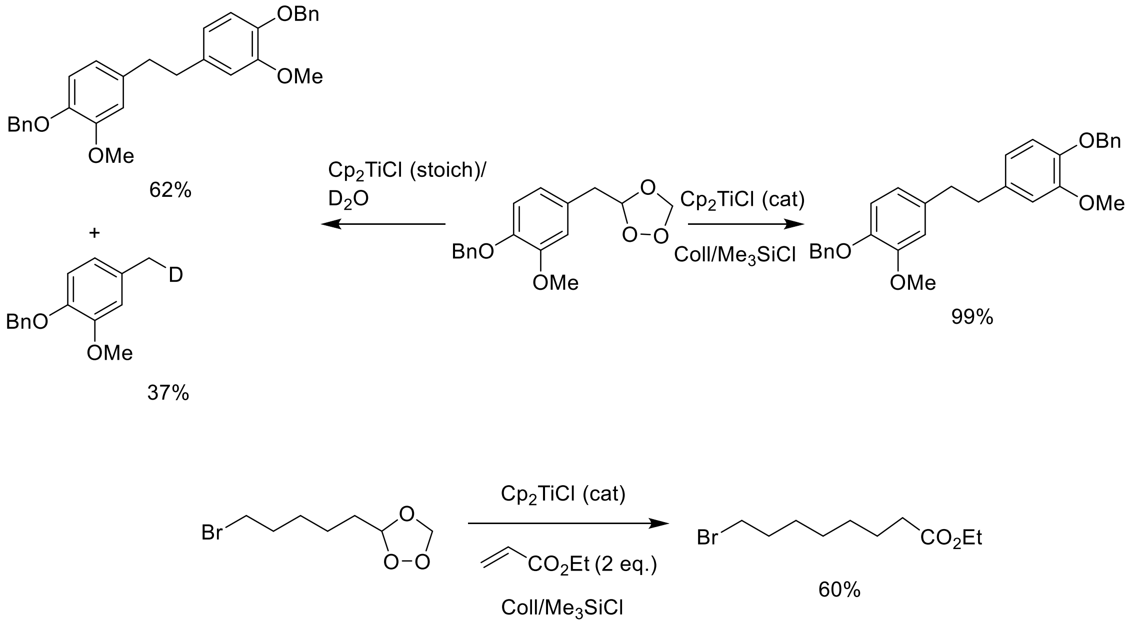
3.1.3. Radical opening of ozonides

Rosales and Rodríguez-García *et al.*[27] reported by the first time the unprecedented homolytic opening of ozonides promoted and catalyzed by Cp_2TiCl. This novel reaction describes the use of ozonides as useful carbon radical precursors, suitable to form C-C bonds via, either homo- or cross-coupling processes. On the other hand, these radicals can also be reduced to alkanes with hydrogen donors such as water. The presumably weak O-O bond of this new functional group offered an attractive starting point to initiate reagent-controlled free-radical processes under mild conditions.[28] The homolytic opening of ozonides by oxophilic Cp_2TiCl can generate two oxygenated radicals, which, via two alternative decarbonylation pathways, could eventually converge to a carbon radical suitable for the formation of new C-C bonds or for reduction to alkanes (Scheme 17).



Scheme 17. Cp_2TiCl homolytic ozonide opening in synthetic organic chemistry

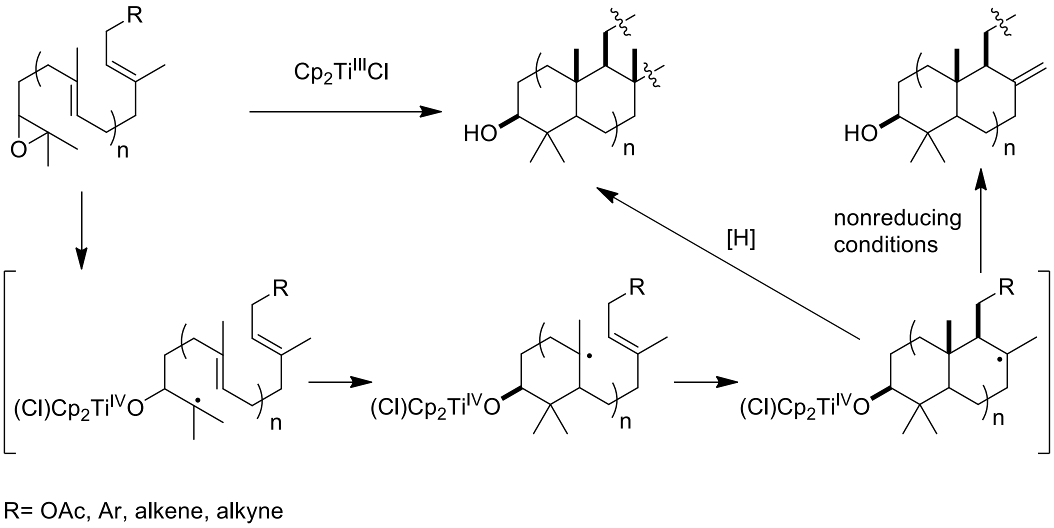
Thus, when ozonides were treated with Cp_2TiCl, homocoupling, cross-coupling and reduction products were obtained in high yields (60-99%), depending on the experimental conditions (Scheme 18). In the presence of stoichiometric amounts of Cp_2TiCl two competing processes are observed: homodimerization of the carbon radical and formation of an alkyltitanium species, which suffers D_2O hydrolysis leading to the deuterated reduction product.



Scheme 18. Stoichiometric versus catalytic Cp_2TiCl homolytic ozonide opening

3.2. Radical cascade cyclizations

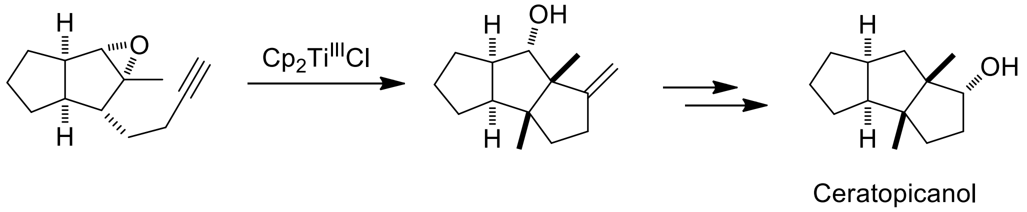
The use of Cp_2TiCl-mediated radical cascade poly- and monocylization reactions of monoepoxides of acyclic polyprenes constitutes a straightforward, biomimetic like, synthetic strategy of natural terpenes. Therefore, it has been extensively used during the last 15 years.[3d, 29, 36] In the context of terpene synthesis, the radical obtained after the regioselective homolytic ring opening of the epoxide provides the starting point of multiple intramolecular additions to alkenes and alkynes, thus generating the corresponding cyclic products (Scheme 19).



Scheme 19. Synthesis of terpenes through Cp_2TiCl cascade cylizations of acyclic monoepoxi-polyprenes.

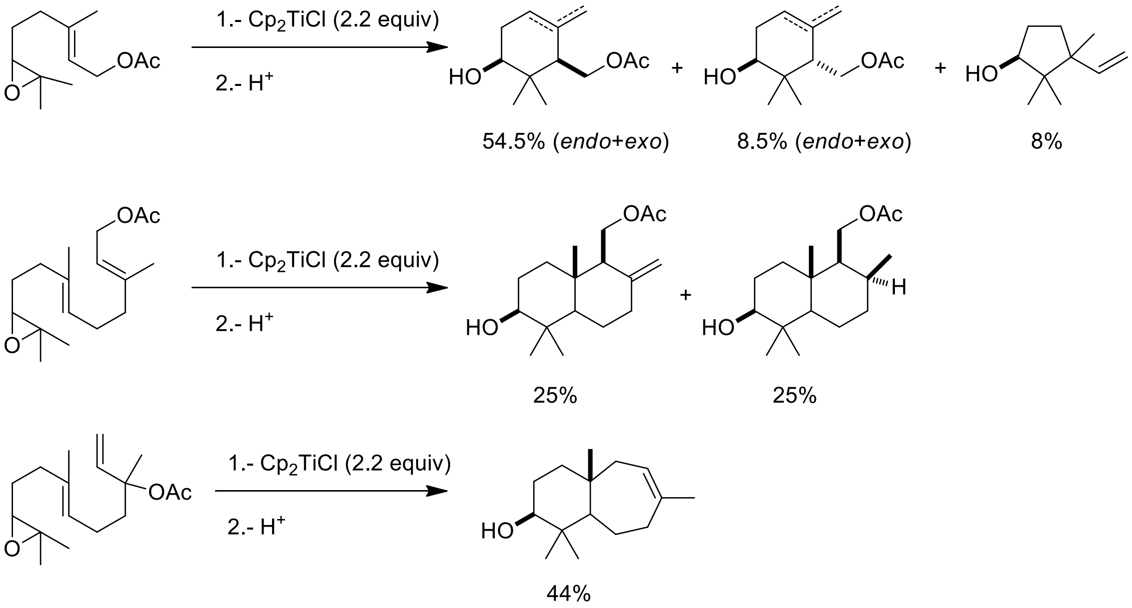
Cationic initiated cascade cyclization is a well know procedure for the synthesis of natural products.[30] However, the more important advantage of these radical cascade cyclizations, however, is the high diastereoselectivity of the tandem cyclization process. Furthermore, Cp_2TiCl promoted radical cascade cyclizations proceed under milder conditions than their cationic analogues, and can be terminated by a β-hydride elimination. This last point is of paramount importance for the completion of the synthesis of a lot of natural products (aureol, umbrosone, puupehedione, natural furanoditerpenoids, among others).

In a seminal work, Clive *et al.*[31] reported the first example of Cp_2TiCl-mediated cyclization as the key step for the synthesis of ceratopinacol, a natural sesquiterpene (Scheme 20).



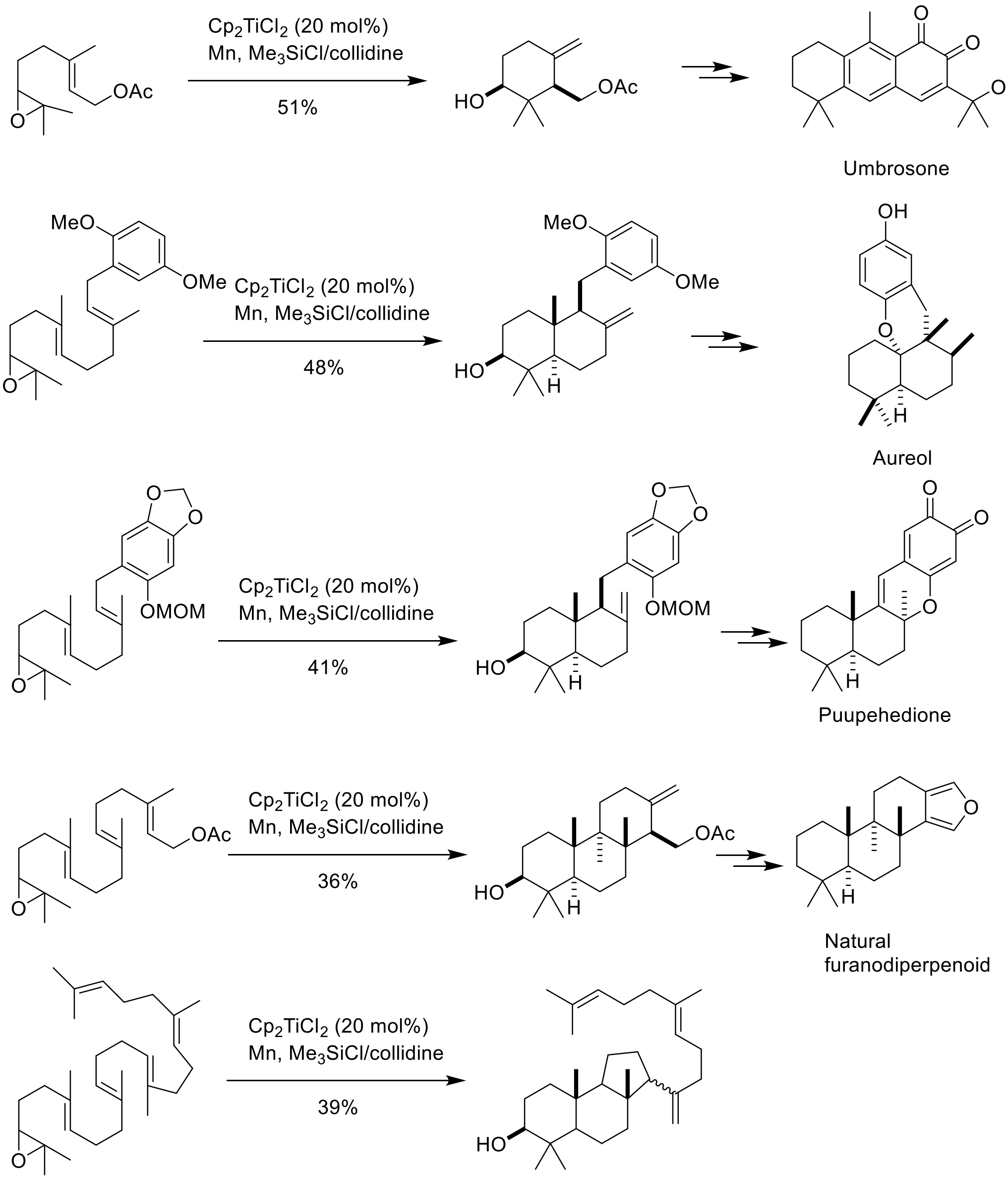
Scheme 20. Cp_2TiCl mediated synthesis of ceratopicanol.

In 2001, a general procedure for the synthesis of terpenoids by homolytic opening of monoepoxides of acyclic polyprenes was reported by Barrero *et al.* [32] (Scheme 21).



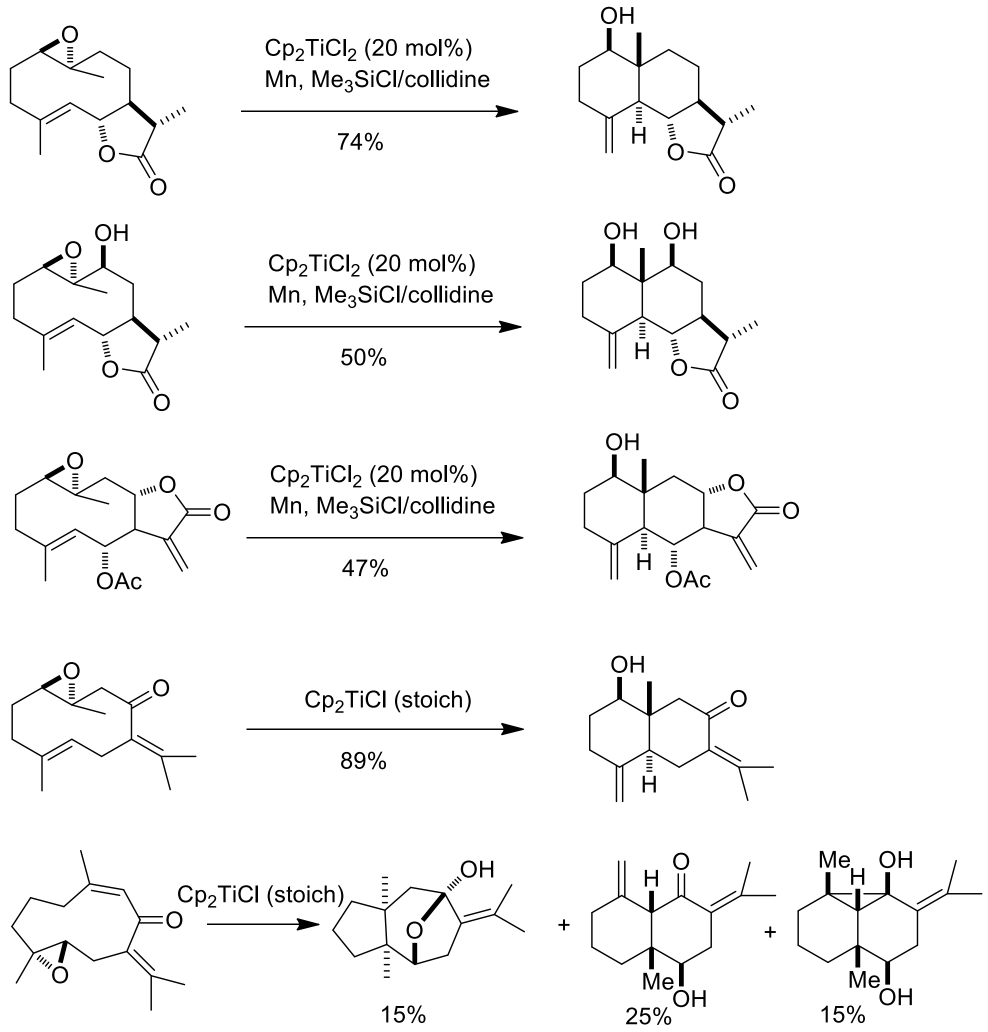
Scheme 21. Cp_2TiCl mediated synthesis of mono and sesquiterpenes.

The use of stoichiometric amounts of Cp_2TiCl was the main drawback of a synthetic strategy that allowed for the stereoselective preparation of polycyclic systems with several chiral centers in a single reaction. However, the introduction of Oltra's catalytic cycle[17] in order to regenerate Cp_2TiCl_2 from derivates of titanium such as $Cp_2Ti(Cl)H$ revalued this general procedure of synthesis of terpenoids by homolytic opening of acyclic epoxypolyprenes (Scheme 22, yielding high quantities of terpenoids with excellent stereoselectivities, specifically cyclization products with exo double bonds.[17, 33]



Scheme 22. Cp_2TiCl catalyzed synthesis of terpenoids.

During the thesis of Rosales, the complex Cp_2TiCl has also been used by Oltra *et al.*[17, 20, 34] and later by Barrero *et al.*[35] in transanular cyclization reactions. In this context, the exposure of epoxygermacrolides to substoichiometric amounts of Cp_2TiCl led to the formation of an array of eudesmanolides in high yields and with excellent selectivities (Scheme 23). The cyclization of an epoxygermacrone with Cp_2TiCl produced bicyclic and tricyclic compounds very useful as intermediates in the synthesis of several bioactive natural sesquiterpenes. This methodology has been used in the synthesis of several different, natural compounds.



Scheme 23. Cp_2TiCl mediated transanular cyclization of epoxygermacrolides.

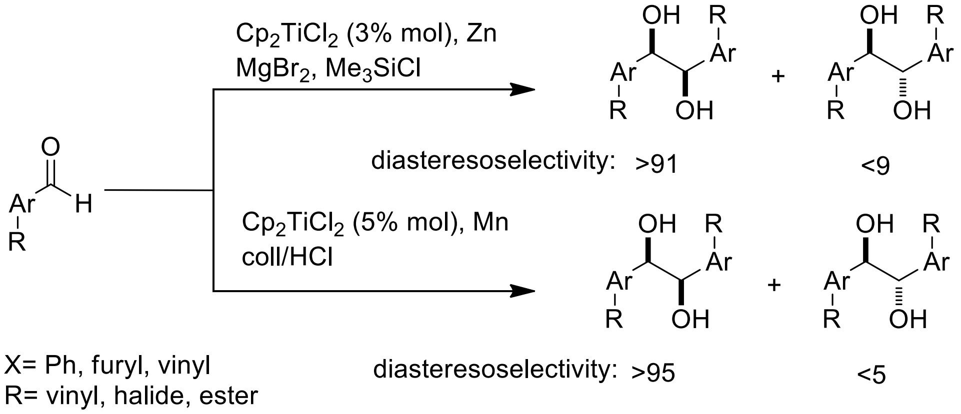
In summary, this general procedure has considerably facilitated the straightforward synthesis of several cyclic terpenes, including monoterpenoids, sesquiterpenoids, diterpenoids, triterpenoids, meroterpenoids and the ambergris-type odorant α-ambrinol. For excellent reviews on the applications of

Cp_2TiCl to the synthesis of natural products see Oltra *et al.*,[36, 3d] Barrero *et al.*,[29a] Gansäuer *et al.*[29c] and Cuerva *et al.*[29b]

3.3. Coupling reactions

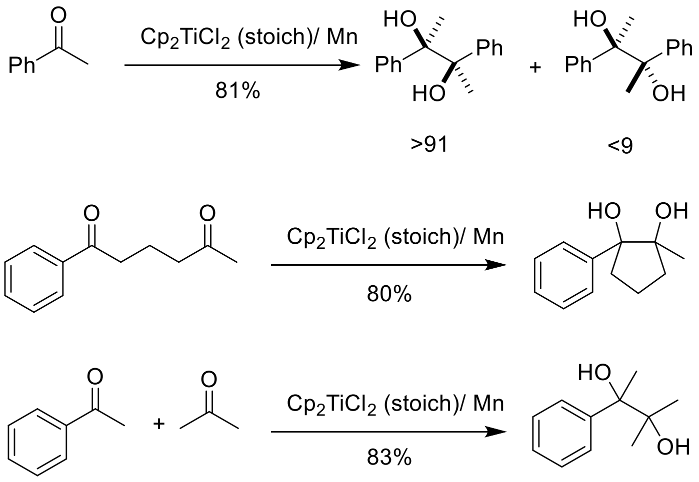
3.3.1. Coupling reactions of aromatic and α,β-unsaturated aldehydes and ketones

The selective coupling of carbonyl compounds is the most direct way to 1,2-diols by forming a functionalized C-C bond. In 1987, Inaga *et al.*[37] reported the first pinacol coupling of aromatic and α,β-unsaturated aldehydes using equimolecular quantities of Cp_2TiCl. Later, Gansäuer *et al.*[38] developed a new procedure using catalytic amounts of Cp_2TiCl, yielding the corresponding 1,2-diols at room temperature with good yields and diastereoselectivities (Scheme 24).



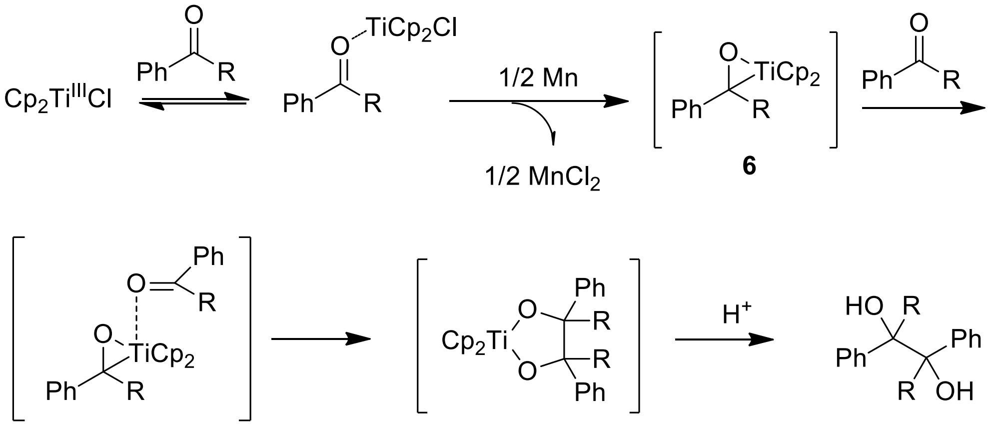
Scheme 24. Cp_2TiCl catalytic pinacol couplings.

Oltra *et al.*[39] presented a new application for the reductive coupling of carbonyl compounds promoted by Cp_2TiCl using as starting materials aromatic ketones (Scheme 25).



Scheme 25. Inter and intramolecular Cp_2TiCl pinacol couplings.

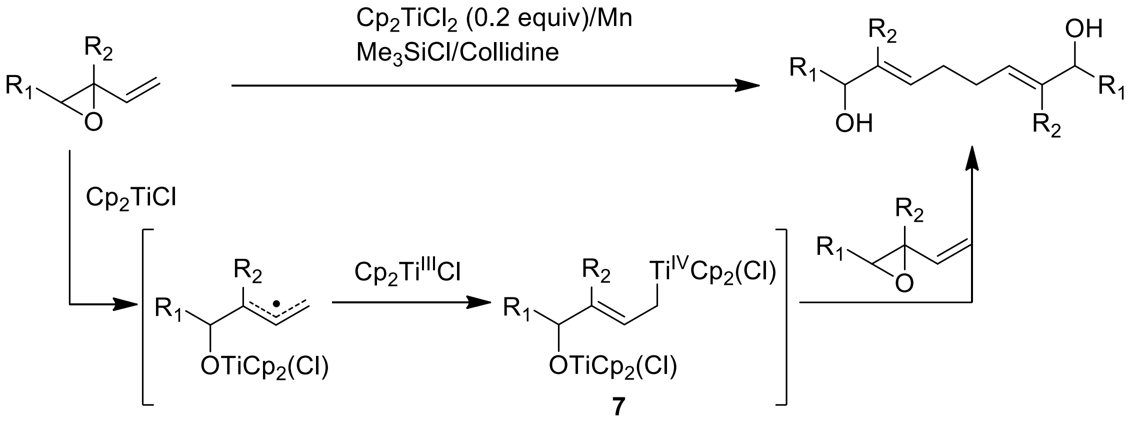
The pinacolization of aromatic and α,β-unsaturated aldehydes mediated by Cp2TiCl were reported as an inner-sphere electron transfer generating the corresponding titanoxy radicals.[37-40] However, the free-radical character conventionally assumed for these chemical processes should be reconsidered on the basis of the study by Rosales and Oltra *et al.*[41] These authors reported a detailed experimental study of the role played by each of the reagents involved in the homocoupling and in the selective reduction of aromatic ketones in aqueous medium, promoted by Cp2TiCl/Mn. It was observed that Mn is not only required to reduce $Cp_2Ti^{IV}Cl_2$ to $Cp_2Ti^{III}Cl$ but also for the irreversible generation of a titanaoxirane **6**, which, under anhydrous conditions is transformed into pinacol-coupling products (Scheme 26). These results will change the way chemists think about these systems.



Scheme 26. Plausible mechanism for the Cp_2TiCl pinacol coupling.

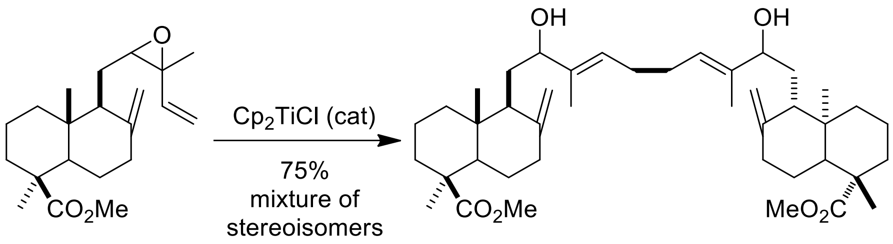
3.3.2. Homocoupling of vinylepoxides

Barrero *et al.*[42] developed a new homolytic opening of vinylepoxides mediated by Cp_2TiCl. This work completed the study of vinylepoxides reactivity with Cp_2TiCl that had been initiated originally by Yaday *et al.*[43] The homocoupling reaction reported by Barrero *et al.*[42] involved a new C-C bond-forming method and took place via an ionic SN2´process between the allyltitanium **7** species and a second molecule of vinylepoxide (Scheme 27).



Scheme 27. Cp_2TiCl catalyzed homocoupling of vinylepoxides.

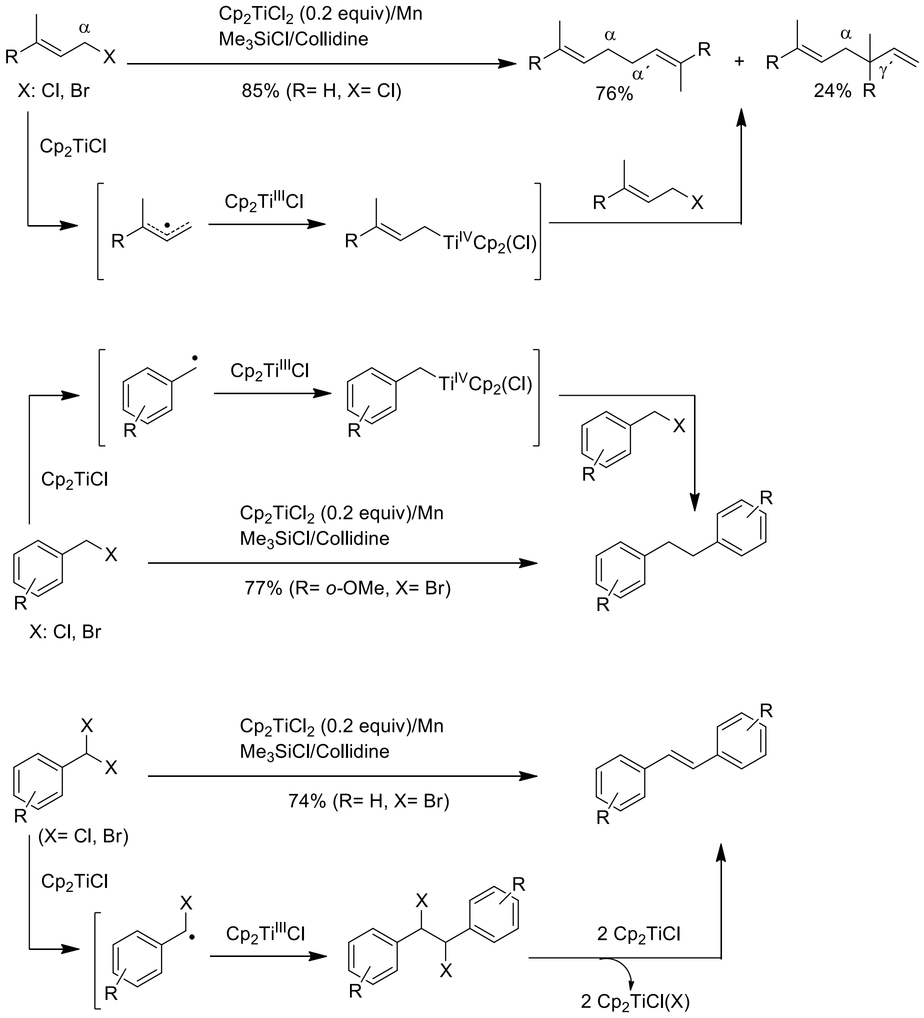
The reaction affords medium-to-high yields of homocoupling products under mild and neutral conditions (Scheme 28).



Scheme 28. Synthesis of homo-onoceranes by Cp_2TiCl catalyzed homocoupling of vinylepoxides.

3.3.3. Homocoupling of allyl halides and benzyl halides

The first report on the coupling reaction of benzylic and allylic halides using equimolecular quantities of Cp_2TiCl to yield the corresponding homocoupling products was reported by Yalong *et al*.[44] Later, Barrero *et al*.[45] reported the reduction of benzylic halides, benzylic gem-dibromides and allylic halides by catalytic Cp_2TiCl to give the corresponding homocoupling products in high yields. Several experiments suggested the presence of an allylic or benzylic titanium intermediate, which reacts with the starting allylic or benzylic halide to yield the corresponding homocoupling product (Scheme 29).

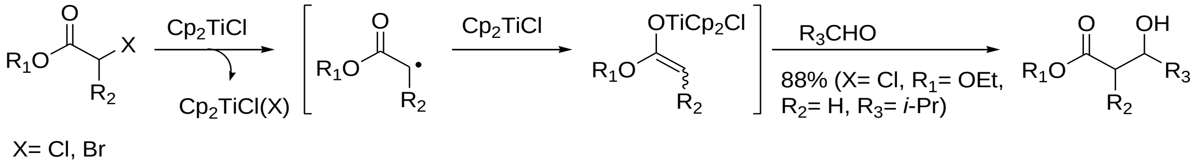


Scheme 29. Cp_2TiCl catalyzed homocoupling of allyl and benzyl halides.

This method has been used for the synthesis of natural products in high yields.[41]

3.3.4. Cp2TiCl-promoted Reformatsky additions

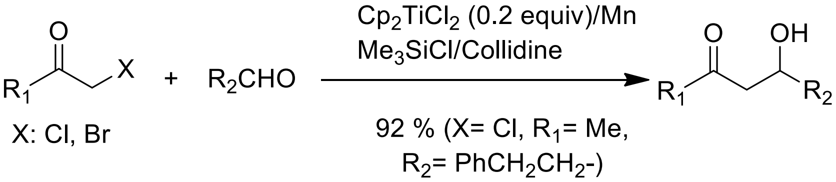
The Reformatsky reaction is a well-established method for the formation of β-hydroxy esters.[46] A novel methodology employing Cp_2TiCl to promote Reformatsky-type reactions between α-halo esters and aldehydes was reported by Little *et al.*[47] In this reaction the halide is extracted via a single electron transfer by a stoichiometric amount of Cp_2TiCl to produce a radical adjacent to the carbonyl ester (Scheme 30). The reduction of the radical by another equivalent of Cp_2TiCl resulted in the formation of an enolate. Trapping of this enolate with an aldehyde leads to the synthesis of more complex β-hydroxy esters (Scheme 30).



Scheme 30. Synthtesis of β-hydroxyesthers by Cp_2TiCl promoted Reformatsky additions.

This new reaction is operationally simple, with an anti diastereoselectivity and compatible with a wide range of functionalities.

Subsequently Oltra *et al*.[48] reported the first Cp_2TiCl-catalyzed Reformatsky-type reactions between α-haloketones and aldehydes (Scheme 31). The mechanism reported was similar to that described by Little *et al*. [47] in the reaction between α-halo esters and aldehydes.

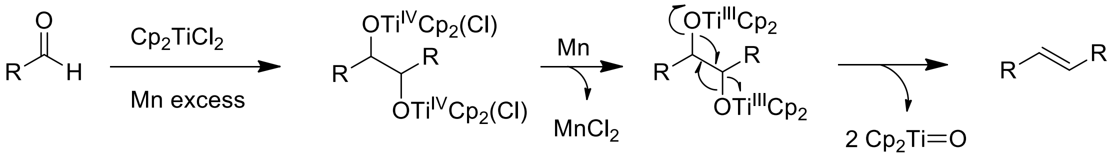


Scheme 31. Cp_2TiCl catalyzed Reformatsky additions.

The reaction affords medium-to-high yields of β-hydroxy ketones under mild and neutral conditions compatible with ketones and other electrophiles.

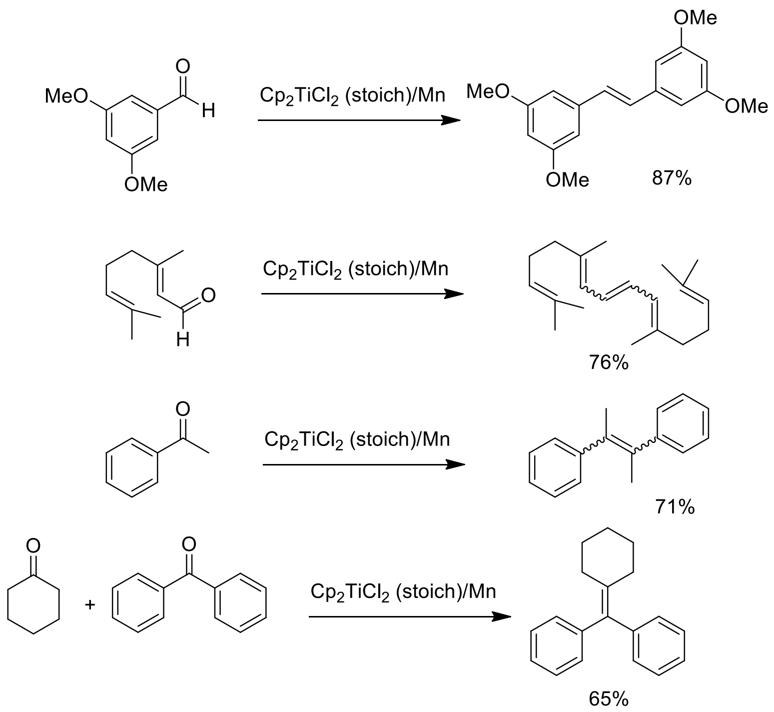
3.3.5. McMurry-type coupling reactions

Barrero *et al*.[49] reported that Cp_2TiCl was able to induce reductive carbonyl coupling in short reaction times and with total reproducibility. The mechanistic evidence reported proved for the first time the involvement of Ti(III) pinacolates in the deoxygenation step of this McMurry olefination (Scheme 32). For over 35 it years was widely accepted that either Ti(II) or Ti(0) was the active species in the reductive process of the McMurrry reaction.[50] However, Barrero *et al.*[49] showed conclusively that Ti(III) was an active species in the reductive process of the Cp_2TiCl McMurry-type reaction. This observation has shed new light on one of the mechanistically more complex transformations in organic chemistry (McMurry reaction).[51]



Scheme 32. Plausible Cp_2TiCl promoted McMurry coupling mechanism.

Different aromatic and α,β-unsaturated aldehydes and ketones were transformated into corresponding olefins using catalytic and stoichiometric amounts of Cp_2TiCl (Scheme 33).

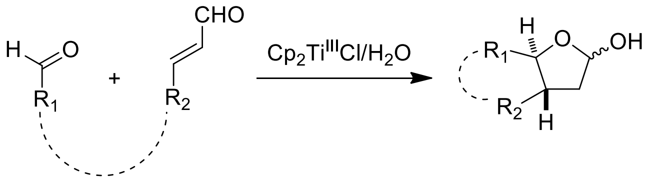


Scheme 33. Cp_2TiCl mediated McMurry couplings.

3.4. Umpolung reactions

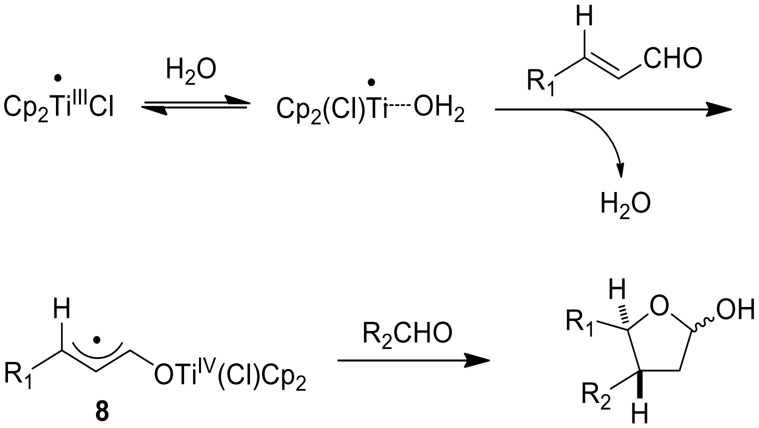
3.4.1. Michael-type additions of ldehydes to conjugated enals

Oltra *et al.*[52] reported the first example of Umpolung type reactions promoted by Cp_2TiCl in the presence of water. Specifically, a novel, stereoselective C-C bond-forming method was described that provided γ-lactols by radical coupling between aldehydes and conjugated alkenals mediated by Cp_2TiCl/H_2O (Scheme 34).



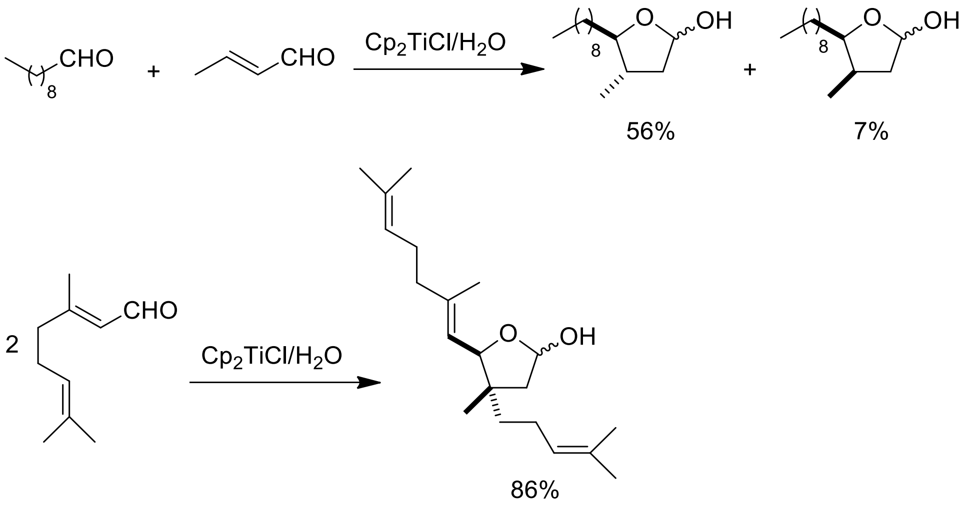
Scheme 34. Umpolung-like addition of aldehydes to α,β-usaturated aldehydes promoted by Cp_2TiCl/H_2O.

These authors reported that in the presence of water, Cp_2TiCl presumably coordinates H_2O to yield the aqua-complex (Cp2TiCl-H2O). By coordination between the aqua-complex and a conjugated alkenal, a titanoxy-allyl-type radical **8** is formed, a complex having only 16 electrons in the valence shell, and therefore having the ability to coordinate again with the oxygen atom of an aldehyde to generate the corresponding γ-lactol (Scheme 35).



Scheme 35. Proposed mechanism for the umpolung-like addition of aldehydes to α,β-unsaturated aldehydes promoted by Cp_2TiCl/H_2O.

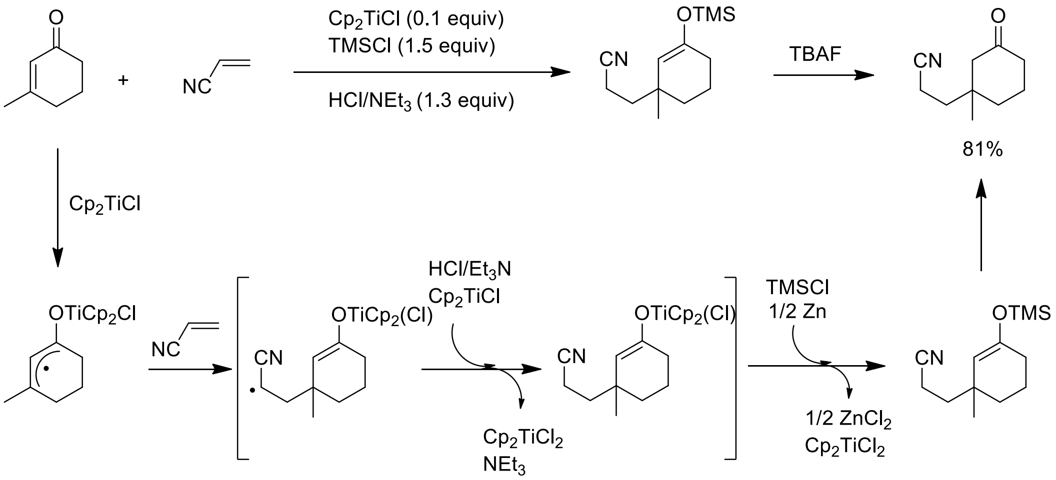
This method was used for both intramolecular reactions and cyclizations providing γ-lactols in high yields (Scheme 36).



Scheme 36. Synthesis of γ-lactols from aldehydes and α,β-unsaturated aldehydes in the presence of Cp_2TiCl/H_2O.

3.4.2. Reductive cross-coupling of enones with acrylonitriles

In 2011, Streuff[53] reported that Cp_2TiCl can catalyze the reductive alkylation of enones with acrylonitriles to yield 1,6-difunctionalized ketonitriles by a redox Umpolung process (Scheme 37).



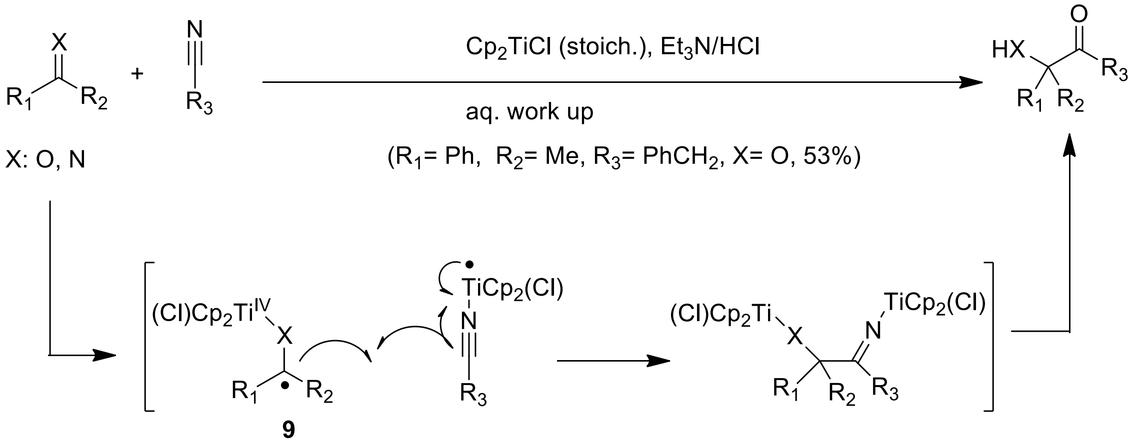
Scheme 37. Umpolung-like coupling of enones with acrylonitriles catalyzed by Cp_2TiCl.

In this reaction, Cp_2TiCl transfers a single electron to the enone substrate and generates an allylic radical. This electron-rich radical adds to acrylonitrile at the β position. The intermediate is quickly reduced and protonated by a second Cp_2TiCl and the resulting Ti^{IV} enolate is displaced by chlorotrimethylsilane (Scheme 37).

This new reaction allowed the catalytic formation of sp^3-sp^3 carbon-carbon bonds by a redox Umpolung process. This procedure was the first example of a transition metal catalyzed reductive cross-coupling reaction of activated alkenes.

3.4.3. Cross coupling reaction of ketones or iminies and nitriles

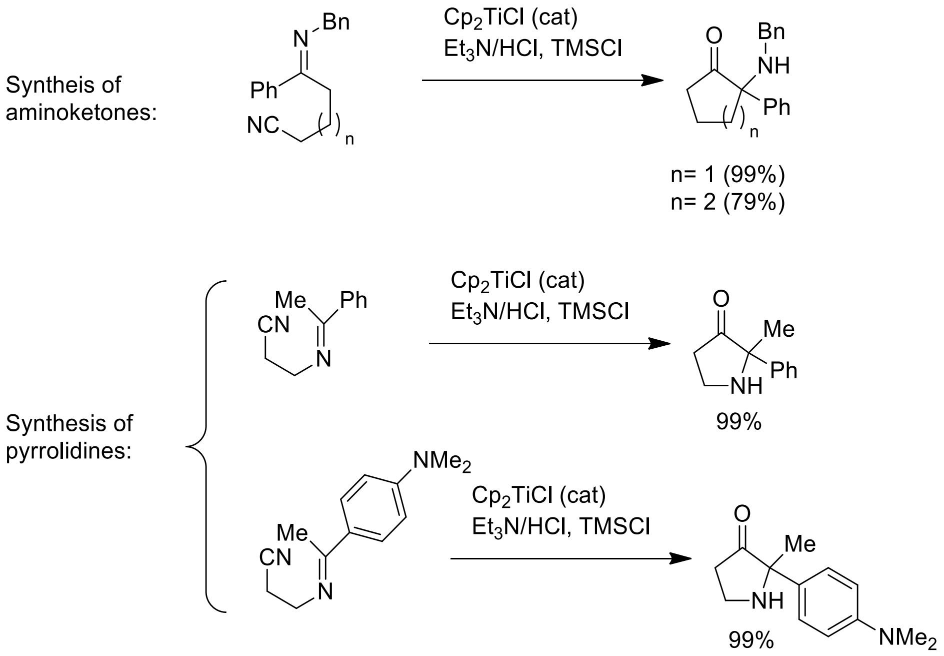
Recently, Streuff *et al*. [54] reported an inter- and intra-molecular acyloin-type cross coupling reaction in the presence of Cp_2TiCl and other titanium(III) catalyst. This reaction is another example of Umpolung reaction promoted and/or catalyzed by Cp_2TiCl. This type of reaction enables the connection of similarly polarised coupling partners by single-electron transfer (Scheme 38). The mechanism of these reactions involve the coordination of Cp_2TiCl to ketones or imines to generate the radical **9**, which reacts with a nitrile group also activated by a second Cp_2TiCl (Scheme 38).



Scheme 38. Umpolung-like cross coupling of ketones or imines and nitriles promoted by Cp_2TiCl.

This reaction connects ketones or imines with nitriles to the direct formation of α-hydroxy and α-aminoketones in high yields.

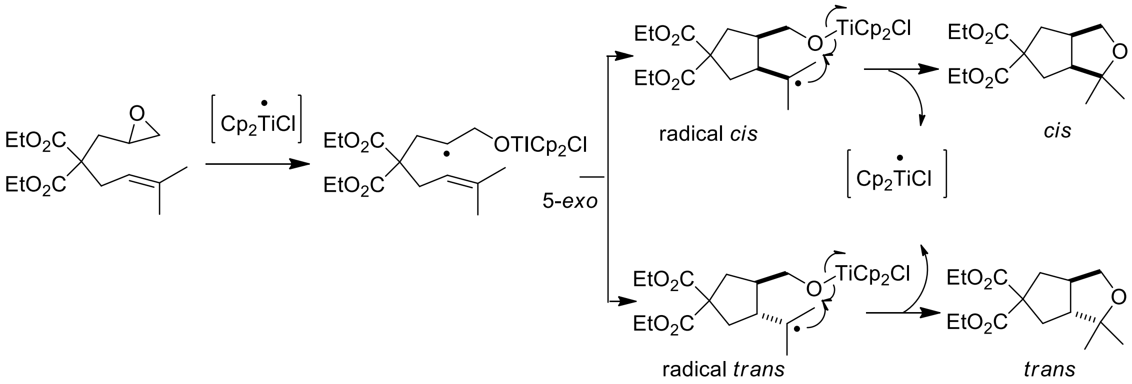
In addition, very good results were obtained in the intramolecular reductive imine-nitrile coupling which provided direct access to carbocyclic α-aminoketones and pyrrolidin-3-ones with tetrasubstituted α-carbons (Scheme 39).



Scheme 39. Intramolecular coupling of imines and nitriles catalyzed by Cp2TiCl.

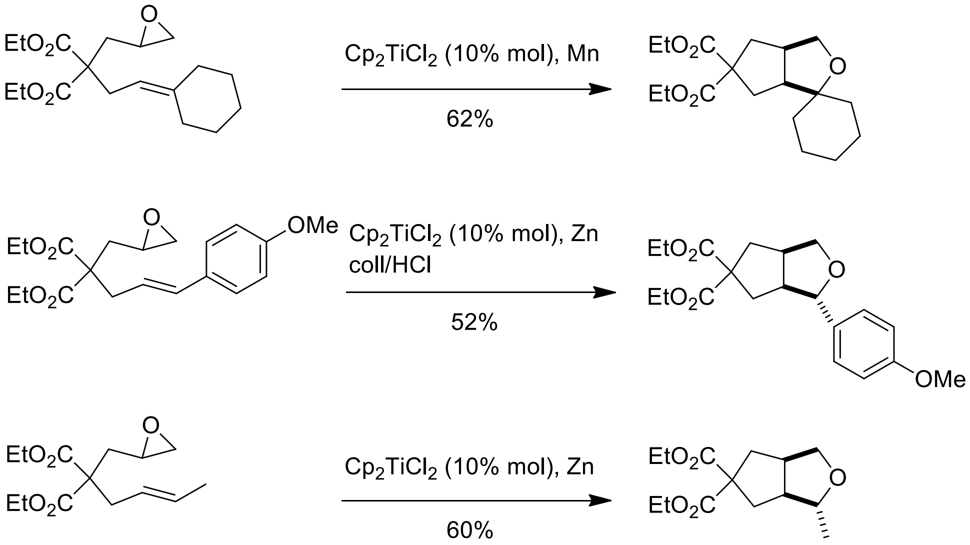
3.5. THF-ring formation reactions

A novel radical tandem reaction that introduces titanium-oxygen bonds as a useful class of tertiary, secondary or benzylic radical traps for the formation of tetrahydrofurans was reported by Gansäuer *et al*.[55] and Trost *et al*.[56] in the synthesis of siccanin. The initial step is based on the Cp_2TiCl-mediated opening of epoxides to give the cis- and trans- radical (Scheme 40). The second step constitutes the attack of the stable tertiary, secondary or benzylic radical on the Ti-O bond. The overall process is a redox-neutral reaction that requires only a substoichiometric amount of the reductant (Scheme 40).



Scheme 40. Plausible mechanism for the Cp_2TiCl epoxide opening with concomitant tetrahydrofuran formation.

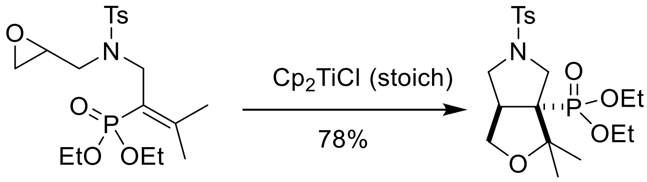
Despite of the thermodynamic preference for the trans radical intermediates compared to the cis ones, the formation of the cis-THF ring is kinetically favoured according to the Beckwith-Houk rules.[57] Experimental and theoretical data[55, 58] indicate only the formation of cis-THF ring (Scheme 41).



Scheme 41. Tetrahydrofurans from Cp_2TiCl epoxide opening.

Gansäuer *et al.*[59] reported a combined theoretical and experimental study on the development of much more efficient conditions for epoxide opening and THF ring formation.

THF-ring formation reactions have been also reported by Malacria *et al.*[60] from vinyl phosphonate and Cp_2TiCl (Scheme 42).

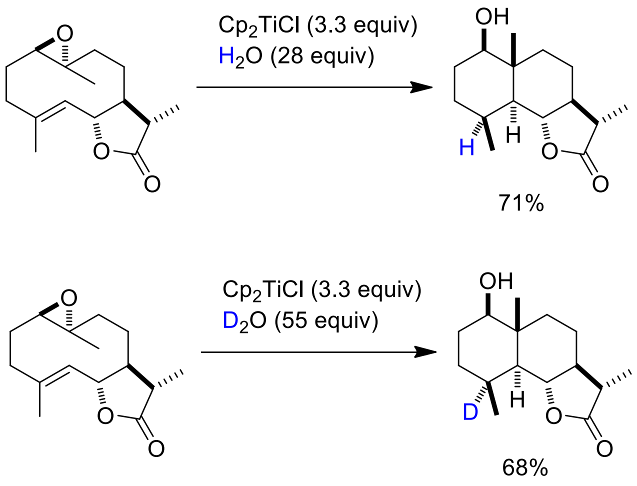


Scheme 42. Vinyl phosphonates in the Cp_2TiCl promoted tetrahydrofuran formation.

3.6. H-atom transfer

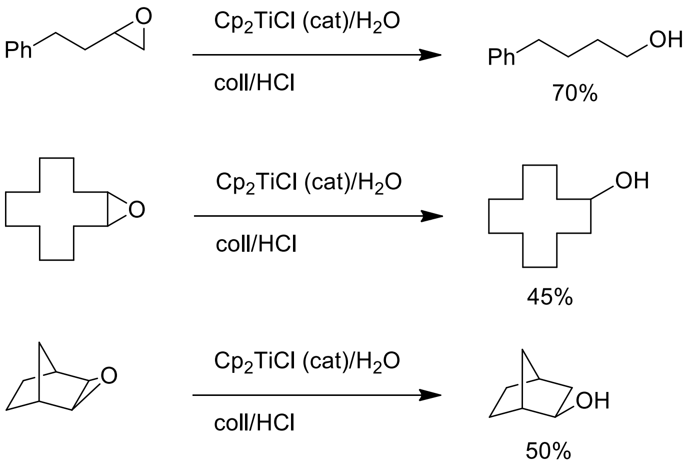
3.6.1. H-atom transfer from water to free radicals, ketones, alkenes and alkynes

Oltra *et al.*[20a, 17b] observed that the tertiary radicals were reduced effectively in the presence of Cp_2TiCl and water. At that particular moment, the idea of water acting as a hydrogen-atom source seemed to be counterintuitive, because since Gomberg discovered that radicals can be reaction intermediates,[61] it was commonly believed that water was inert towards free radicals.[62] However, in the transannular cyclizations of epoxygermacrolides using Cp_2TiCl/H_2O (Scheme 43), the authors observed for the first time a hydrogen-atom transfer (HAT) from water to a carbon-centered radical. Their results demonstrated that in Cp_2TiCl-mediated free-radical chemistry, water can indeed act in a reductive way, working as a hydrogen atom donor.



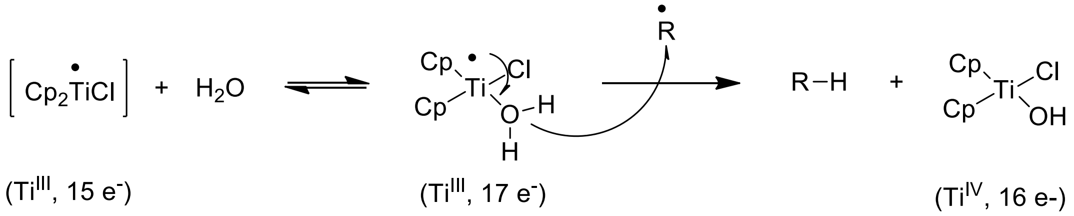
Scheme 43. Cp_2TiCl mediated transannular cyclization of epoxygermacrolides terminated by HAT from water.

Oltra *et al.*[20b, 17b] had reported solid theoretical and experimental evidence that indicating that water can act as an efficient hydrogen-atom source in radical reduction mediated by Cp_2TiCl. This property was initially exploited for the reductive opening of epoxides to provide a mild, safe and inexpensive two-step procedure (complementary to the hydroboration-oxidation method) for the preparation of anti-Markonikov alcohols from alkenes, even as deuterated derivatives (Scheme 44).



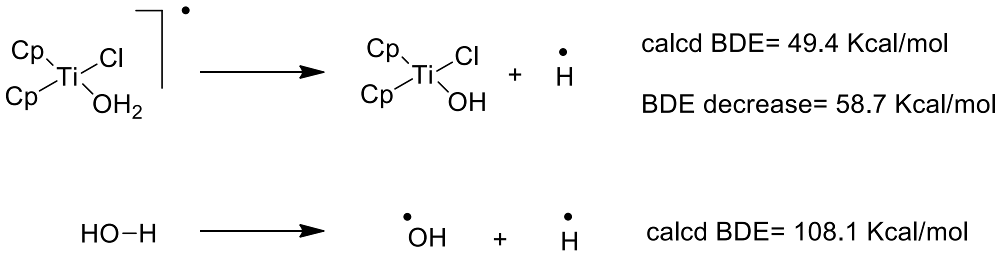
Scheme 44. Cp_2TiCl catalyzed epoxide opening with HAT termination.

To explain this unprecedented HAT from water to radicals, it was proposed that the coordination of water to Cp_2TiCl might weaken the strength of the O-H bond. In this manner, a single-electron transfer from titanium to oxygen might facilitate the HAT from the titanocene aqua-complex to the free radicals (Scheme 45).



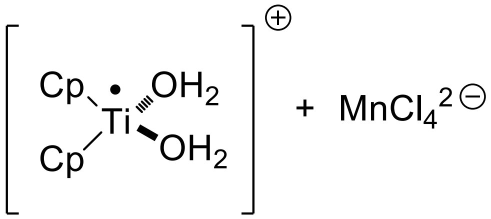
Scheme 45. Proposed formation of a titanocene aqua-complex as HAT.

Theoretical calculations supported this hypothesis, indicating a bond-dissociation energy (BDE) for the titanocene aqua-complex of only 49.4 Kcal/mol; a decrease of almost 60 Kcal/mol compared to the calculated BDE of water (Scheme 46).[20b, 63]



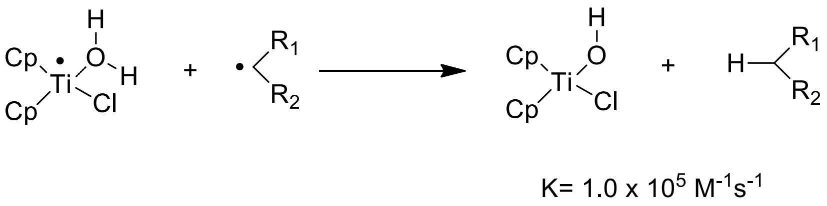
Scheme 46. Theoretical calculations of BDE in the titanocene aqua-complex.

Recently, Gansäuer *et al.*[64] revised the structure of the titanocene(III) aqua-complex (Scheme 47) on the basis of the results obtained from electro-paramagnetic resonance techniques, cyclic voltammetry and theoretical calculations.



Scheme 47. Gansäuer's revised structure of the titanocene(III) aqua-complex.

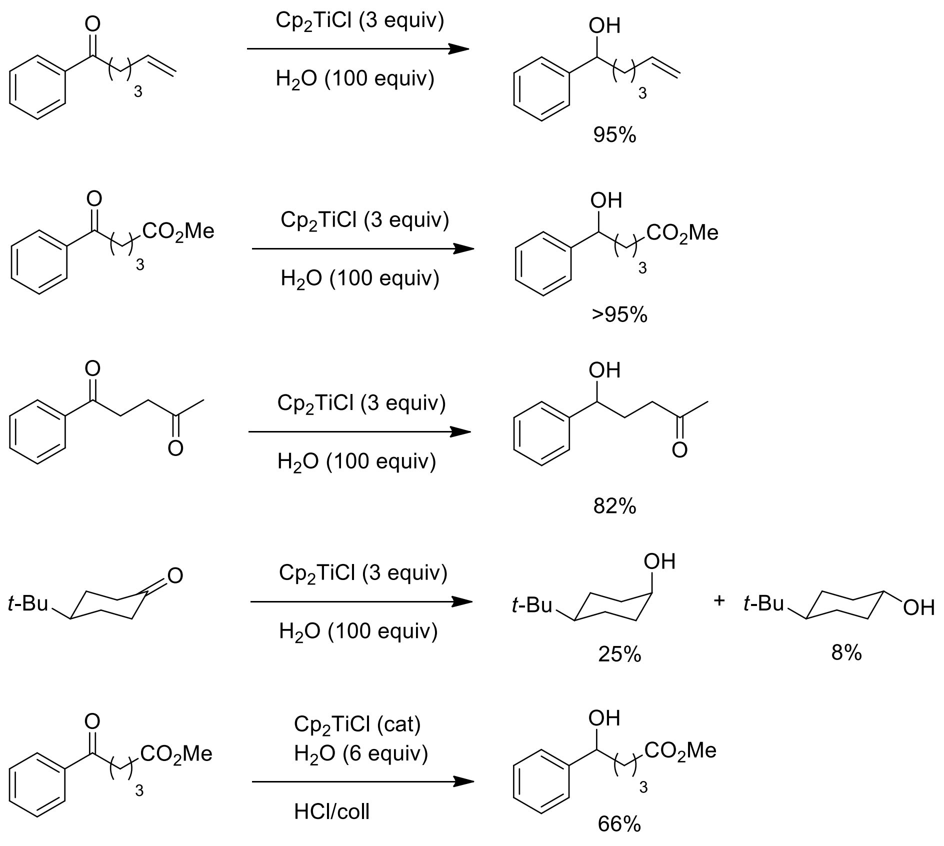
Jin and Newcomb[65] confirmed the findings on the activation of water as a hydrogen atom donor by Cp_2TiCl and, by using radical clocks, determined the rate constant for the HAT from titanocene aqua-complex to secondary radicals (Scheme 48).



Scheme 48. Rate constant for the HAT from Cp_2TiCl/H_2O to secondary radicals.

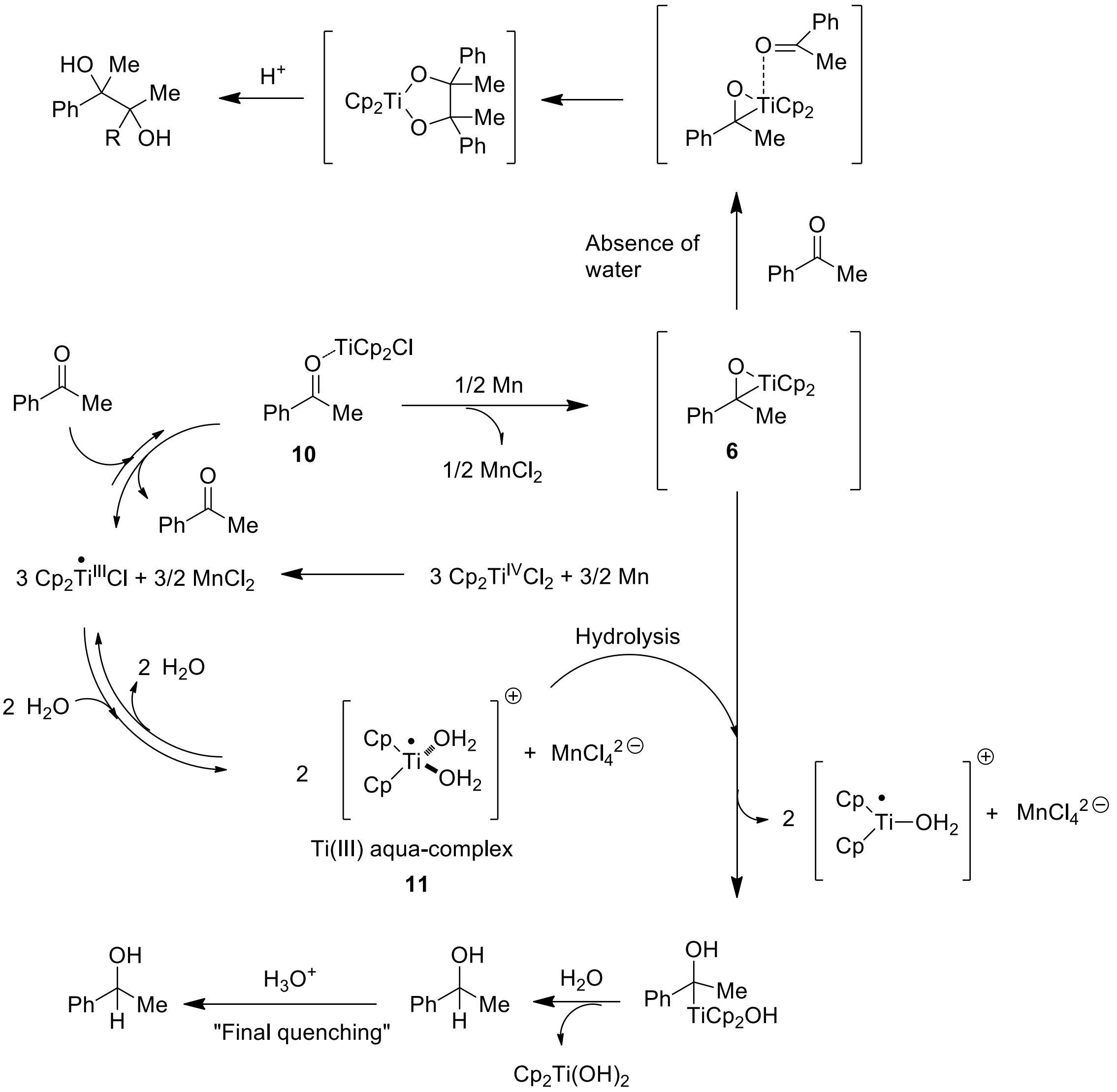
Therefore, Cp_2TiCl/H_2O has thus emerged as an excellent reagent for the reduction of free radicals to the corresponding hydrocarbons through HAT avoiding the use of conventional hydrogen-atom donors such as 1,4-cyclohexadiene, tert-butyl thiol, or Bu_3SnH, which are toxic, expensive, and/or foul-smelling.

The Cp_2TiCl/H_2O combination was also used by Oltra *et al.*[66] for the selective reduction of aromatic and cyclic ketones. The reaction discriminated between ketones and alkenes, between ketones and esters and, remarkably, between conjugated and non-conjugated ketones (Scheme 49).



Scheme 49. Selective reduction of ketones by Cp_2TiCl/H_2O.

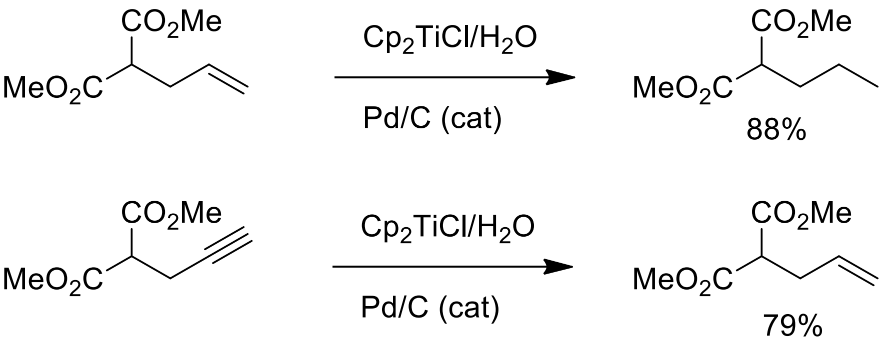
Recently, an experimental study on the role played by each of the reagents involved in the selective reduction of aromatic ketones in aqueous medium has been reported by Rosales and Oltra *et al*.[41] In this study, the authors reported that the reduction of aromatic ketones are mediated by Cp_2TiCl and that the presence of Mn in the reaction medium is mandatory. The coordination between acetophenone and Cp_2TiCl was proposed to provide the intermediate **10** in an equilibrium reaction shifted towards Cp_2TiCl and acetophenone, because in the absence of Mn, acetophenone was recovered unchanged. When Mn is present in the reaction medium, the reduction of Cp_2TiCl coordinated to acetophenone proceeds irreversibly leading to titanaoxirane **6**. This type of metalloxirane is well known.[67] In the absence of Mn, the key intermediate **6** was not formed and, consequently, neither pinacol-coupling nor reduction products were observed. In the presence of Mn, but absence of water, formation of **6** and subsequent coordination to a second molecule of acetophenone would lead to pinacol-coupling products via five-membered titanadioxolanes as previously reported.[67c] In aqueous medium, however, a Ti(III) aqua-complex such as **11** was formed. [20b, 64] It is known that this aqua-complex can act as an efficient H-atom donor for the reduction of carbon-centered free radicals.[20, 63] Nevertheless, in the absence of radicals, aqua-complex **11**, which would probably be more acidic than uncomplexed water, could promote the hydrolysis of **6** to alkyl-Ti(IV) products; the precursors of the reduction products (Scheme 50).



Scheme 50. Proposed mechanism for the reduction of ketones by Cp_2TiCl/H_2O.

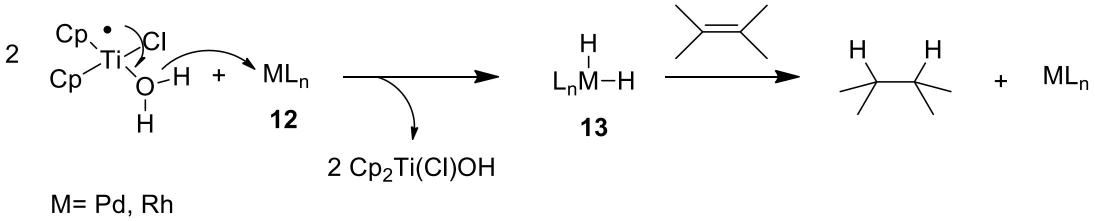
On the basis of this newly proposed mechanism, the free-radical character conventionally assumed for these chemical processes should be reconsidered.

Finally, Oltra *et al.*[68] observed that the Cp_2TiCl/H_2O combination, in the presence of Pd or Rh catalysts, can also be used for the hydrogenation of alkenes and alkynes by HAT from water, avoiding the use of highly inflammable and expensive hydrogen gas (Scheme 51).



Scheme 51. Pd/Cp_2TiCl/H_2O hydrogenation of alkenes or alkynes.

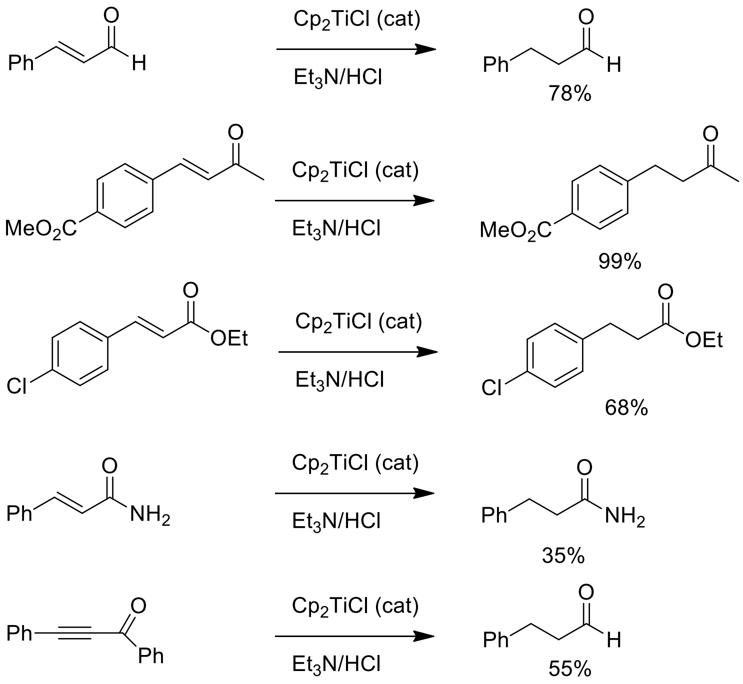
The authors rationalized the process suggesting that the aqua-complex (Cp_2TiCl/H_2O) could facilitate the HAT from water to late transition metals, those which are usually employed as hydrogenation catalysts **12** to give metal-dihydride species **13**. These species could subsequently bring about alkene (and alkyne) hydrogenation (Scheme 52).



Scheme 52. Mechanism for the Cp_2TiCl/H_2O hydrogenation of alkenes in the presence of Pd or Rh catalysts

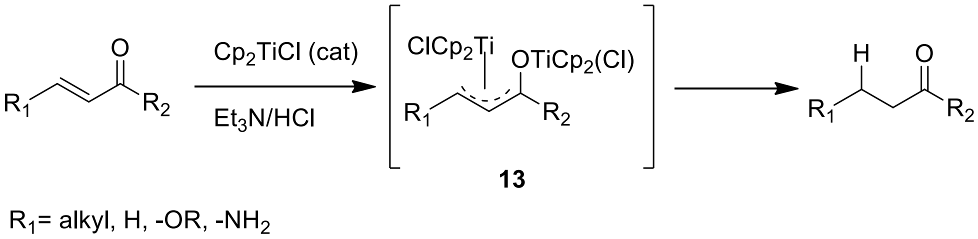
3.6.2. H-atom transfer to α,β-unsaturated carbonyl derivatives

Ashfeld *et al.*[69] reported the conjugated reduction of α,β-unsaturated carbonyl derivatives catalysed by Cp_2TiCl. Different carbonyl compounds including aldehydes, ketones, esters and amides proved viable in the reduction process providing a chemoselective and efficient method for the catalytic reduction of unsaturated carbonyl derivatives (Scheme 53).



Scheme 53. C-C bond reduction by Cp_2TiCl/Et_3•NHCl of α,β-unsaturated carbonyl compounds.

The authors proposed that the coordination of Cp_2TiCl to the carbonyl moiety of the unsaturated carbonyl derivative initiates a reallocation of electron density to yield an intermediate ketyl radical that, after sequestering a second equivalent of titanocene(III), provides the bis-titanium(IV)-bound intermediate **14**. Protonation of the titanium alkoxide and allyl motifs by $Et_3N.HCl$ yields the saturated carbonyl derivative (Scheme 54).



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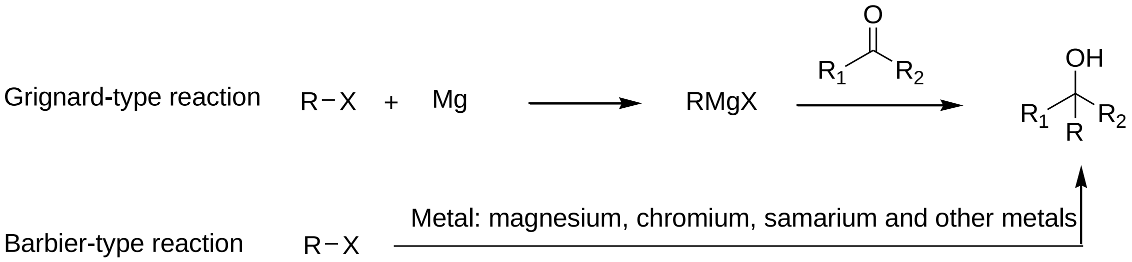
Scheme 54. Plausible mechanism for the reduction of α,β-unsaturated carbonyl compounds with Cp_2TiCl/Et_3•NHCl.

3.7. Babrier-type reactions

3.7.1. Barbier-type reactions catalyzed by Cp_2TiCl

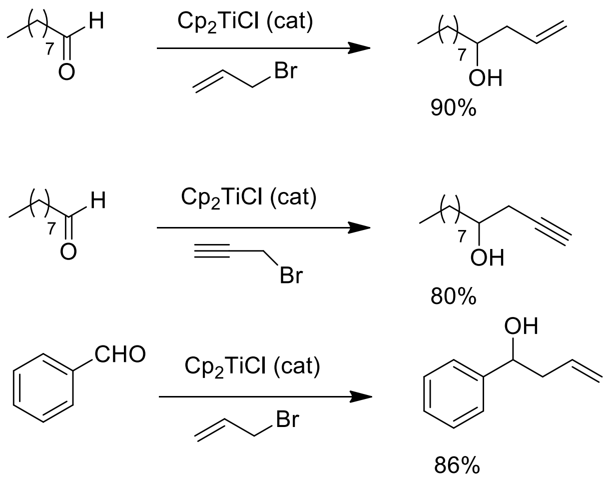
Allylation, benzylation, propargylation, crotylation and allenylation of carbonyl compounds are useful C-C bond forming reactions in organic synthesis. Within this context, the one-step mechanism of Barbier-type reactions is often more convenient than the two-step reaction (preparation of the propargylic organometallic reagent and subsequent coupling with the carbonyl derivative) characteristic of Grignard-type strategies (Scheme 55).



Scheme 55. Metal promoted C-alkylation of carbonyl compounds.

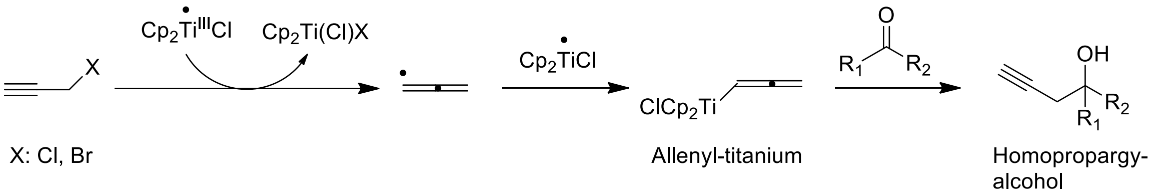
Although, titanium complexes were used in Barbier-type reactions, the requirement of stoichiometric proportions of titanium complexes was a serious drawback in the methods described.[70]

In 2004, our group[71] reported the first Barbier-type reaction between carbonyl compounds and activated alkyl halides using Cp_2TiCl as catalyst. In this context, selective Barbier-type allylations, benzylations and propargylations were carried out under extremely mild conditions (Scheme 56).



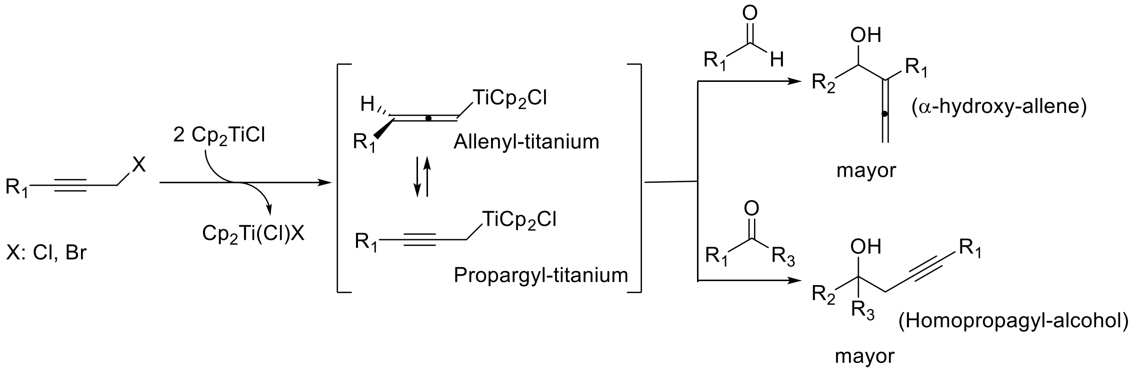
Scheme 56. Barbier-type reactions catalyzed by Cp_2TiCl.

Later, Oltra and Rosales *et al*.[72] reported in detail the scope and limitations of the Barbier-type propargylation of aldehydes and ketones and the allenylation of aldehydes catalyzed by Cp_2TiCl supporting the preliminary results obtained in our laboratory.[71] Mechanistic studies strongly suggested that Cp_2TiCl reacts with unsubstitued propargyl halides to yield allenyl titanium species, which in turn, attack aldehydes and ketones to exclusively provide terminal homopropargylic alcohols (Scheme 57).



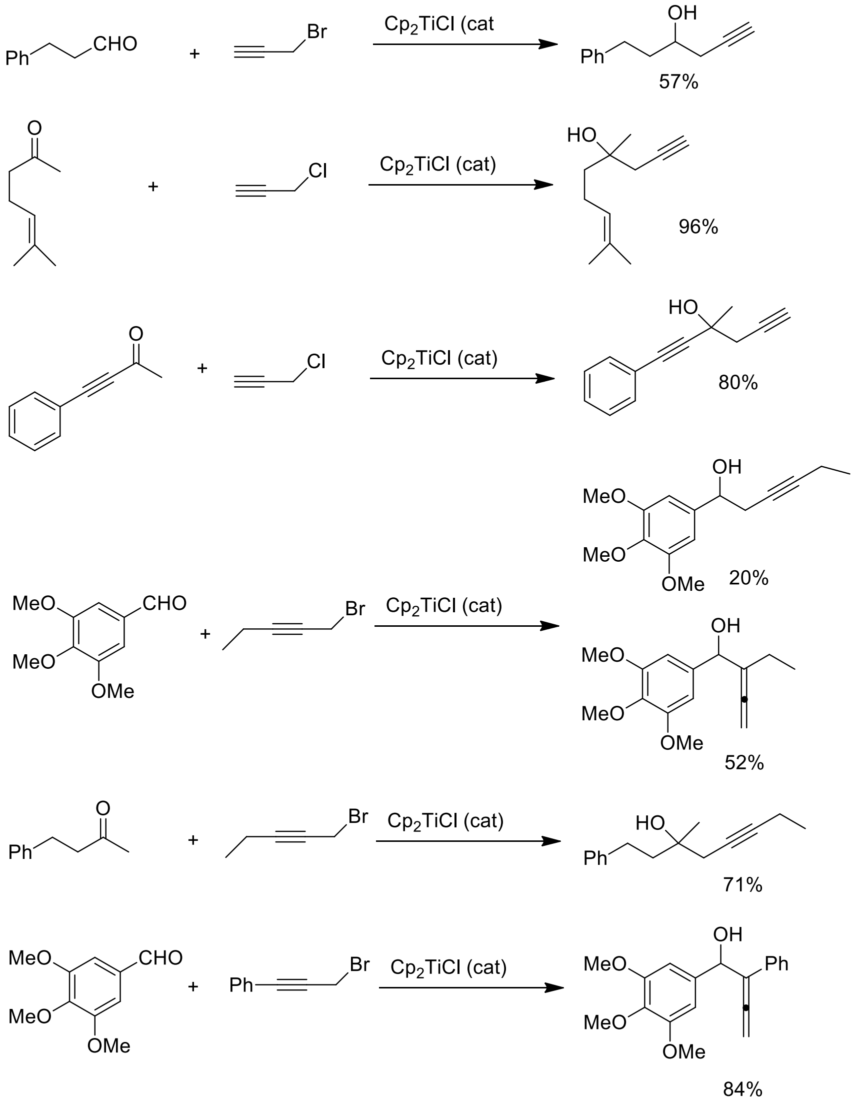
Scheme 57. Proposed mechanism for the Cp_2TiCl catalyzed addition of unsubstituted propargyl halides to aldehydes or ketones.

On the other hand, Cp_2TiCl reacts with substituted propargyl halides to yield an equilibrium mixture of propargyl-titanium and allenyl-titanium complex. As a result, aldehydes react to give mainly α-hydroxy-allenes, while ketones afford mainly internal homopropargylic alcohols (Scheme 58).



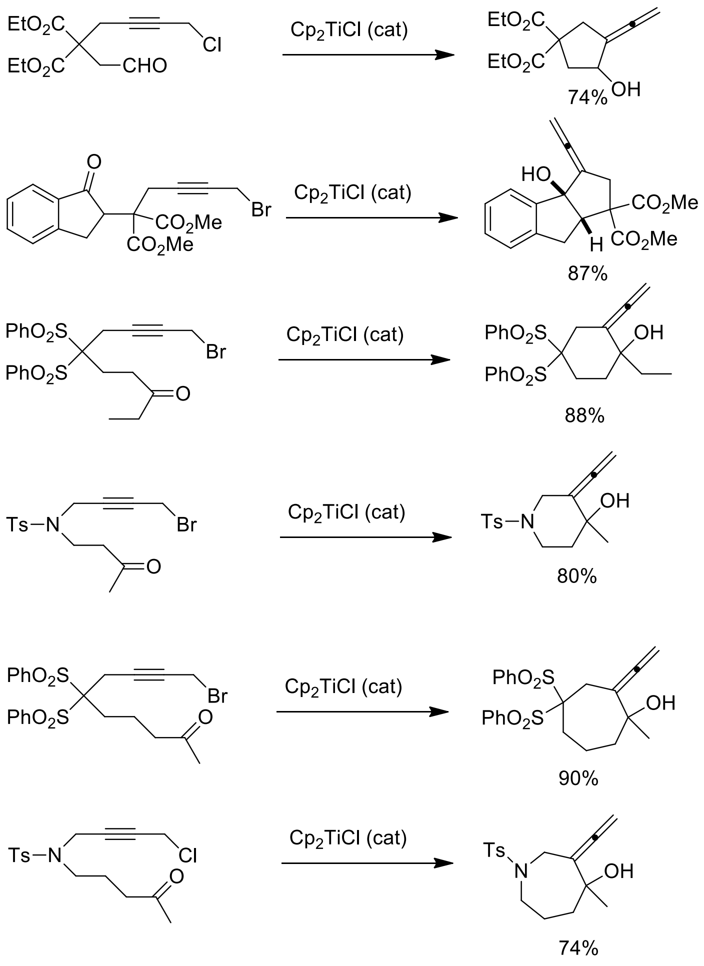
Scheme 58. Proposed mechanism for the Cp_2TiCl catalyzed addition of substituted propargyl halides to aldehydes or ketones.

In both cases, the reactions proceed at room temperature under extremely mild conditions compatible with numerous functional groups and in very high yields (Scheme 59).



Scheme 59. Barbier type propargylations and allenylations catalyzed by Cp_2TiCl.

Finally, in 2014 Oltra, Rodríguez-García and Rosales *et al*.[73] reported the first general procedure for the straightforward synthesis of exocyclic allenes. The reaction was catalyzed by Cp_2TiCl and provided good yields of five-, six-, and seven-membered carbocycles and nitrogen-containing heterocycles bearing an exocyclic allene group (Scheme 60).

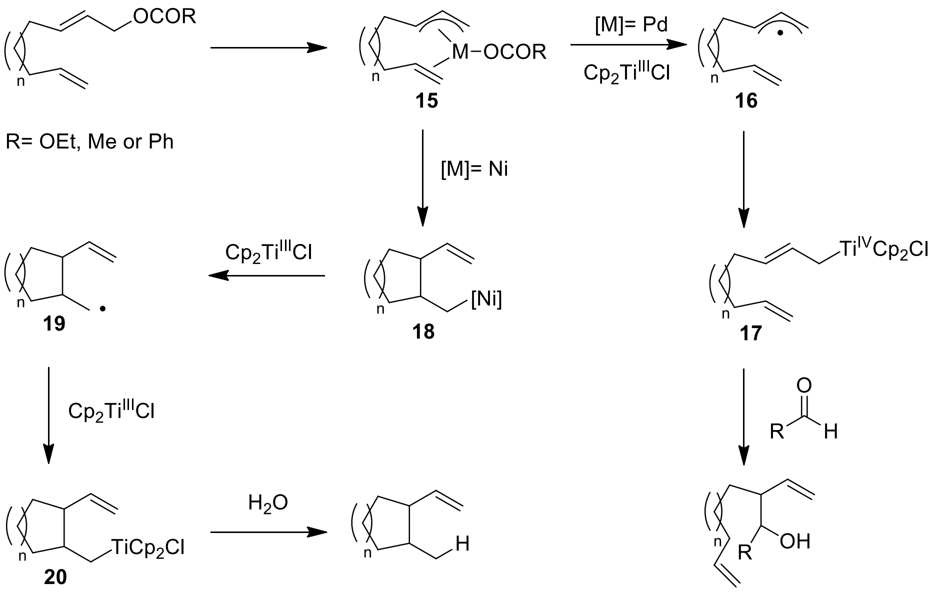


Scheme 60. Cp_2TiCl catalyzed synthesis of cyclic α-allenols.

3.7.2. Barbier-type reactions catalyzed by multimetallic systems

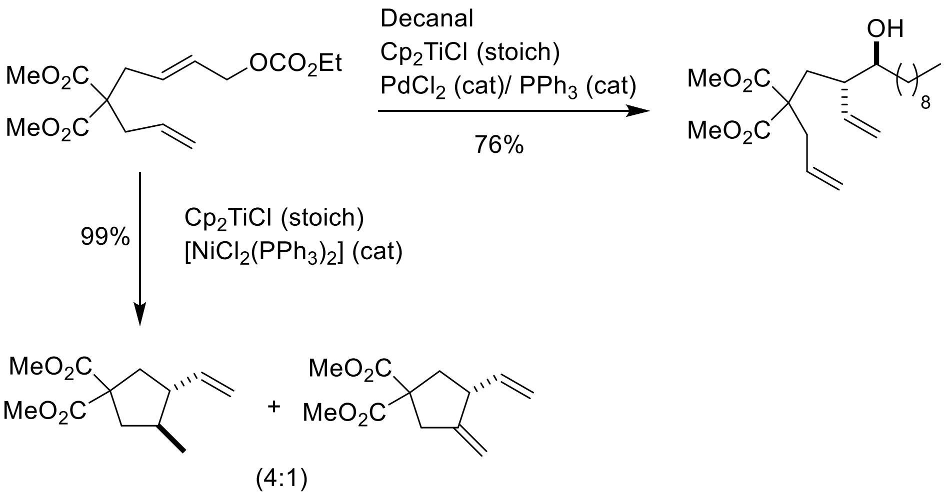
In 2008, Echavarren´s group an our's[74] demonstrated for the first time that 3d and 4d transition metals, nickel and palladium respectively, are capable of modulating titanium(III) reactivity to achieve selective allylations of either carbonyl compounds or alkenes using allylic carbonates and carboxylates (Scheme 61).

It is known that nickel and palladium complexes react with activated allylic carbonates and carboxilates to form η^3-allyl metal complexes **15** (Scheme 56). In the case of palladium catalysis, the cyclization of organometallic species (**15**, M= Pd) to cyclic derivatives is slow at room temperature.[75] Thus, reduction of this organometallic species **15** by Cp_2TiCl leads to the allylic radical **16**, which may be eventually trapped by a second Cp_2TiCl species to give an allylic titanium(IV) complex **17**. Finally, nucleophilic attack of the organometallic derivative **17** on an aldehyde provides the corresponding allylation product (Scheme 61). In the case of nickel catalysis, the cyclization of organometallic species **15** is faster.[68] Once formed, the cyclic product **18** can be reduced by Cp_2TiCl to a primary radical **19**, which can be trapped by a second Cp_2TiCl species to give an alkyl titanium (IV) complex **20**. Finally, hydrolysis of the organometallic derivative would yield carbocycles (Scheme 61).



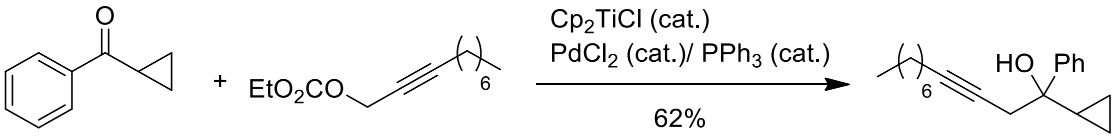
Scheme 61. Reactivity of ω-alkenyl allylic carbonates towards Cp_2TiCl and Pd or Ni catalysts.

Although this new methodology is nice and gives good yields (Scheme 62), it is more expensive and laborious than the Barbier type reaction using activated halides and Cp_2TiCl.



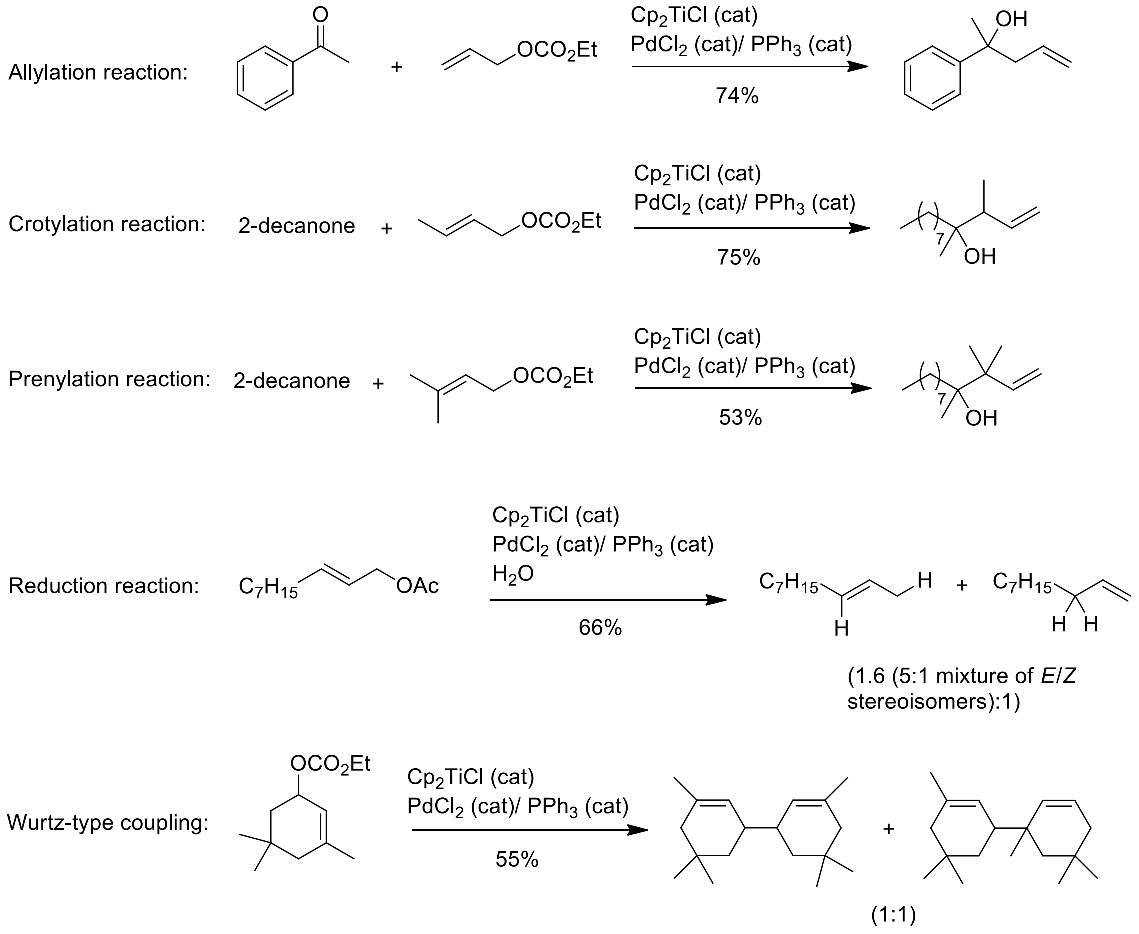
Scheme 62. Inter or intramolecular couplings of ω-alkenyl allylic carbonates with Cp_2TiCl and Pd or Ni catalysts.

This procedure was later applied by Cuerva *et al.*[77] to the regioselective propargylation of ketones using propargylic carbonates as pronucleophiles and Cp_2TiCl and $PdCl_2$ as catalysts (Scheme 63).



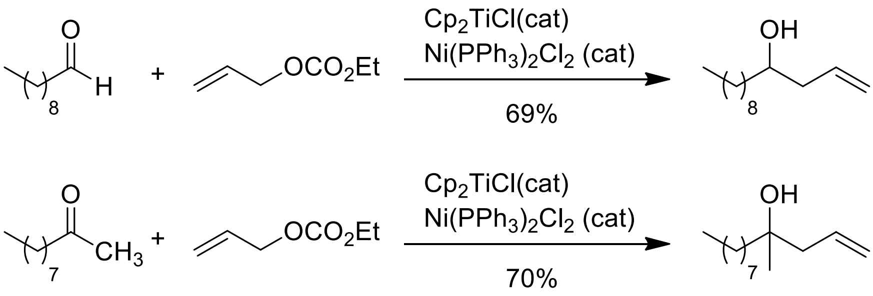
Scheme 63. Ti/Pd catalyzed addition of substituted propargyl carbonates to ketones.

Cuerva *et al.*[78] reported that Cp_2TiCl can catalyze allylation, crotylation and prenylation of carbonyl compounds, reduction reactions and Wurtz-type coupling, in the presence of a palladium complex, from allylic carboxylates and/or allylic carbonates (Scheme 64).



Scheme 64. Synthetic applications of the Ti/Pd catalyzed radical reactions of allylic carbonates.

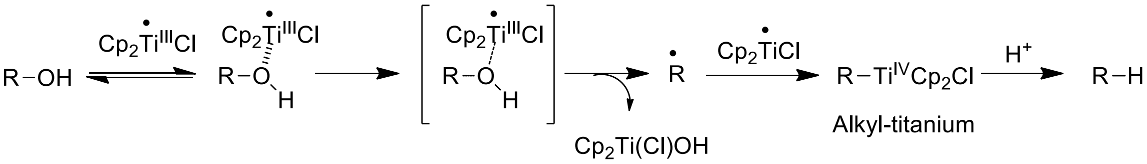
Finally, Cuerva *et al*.[79] reported a mild method for the allylation of carbonyl compounds using allyl carbonates as pronuclophiles and catalytic amounts of both Ni catalyst and Cp_2TiCl (Scheme 65).



Scheme 65. Synthesis of homoallylic alcohols by means of $Cp_2TiCl/Ni(PPh_3)_2Cl_2$.

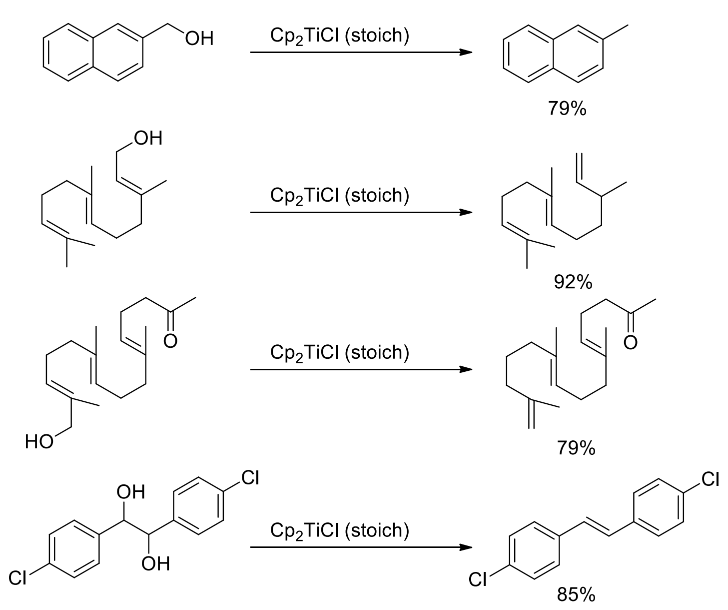
3.8. Deoxygenation of alcohols

The significant decrease of the homolytic C-O BDE[20b, 65] for RCH_2-OH compared to that for the complex $Cp_2Ti(Cl)/HO-CH_2R$ allowed Barrero *et al.*[49] to develop a new application of Cp_2TiCl in organic synthetic chemistry. This application was a simple and efficient deoxygenation-reduction procedure of alcohols and 1,2-diols. The mechanistic proposal for this reaction involved a C-centered radical obtained from homolysis of the corresponding C-O bond, which can be trapped by another molecule of Cp_2TiCl, generating alkyl-titanium, which is protonated to yield an alkane (Scheme 66).



Scheme 66. Proposed mechanism for the deoxygenation of alcohols with Cp_2TiCl.

Different benzylic and allylic alcohols were transformed efficiently into their corresponding deoxygenated-reduced compounds using catalytic and stoichiometric amounts of Cp_2TiCl (Scheme 67), while, the treatment of 1,2-diols with stoichiometric amounts of Cp_2TiCl led almost quantitatively to trans-stilbene (Scheme 67).

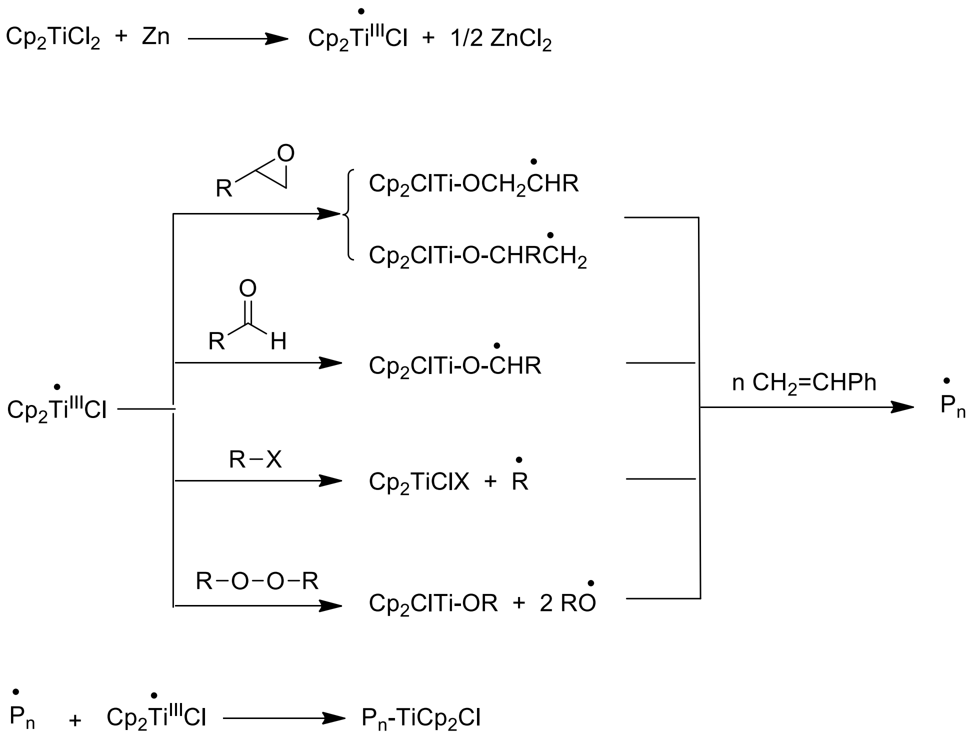


Scheme 67. Deoxygenation of alcohols with Cp_2TiCl.

This method complements alternative, and previously reported deoxygenation reactions and is of general interest in organic synthesis.

3.9. Polymerization reactions

Asandei *et al*.[80] reported for the first time that the opening of oxiranes by Cp_2TiCl can be successfully used in the initiation of radical polymerization. Later, four different radical sources (1,4—butanediol diglycidyl ether, benzaldehyde, 1-bromoethylbenzene and benzoyl peroxide) were investigated as initiators in the Cp_2TiCl-catalyzed radical polymerization of styrene.[81] Once generated by the Ti activation of the initiator, the corresponding radicals subsequently added to styrene, thereby starting the polymerization. The termination step can be achieved with a second equivalent of Cp_2TiCl (Scheme 68).



Scheme 68. Initiation of radical polymerization by Cp_2TiCl opening of epoxides, aldehydes, halides and peroxides.

This study classified the effectiveness of the initiators in the order: aldehydes> peroxides>epoxides>halides.

4. CONCLUSIONS

In summary, we describe herein the principal chemical reactivity of the titanocene monochloride (Cp_2TiCl). This single-electron-transfer reagent has experienced an unprecedented development in the last two decades due to its ability to promote and/or catalyse different efficient transformations under mild and environmentally safe reaction conditions. Although most of the reactions mediated by Cp_2TiCl have been classified as radical chemistry, it seems possible that some of them combine radical intermediates with transition metal catalysis. We foresee that in the near future a combination of radical intermediates and transition metal catalysis will allow the development of new synthetic methodologies.

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5. REFERENCES

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