



## $Cp_2TiCl$ is a useful reagent to teach multidisciplinary chemistry

*$Cp_2TiCl$  es un reactivo útil para enseñar química multidisciplinar*

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### Resumen

$Cp_2TiCl$  es un único reactivo de transferencia de electrones que ha contribuido en varios campos del conocimiento científico, como la química orgánica, inorgánica, ecológica y analítica. En este artículo, las revisiones principales y parte de la literatura química primaria se convierten en un breve manuscrito que sirve para ilustrar cómo se puede usar un reactivo para enseñar química multidisciplinaria a químicos e ingenieros químicos de pregrado.

### Palabras clave

Química multidisciplinar, química verde, ingeniería química, titanoceno, aprendizaje por descubrimiento.

### Abstract

$Cp_2TiCl$  is a single electron transfer reagent which has contributed to several field of scientific knowledge, such as organic, inorganic, green and analytical chemistry. In this article the main reviews and some primary chemical literature is converted to a brief manuscript that serves to illustrate how a reagent can be used to teach multidisciplinary chemistry to undergraduate chemists and chemical engineers.

### Keywords

Multidisciplinary chemistry, green chemistry, chemical engineering, titanocene, discovery learning.

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## Introduction

In recent decades, a considerable increase in multidisciplinary chemical research has been observed, allowing greater scientific achievements to be achieved. However, at the curricular level, it is necessary to make a greater effort to transfer the inherent advantages of multidisciplinary development to the curricula of university teaching in chemistry and chemical engineering [Wiggins, M. B., 2019]. In this context, titanocene monochloride (Cp<sub>2</sub>Ti<sup>III</sup>Cl) is a single-electron transfer (SET) complex that is at the forefront of multidisciplinary research. This SET has been shown to be capable of catalysing and/or promoting homolytic cleavage of C-X bond (X being a heteroatom with free valence electrons), present in several functional groups, giving a carbon-centered radical that can undergo different reactions of great utility in organic and organometallic synthesis (see next section). While there are excellent reviews that exhaustively cover recent developments within a specific area, such as its chemical reactivity [Gansäuer, A., 2007; Streuff, J., 2014; Rosales, A., 2015], as new green reagent [Rosales Martínez, A., 2017], and application towards the synthesis of natural products [Barrero, A. F., 2006; Justicia, J., 2011], this article seeks to emphasize the wide diversity of uses for this SET by briefly reviewing a number of different fields of research, such as organic synthesis, green chemistry and analytical techniques. The result is a didactic manuscript capable of simultaneously presenting novel concepts focused as multidisciplinary chemistry.

The author considers this article helpful to chemistry educators and students in three ways. This article can be used as a complementary reading material to the topics of organometallic and radical chemistry. Also, this article describes the effectiveness of Cp<sub>2</sub>TiCl as a green reagent that fulfils many of the twelve principles of the green chemistry. Finally, this article can also be used by students to learn inert atmosphere techniques.

## Synthesis and properties of Cp<sub>2</sub>TiCl

The synthesis of Cp<sub>2</sub>TiCl is straightforward via Mn or Zn dust reduction of Cp<sub>2</sub>TiCl<sub>2</sub> in a solvent such as tetrahydrofuran, toluene or acetonitrile [Green, M. L. H., 1972; Gansäuer, A., Bluhm, H., Pierobon, M. 1998; Enemaerke, J. R., 2001]. Alternatively, organosilicon reducing agents [Saito, T., 2014], electrochemical reduction [Liedtke, T., 2019] and photoredox catalysis [Zhang, Z., 2019] can be employed to obtain Cp<sub>2</sub>TiCl from Cp<sub>2</sub>TiCl<sub>2</sub>. In THF solution, Cp<sub>2</sub>TiCl is in an equilibrium between dinuclear and mononuclear species (Scheme 1) [Castro Rodríguez, M., 2017; Rosales Martínez, A., 2021].

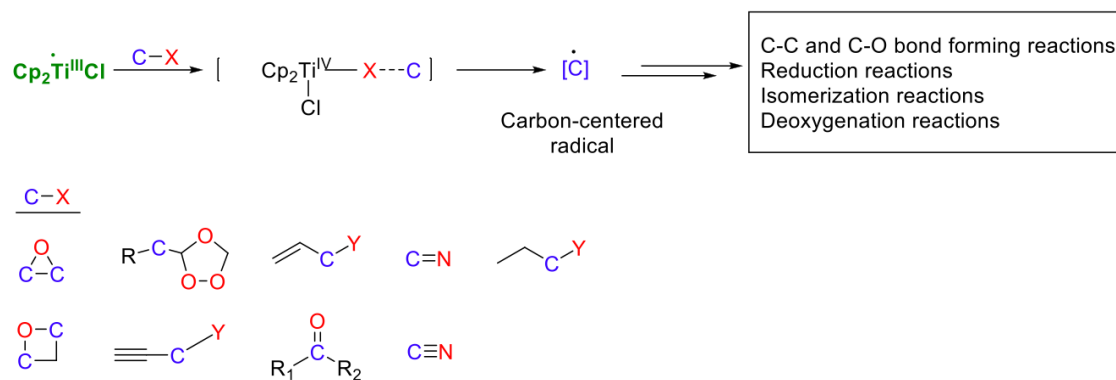


**SCHEME 1.** Equilibrium of species in the preparation of Cp<sub>2</sub>TiCl from Cp<sub>2</sub>TiCl<sub>2</sub>.

M= Mn or Zn  
S= THF

These structure each have an unpaired *d* electron, giving them mild electron-reducing character ( $E^{\circ} = -0.8$  V vs. Fc<sup>+</sup>/Fc) [Enemaerke, J. R., 2004]. Furthermore, this reagent has a

vacant site, allowing the coordination a heteroatom with free valence electrons to initiate the mono-electronic transfer through an inner-sphere mechanism [Ogoshi, S., 1998]. So, Cp<sub>2</sub>TiCl has ability to generate carbon radicals by homolytic cleavage of C-X bonds (X being heteroatoms with free valence electrons) present in several functional groups (Scheme 2). From this carbon-centered radical, depending on the experimental conditions, several reactions can be promoted (Scheme 2) [Rosales Martínez, A., 2021].



**SCHEME 2.** Target functional groups of Cp<sub>2</sub>TiCl.

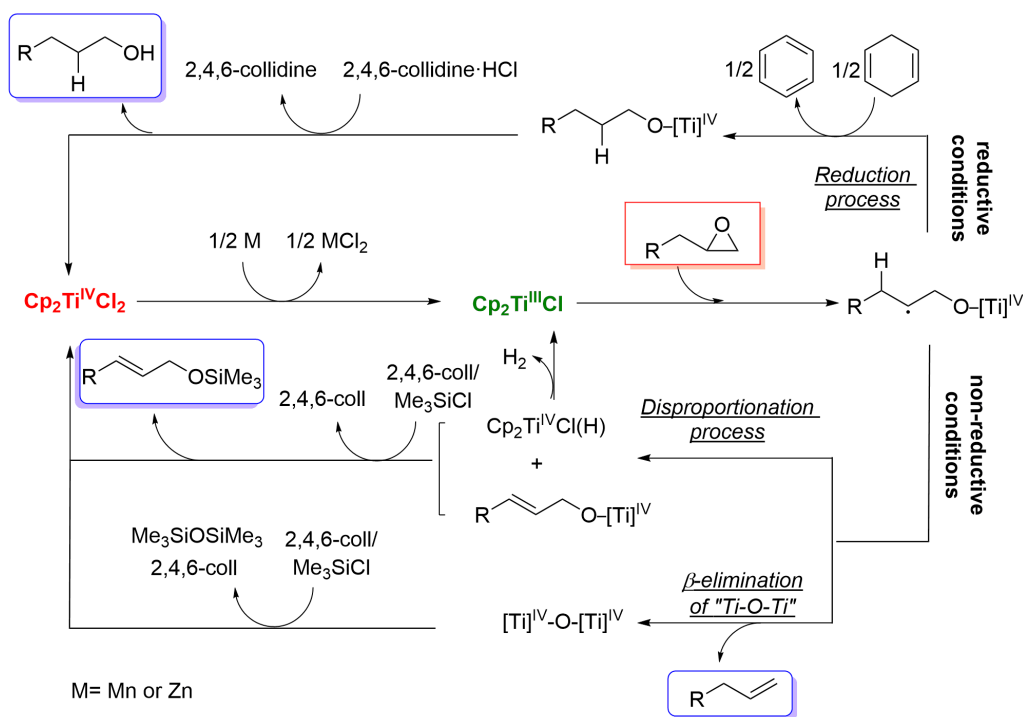
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X: O, Cl, Br  
R: H, alkyl, phenyl...

## Cp<sub>2</sub>TiCl as a green chemistry reagent

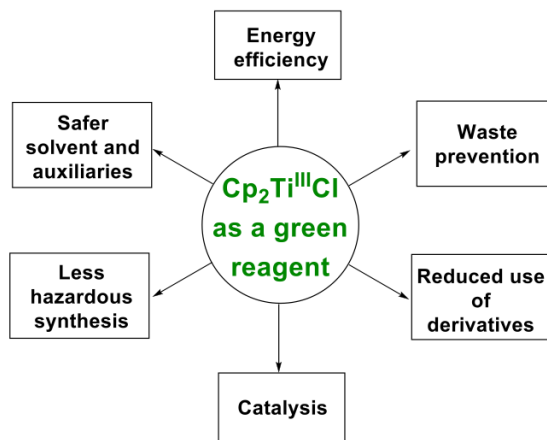
After the seminal works reported by Nugent and Rajanbabu [Nugent, W. A., 1998; RajanBabu, T. V., 1989; RajanBabu, T. V., 1990; RajanBabu, T. V., 1994], Cp<sub>2</sub>TiCl has been postulated as a new green reagent which complies with, if not all, at least some to the twelve principles of green chemistry reported by Anastas, P., 2010, being this reagent a perfect opportunity for teaching green chemistry [Franco Moreno, R. A., 2020 and references cited]. So, it is worth to mention that this SET is a non-hazardous material, and although this SET is not a renewable feed stock it derives from transition metal (titanium), the second most abundant transition metal in the upper continental Earth's crust [Yaroshevsky, A. A., 2006]. On the other hand, the use of Cp<sub>2</sub>TiCl as a catalyst was a breakthrough in the application of this reagent with the development of two catalytic cycles, which allowed regeneration of Cp<sub>2</sub>TiCl<sub>2</sub> from the titanium species formed in homolytic cleavage of bonds. Under reductive conditions [Gansäuer, A., Pierobon, M., and Bluhm, H., 1998] hydrochloride-substituted pyridines was used a regenerator of titanium(IV), and under non-reductive conditions [Barrero A. F., Rosales A., Cuerva J. M., and Oltra J. E. 2003] 2,4,6-trimethyl-1-trimethylsilylpyridinium chloride [Coll/TMSCI]. Recently the role of the intermediate Cp<sub>2</sub>TiCl(H) was found that spontaneously decomposes to regenerate titanocene(III) and molecular hydrogen [Gordon J. 2018]. Both catalytic cycles for epoxides opening are reported in scheme 3, giving alcohol (reduction process) or alkene and/or allylic alcohol (non-reduction process) [Rosales Martínez, A., 2021].

Another principle of green chemistry that Cp<sub>2</sub>TiCl meets is the energy efficiency, since the reactions catalysed by this single electron transfer are conducted at room temperature and atmospheric pressure. Also, Cp<sub>2</sub>TiCl is a highly diastereoselective reagent that maximizes the selectivity and atom and step economy. This makes the radical cascade mono- and polycyclisation reactions of monoepoxides of acyclic polyenes catalysed by

Cp<sub>2</sub>TiCl -yielding C<sub>10</sub>, C<sub>15</sub>, C<sub>20</sub> and C<sub>30</sub> terpenoids- especially relevant [Barrero A., 2006; Justica J., 2011]. Another advantage of Cp<sub>2</sub>TiCl is that it allows to reduce the use of derivatives since this SET is compatible with numerous functional groups such as silanes, esters, and ethers. Finally, tetrahydrofuran and toluene are solvents commonly used to generate Cp<sub>2</sub>TiCl from Cp<sub>2</sub>TiCl<sub>2</sub> and Mn or Zn. Both solvents are considered usable by the guidelines for solvents used in the pharmaceutical industry [Tables and List Guidance for Industry, U.S. Department of Health and Human Services. FDA. 2017, (accessed 03/19/2020)] and their hazardous impact is thus minimal. Therefore, many of the twelve principles of green chemistry are verified by Cp<sub>2</sub>TiCl [Castro Rodríguez M., 2017; Rosales Martínez A., 2021.] (Figure 1). This reagent is a good example to teach green chemistry to chemistry and chemical engineering students.



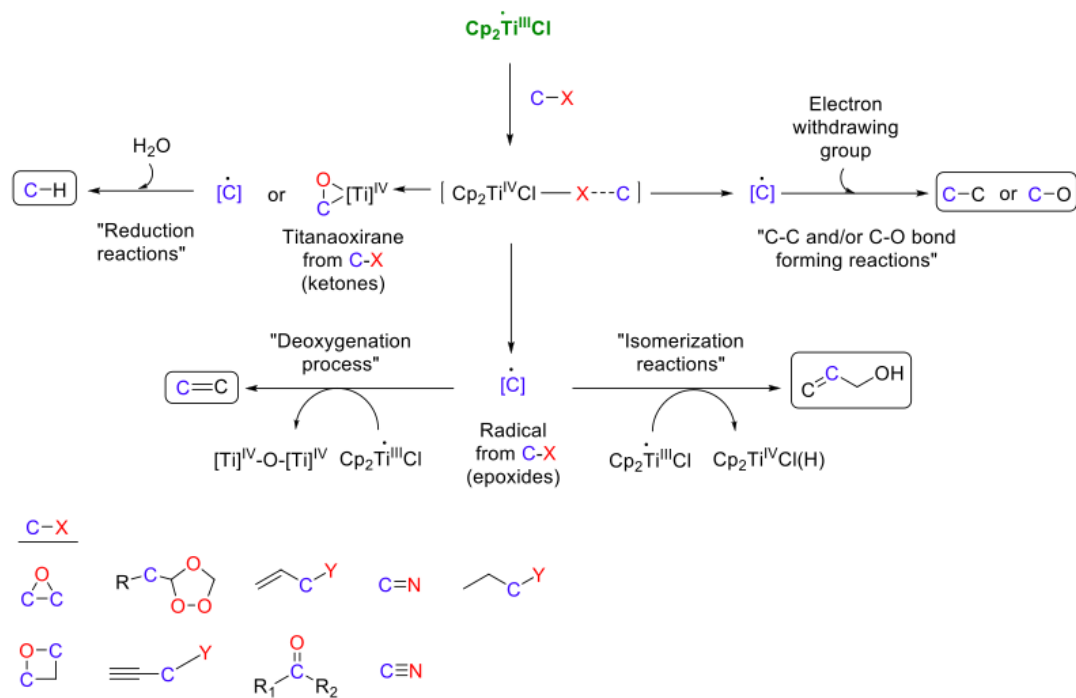
**SCHEME 3.** Ti(III)-catalyzed reductive and non-reductive epoxide ring-opening reactions.



**FIGURE 1.** Principles of green chemistry that meets Cp<sub>2</sub>TiCl.

## Cp<sub>2</sub>TiCl as a reagent widely used in organic and organometallic chemistry

The main applications in organic and inorganic chemistry of this SET reagent are briefly summarized below. One of the most useful features of Cp<sub>2</sub>TiCl complex is its ability to form carbon radicals by the homolytic cleavage of C-X bonds (X being a heteroatom with free valence electrons) present in different functional groups (Scheme 4). In the presence of electron withdrawing groups and in the absence of a hydrogen atom-donor, these carbon radicals can normally be used to generate a new C-C or C-O bond, either inter- or intramolecular (C-C and C-O bond forming reactions, Scheme 4) [Rosales A., 2015]. In the presence of a good hydrogen-atom donor, such water, a H-atom transfer to the carbon radical [Cuerva J. M., 2006] or to the titanaoxirane intermediate [Rosales A., 2014] takes place (reduction reactions, Scheme 4). The reduction of ketones catalysed by Cp<sub>2</sub>TiCl using water as H-atom donors takes place through organometallic mechanisms, rather than via radical mechanism (titanaoxirane intermediate), as previously reported [Barrero A. F., Rosales A., Cuerva J. M., Gansäuer A., and Oltra J. E., 2003]. On the other hand, in the absence of electron withdrawing functional groups or good hydrogen-atom donors, epoxides react to yield allylic alcohols or alkenes [Justicia J., 2009]. Thereby, tertiary carbon radicals lead to allylic alcohols through a reaction in which Cp<sub>2</sub>TiCl removes a  $\alpha$  radical hydrogen atom (isomerization process, Scheme 4) [Justicia J., 2009]. If the radical is on a *di*-substituted carbon, an alkene is formed (deoxygenation process, Scheme 4) [Justicia J., 2009]. In this case, the radical is trapped by a second Cp<sub>2</sub>TiCl species to generate a bimetallic specie that eventually leads to the formation of an alkene.

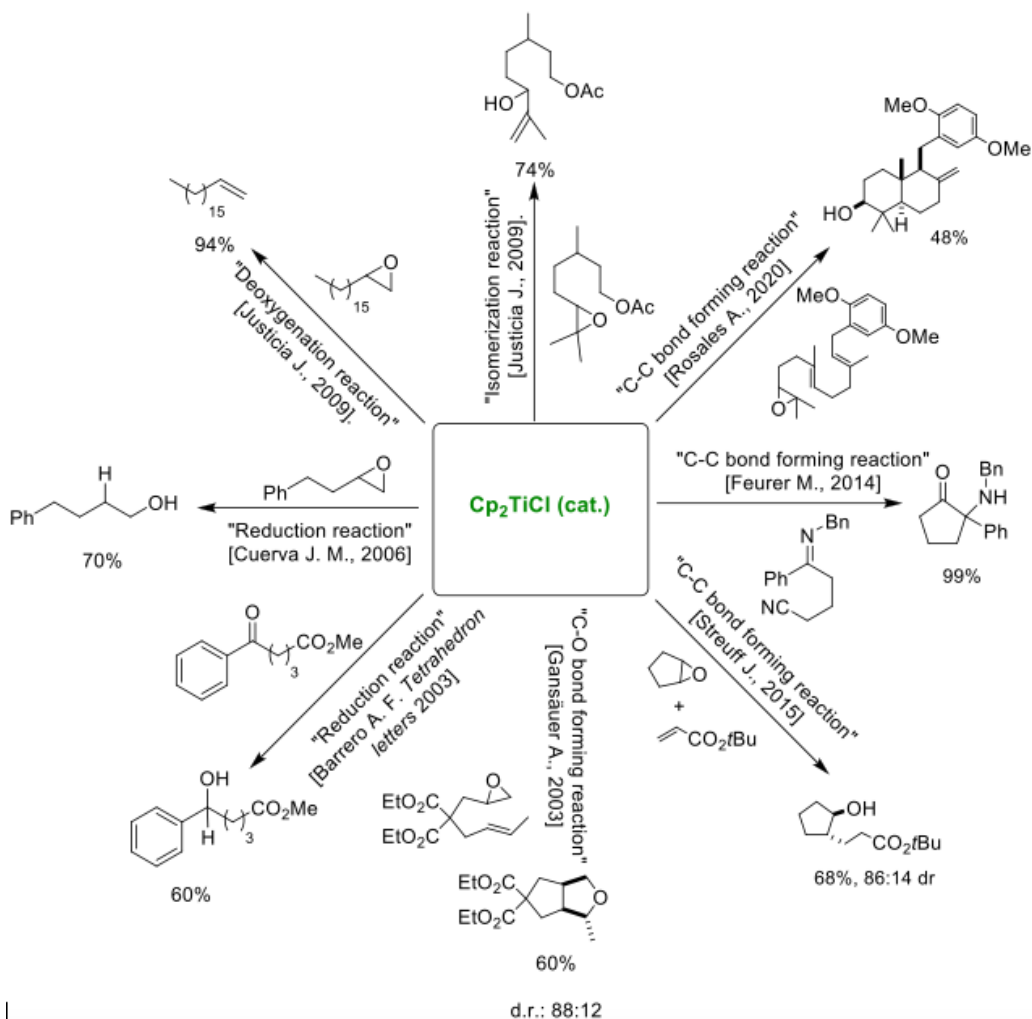


Y: Cl, Br  
 X: O, Cl, Br

R: H, alkyl, phenyl...

**SCHEME 4.** Reactivity of Cp<sub>2</sub>TiCl.

Therefore, without describing the mechanistic consideration in detail and depending on the reaction conditions, many important chemical transformations are catalysed by Cp<sub>2</sub>TiCl. Several examples of this catalytic processes are reported in Scheme 5.



**SCHEME 5.** Cp<sub>2</sub>TiCl-catalyzed C-C and C-O bond forming reactions, reduction, deoxygenation, and isomerization reactions.

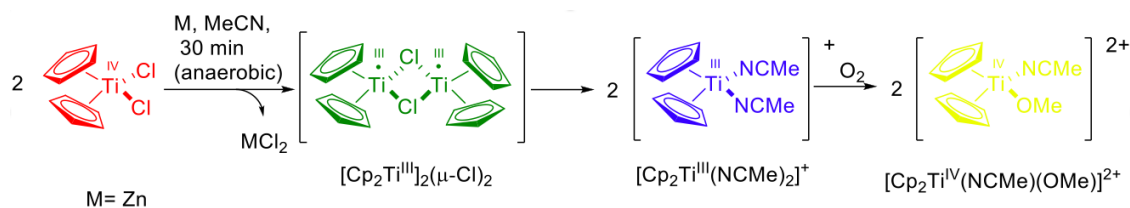
## Cp<sub>2</sub>TiCl as a colorimetric indicator for learning inert atmosphere techniques

The use of Cp<sub>2</sub>TiCl as a very useful visual aid for students learning standard Schlenk vacuum line techniques was reported [Nieter Burgmayer, S. J., 1998]. The students were instructed to practice solvent degassing and filtering through frits using a Cp<sub>2</sub>TiCl solution. The correct degassing of the solvent can be judged by the students if a change in colour in the solution is observed (Scheme 6). The initially orange-red solution of Cp<sub>2</sub>TiCl<sub>2</sub> turns green when Cp<sub>2</sub>TiCl is formed. Additionally, if the solvent is acetonitrile the green colour changes to deep blue indicating the formation of [Cp<sub>2</sub>Ti(NCCH<sub>3</sub>)<sub>2</sub>]<sup>+</sup>, a result of facile dimer cleavage in the coordination solvent acetonitrile. Finally, the students observed that when the solution of titanocene(III) is exposed to O<sub>2</sub>, the deep blue colour is rapidly bleached to yellow as titanocene(III) species is oxidized back to titanium(IV) [Nieter Burgmayer, S. J., 1998].



(Scheme 6). This colour change is used as a colorimetric analytical indicator to determine the presence of oxygen. Later, colorimetric analysis and mass spectrometric indicated that oxidation from Ti(III) to Ti(IV) gives a host of oxygen-containing intermediates, where appearance parallels the observed color change [Yeung D., 2018]. In all cases, the use of Cp<sub>2</sub>TiCl in radical-initiated catalysis needs an inert atmosphere to avoid the oxidation to Ti(IV). Representative examples where Cp<sub>2</sub>TiCl is used under an inert atmosphere are radical cascade cyclization, coupling reactions, umpolung reactions, THF-ring formation reactions, H-atom transfer, Barbier-type reactions and deoxygenation of alcohols [Rosales A., 2015].

**SCHEME 6.** Reaction scheme for synthesis of the colorimetric indicator [Cp<sub>2</sub>Ti(NCMe)<sub>2</sub>]<sup>+</sup> and its reaction with oxygen.



## Conclusions

The synthesis and applications in multidisciplinary chemistry of Cp<sub>2</sub>TiCl reveal a valuable reagent that can be used as didactic material in the teaching of chemical sciences and chemical engineering as a model reagent capable of transmitting new advances in different areas of chemical knowledge. This article shows the multidisciplinary character of this monoelectronic transfer reagent and allows the student the possibility of handling concepts of green, organic, organometallic and analytical chemistry.

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