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Shining light on Ti^{IV} complexes: exceptional tools for metallaphotoredox catalysis

Andrea Fermi,^{*,[a]} Andrea Gualandi,^{*,[a]} Giacomo Bergamini,^{*,[a]} and Pier Giorgio Cozzi^[a]

[a] Dr. Andrea Fermi
Dr. Andrea Gualandi
Prof. Dr. Giacomo Bergamini
Prof. Dr. Pier Giorgio Cozzi
Dipartimento di Chimica "G. Ciamician"
Università di Bologna
via Selmi 2, 40126 - Bologna, Italy
E-mail: andrea.fermi2@unibo.it, giacomo.bergamini@unibo.it, andrea.gualandi10@unibo.it
<https://site.unibo.it/stereoselective-metal-photoredox-catalysis-lab/en>
<https://site.unibo.it/bergaminigroup/en>

Abstract: Titanium is one of the most abundant and environmentally innocuous metals. Ti-based organometallic compounds have long been used as versatile homogeneous catalysts in synthetic chemistry and still remain highly attractive for the development of sustainable transformations. With the emerging role of photoredox catalysis, the selectivity of the radical initiation in electron transfer-mediated reactions has been shown to be fundamental in terms of synthesis efficiency. Recent examples have displayed the effectiveness of inorganic and organic chromophores at the excited state in triggering the redox chemistry of $Ti^{IV/III}$ complexes. In this *minireview*, we will illustrate the underlying principles and practicability of these – still uncommon – metallaphotoredox catalytic reactions.

1. Introduction

Photoredox catalysis has become a research topic in continuous expansion in the recent years.^[1–7] The combination of a photoredox catalytic cycle with other catalytic cycles, working cooperatively, opens wide opportunities to innovative and powerful transformations.^[8] The merger of photoredox catalysis with metal catalysis gives life to the so-called metallaphotoredox catalysis.^[9] In these chemical processes, a photoredox catalyst can cooperate with a metal catalyst by managing its oxidation states through a single electron transfer (SET) event. Examples of activation of metal complexes *via* energy transfer (EnTr) from chromophores at the excited state were also recently reported.^[10] Metallaphotoredox catalysis based on different metals such as chromium,^[11,12] cobalt,^[13,14] nickel,^[15–17] copper,^[18] and palladium^[19] was subject of study in the recent years in combination with photoredox catalytic cycles.

Titanium shows a rich redox chemistry, which was elegantly exploited by Fürstner^[20] and Gansäuer^[21] to establish redox catalytic cycles based on this metal. In these seminal works the authors envisaged the possibility to employ catalytic amounts of low valent titanium species, generated *in situ* by reduction with zinc, and take advantage of a scavenger (e.g., R_3SiCl , lutidine hydrochloride) able to liberate the Ti^{IV} complex from the organic product, allowing another possible turn over.

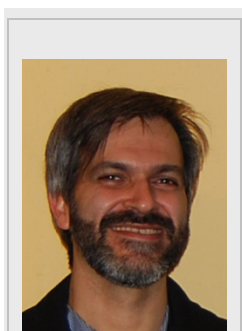
The merging of photoredox catalysis with titanium redox chemistry would allow the use of simple organic electron donor as sacrificial reductant, thus avoiding the requirement of a stoichiometric excess of metal reductant to obtain the titanium in its active (Ti^{III}) oxidation state. This approach opens the metallaphotoredox catalysis scenario to Ti-based complexes from a green chemistry perspective. Herein we report recent examples of this promising marriage.

Andrea Fermi obtained his PhD in Chemistry in supervision of Professors Paola Ceroni and Marc Cardiff University under the guidance of Prof. the University of Bologna. His research mainly opto-electronic properties of molecular materials.



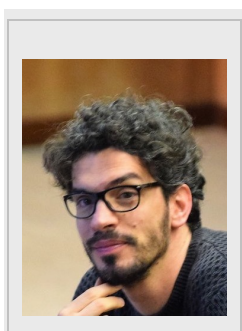
2013 from the University of Bologna and Aix-Marseille Université, under the Gingras. After post-doctoral stays at the University of Namur and at the Davide Bonifazi, he recently joined the group of Prof. Giacomo Bergamini at focuses on photoinduced processes in supramolecular assemblies and on

Andrea Gualandi was born in Bologna, Italy, in 2008 on the diastereoselective synthesis of University of Neuchâtel. Since 2010, he has been Postdoctoral Associate, Junior Assistant same University and his main interests are the



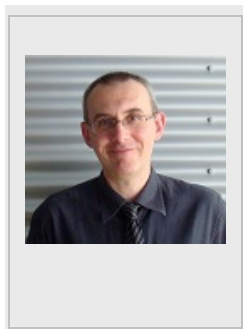
1978. He received his Ph.D. in Chemistry at the University of Bologna in the amines. In the same year, he joined the group of Prof. R. Neier at the working at the University of Bologna in the group of Prof. P. G. Cozzi as a Professor. Now he holds the position of Senior Assistant Professor in the development of new catalytic processes and new organic dyes.

Giacomo Bergamini obtained his Ph.D. in of Prof. Vincenzo Balzani. He is now Associate coauthor of more than 100 scientific papers in ITN-2016 "PHOTOTRAIN" which aims at chemical energies, such as pharmaceuticals, foods



Chemical Science at the University of Bologna in 2007 under the supervision Professor at the Giacomo Ciamician Department in Bologna and he is refereed international journals. He is the Coordinator of the H2020-MSCA-converting solar light into useable, sustainable and exploitable forms of and/or solar fuels.

Pier Giorgio Cozzi is full professor in Bologna. The development of new, enantioselective catalytic and inorganic literature and through experimental active in developing new photoredox reactions, new metal photoredox catalytic reactions. In 2020, PGC Society.



University and Degree Programme Director for the MSc in Chemistry. reactions through an extensive knowledge of organic, organometallic, planning are the main topics of his researches. Currently, his group is dyes for photocatalysis and photopolymerizations, and synergistic was appointed *Chemistry Europe Fellow* from the European Chemical

2. $\text{Ti}^{\text{IV/III}}$ catalysis with stoichiometric metallic reductants

Due to its intriguing redox properties, Ti-based organometallic chemistry was carefully described and fruitfully employed in the past decades for synthetically useful organic transformations.^[22–26] Specifically, the $\text{Ti}^{\text{IV/III}}$ redox couple facilitates the access to radical intermediates with peculiar regio- and chemoselectivity otherwise not feasible by using other metal complexes.^[27,28]

Titanocenes (and mainly titanocene dichloride, $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$) offer a wide range of possible applications.^[29] $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ is generated by reduction of commercially available $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ (stage *a*, Figure 1). The oxophilic $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ generally endorses the binding of hard Lewis bases (stage *b*, typically epoxides), but recent developments demonstrated the possibility to use other substrates such as enones,^[30] nitriles,^[31] *N*-acylaziridines,^[32] chloroalkanes^[33] and cyclopropyl ketones.^[34] The key-feature provided by the Ti center in titanocenes implies an inner-sphere electron transfer from Ti^{III} to the coordinated organic moiety (stage *c*). This step is usually followed by a bond cleavage in the organic functional group coordinated to the metal center, leading to the yield of a reactive C-centered radical, with concomitant formation of an oxidized Ti^{IV} center (stage *d*). The so-formed C-radical intermediate can further react with radical acceptors (H-donors or Michael acceptors).

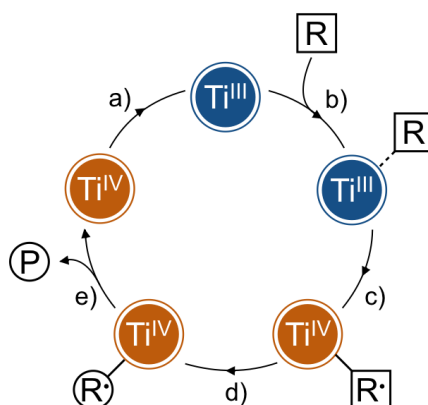
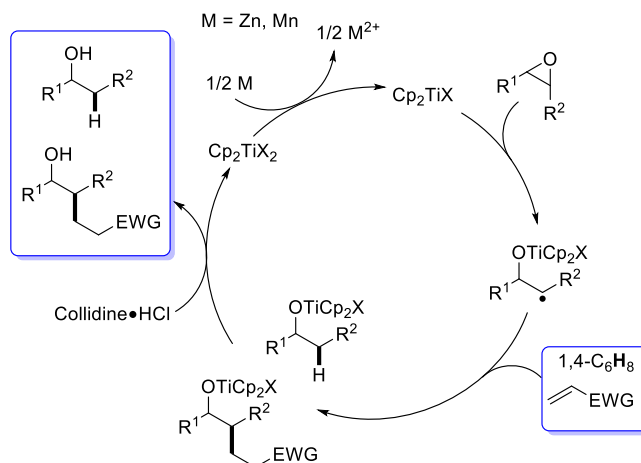


Figure 1. General scheme for a $\text{Ti}^{\text{IV/III}}$ promoted catalytic cycle: a) generation of the Ti^{III} active species via reduction of Ti^{IV} ; b) coordination of the substrate R; c) reductive initiation; d) radical rearrangement; e) product (P) elimination and restoration of the pristine Ti^{IV} complex.

The organic product is then liberated by the cleavage (protonation, stage *e*) of the Ti^{IV} -product bond by the use of a suitable scavenger. The released Ti^{IV} complex is now suitable for *in situ* reduction, normally obtained by a stoichiometric reductant, that yields the Ti^{III} complex and completes the catalytic cycle.

Nugent and RajanBabu introduced $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ as a stoichiometric novel single-electron transfer species capable of generating a C-centered radical from an epoxide.^[35,36] By coupling the opening of epoxide with a hydrogen atom transfer (HAT) donor, the reductive opening of epoxides occurs. A catalytic variant of this chemistry, that started from meso-epoxides, was reported by Gansäuer some years later.^[37,38] The so-introduced catalytic version overcomes the limitation of using stoichiometric amounts of titanocene complexes to achieve reagent control. The proposed catalytic cycle for the titanocene-catalyzed epoxide openings is reported in Scheme 1.

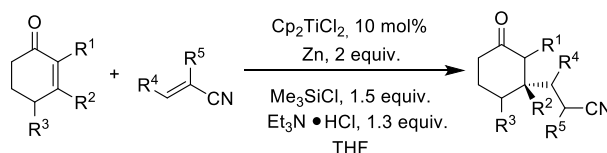


Scheme 1. Titanocene-catalyzed epoxide opening.

Inner-sphere SET from $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ (generated from $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ by reduction with metallic Zn or Mn) to the coordinated epoxide produces the C-O bond cleavage and generates the carbon centered radical. The so-formed C-radical species can engage an HAT reaction with 1,4-cyclohexadiene or water^[39] to give the corresponding Ti-alkoxide; in the presence of a Michael acceptor a Giese-type radical addition can also take place. The Ti^{IV} -alkoxide species generated in the catalytic cycle were protonated by pyridines hydrochloride (e.g. collidine hydrochloride) to give the corresponding alcohol and restore the $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$.

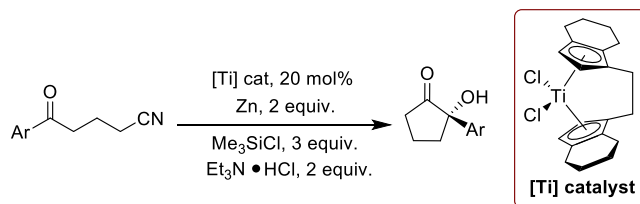
The use of titanium complexes in catalytic amounts made possible interesting application of chiral titanocene derivatives in the catalyzed epoxide opening, fully explored by the Gansäuer group.^[40,41] In order to achieve high enantioselectivity, the titanocene catalyst was designed to allow diversified interactions with the enantiotopic substituents of the epoxide.

The formation of ketyl radical from conjugated aldehydes and ketones was used for the construction of cyclic products by Streuff,^[30] in the reductive cross coupling of enones with acrylonitriles (Scheme 2). The ketyl radical, formed by SET from $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$, is stabilized by resonance and trapped by acrylonitriles, with the concomitant formation of a radical next to the cyano group. This can be reduced by a second molecule of $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ to the corresponding enolate. The intermediate titanium and enolate are protonated by the scavenger, releasing the Ti^{IV} for the turnover. This reaction was further investigated in useful intramolecular versions.^[42–44]



Scheme 2. Reductive cross-coupling of enones with acrylonitriles.

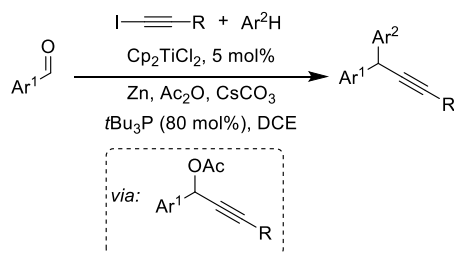
Finally, by the use of the chiral Britzinger's ansa titanocene complex,^[45] Streuff reported a stereoselective intramolecular reaction with aryl and alkyl oxo-pentane derivatives (Scheme 3).^[46] The products isolated after the work up are α -aryl hydroxo cyclopentanones and cyclohexanones, with 60-94% enantiomeric excesses.



Scheme 3. Enantioselective reductive ketone–nitrile coupling in the presence of chiral titanocene catalyst.

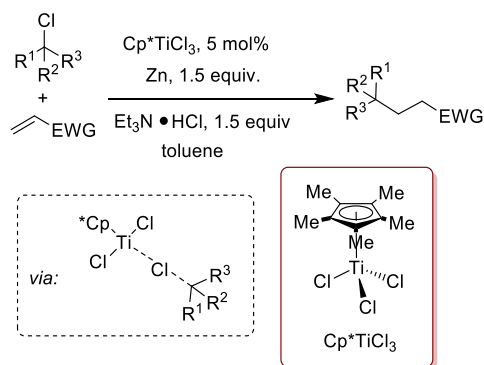
The ability of the titanium to behave as Lewis acid was coupled with titanocene chemistry in an example of three components coupling, reported by Ashfeld (Scheme 4).^[47] The reaction of an iodoacetylide with aldehydes, in the presence of Zn and Ac_2O as scavenger, was performed with nucleophiles such as electron-rich aromatic compounds, allylsilanes, and enol silyl ethers. The titanium acetylide, formed in the reaction conditions, was proposed to undergo transmetalation with ZnCl_2 (obtained upon reduction of the titanium complex with Zn). The zinc acetylide

is then able to react with the aldehyde, forming the corresponding propargylic zinc alkoxides, subsequently acetylated by Ac_2O . The resulting propargylic-benzylic ester undergoes $\text{S}_{\text{N}}1$ -type reaction with an electron-rich aromatic compound, due to the presence of the Ti^{IV} Lewis acid.



Scheme 4. Titanocene-catalyzed multicomponent coupling.

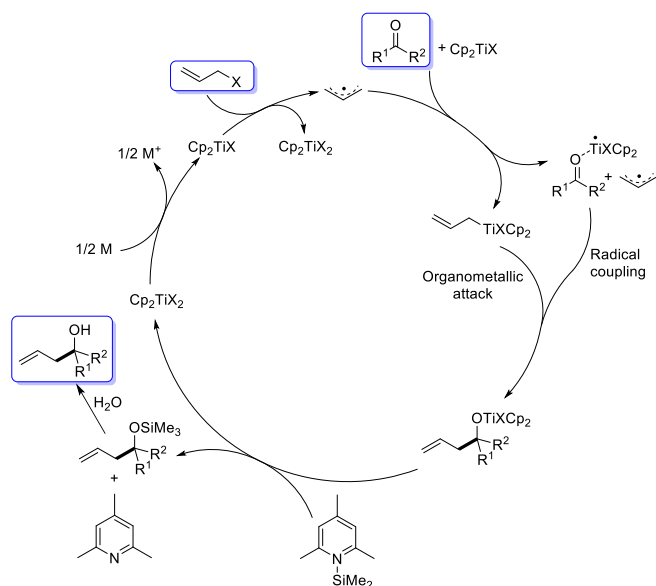
For the Ti^{III} chemistry, all the displayed examples showed an elusive application on tertiary radicals and for the activation of chloroalkenes, due to the high dissociation energy associated to the formation of the C-centered radical. As the chloroalkenes feature high reduction potential ($E_{\text{red}} < -2.0 \text{ V vs SCE}$) an inner sphere SET can favour their direct reduction. In order to accomplish the desired transformation, Lin and co-workers^[33] have reduced the size of the titanium complex, employing $\text{Cp}^*\text{Ti}^{\text{IV}}\text{Cl}_3$ (Scheme 5). The favourable interaction of $\text{Cp}^*\text{Ti}^{\text{IV}}\text{Cl}_3$ with chlorine atoms allowed the generation of secondary and tertiary C-centered radicals, which then were reacted with different Michael acceptors.



Scheme 5. Ti-catalyzed radical alkylation of secondary and tertiary alkyl chlorides using Michael acceptors.

Titanocene (III) complexes find a very interesting application in the Barbier type reactions between activated alkyl halides and carbonyl compounds. Contrarily to chromium^[11,12,48] (Nozaki–Hiyama–Kishi reaction)^[49,50] and nickel,^[17,51,52] titanium represents an excellent green alternative. Oltra, Cuerva, and Gansäuer reported the allylation, prenylation and intermolecular crotylation of aldehydes and ketones using a stoichiometric amount of $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ easily generated *in situ* from $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$.^[53] A Ti-catalyzed version of the reaction was described by the use of a substoichiometric quantity of $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ in the presence of Mn as reducing agent, Me_3SiCl and 2,4,6-collidine as scavenger for the regeneration of the titanocene complex (Scheme 6).^[54] The reaction mechanism pathway was shown to be substrate dependent. The nucleophilic attack of the Ti^{IV} -allyl intermediate (generated from reaction of two molecules of $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ and the allyl halides) to the carbonyl derivative is plausible for the intermolecular reaction of ketones. In the cyclization and intermolecular reactions with unsaturated aldehydes, a radical coupling process is more likely to be active. Finally, for intermolecular reactions with non-conjugated aldehydes both organometallic and radical pathways were proposed.

Propargyl halides are also compelling substrates for Barbier type reactions based on titanium. When unsubstituted propargyl halides were employed in the reaction with carbonyl compound, homopropargylic alcohols were obtained. A different behavior was observed with the substituted propargyl halide, while aldehydes lead mainly to the formation of the α -hydroxy-allenes and ketones afford mainly internal homopropargylic alcohols.^[55] In all the mentioned transformations, the key and important stage for the formation of the reactive Ti^{III} species – *de facto* a single electron transfer – is therefore crucial for the activation of the Ti-centered redox process that leads to the triggering of the catalytic cycle.



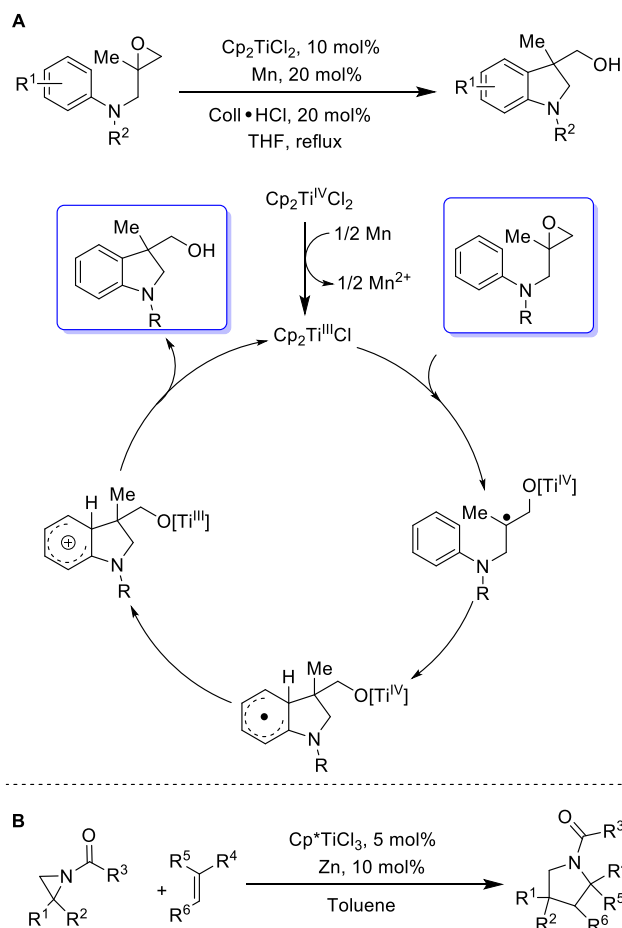
Scheme 6. Titanocene-catalyzed Barbier-type allylation of aldehydes and ketones.

3. $\text{Ti}^{\text{IV/III}}$ catalysis without stoichiometric reductants

From the discussion that we have illustrated, it seems that in order to perform the interesting $\text{Ti}^{\text{IV/III}}$ redox chemistry in the formation of C-centred radicals, the use of a stoichiometric reductant (Zn, Mn, electrochemistry) is necessary. In some cases it is possible to self-sustain the oxidation and reduction steps, thus the need of a stoichiometric reductant is avoided.

In these reactions, a radical intermediate obtained in the cycle needs to act as reductant for the Ti^{IV} species, restoring the Ti^{III} state. Obviously, the cycle can start only if Ti^{III} is present and, therefore, a catalytic amount of external reductant needs to be present in the reaction mixture together with a chemically stable Ti^{IV} species. This concept was envisaged by Gansäuer and Lin. Gansäuer and coworkers reported an intramolecular redox-relay transformation based on tertiary epoxides with pendant π -aromatic substituents (Scheme 7A).^[28,56] A catalytic amount of Mn (20 mol%) is sufficient to reduce the Ti^{IV} to the active $\text{Cp}_2\text{Ti}^{\text{III}}\text{X}$, which induces the opening of the epoxide. The tertiary C-centered radical is then able to attack the π -aromatic system by a sort of Minisci-type reaction, forming a persistent aryl radical. The reduction of the aryl radical reforms the Ti^{III} catalyst, with the concomitant formation of the arenium ion that loses a proton to rearomatize. Taking advantage of these concepts, Lin and coworkers described a reductive [3+2] cycloaddition of *N*-acylaziridines with alkenes (Scheme 7B).^[32]

The main difference introduced by the author consists in the use of $\text{Cp}^*\text{Ti}^{\text{IV}}\text{Cl}_3$. The complex was reduced by a substoichiometric amount of Zn. Interaction of the Ti^{III} with the acyl group of the aziridine favors the formation of the stabilized β -amido radical, that is trapped by the conjugated alkene to give a stabilized electrophilic C-radical. This new radical, stabilized by phenyl or EWG groups, is capable of cyclize with the Ti^{IV} -azaenolate. The Ti-induced opening of cyclopropyl substituted ketones was expanded by Lin to include an interesting enantioselective variant.^[34] However, in this case a stoichiometric amount of reductant was employed. Nevertheless, the reaction is remarkable not only for extending the concept of the achiral version of the reaction, but also for the introduction of Salen ligands^[57] in the Ti^{III} chemistry as valid substituted for the relatively expensive enantiopure chiral metallocene catalysts. Due to the easy fine-tuning of the amine and aldehyde backbones and the facile access to a vast library of stable Ti complexes,^[58] we can predict that further work will be addressed on the use of Ti^{IV} -Salen metal complexes, in this or related areas.



Scheme 7. Redox-neutral methodologies with titanium^{IV} in absence of stoichiometric reductants.

As anticipated above, due to the detrimental air sensitivity of the Ti^{III} species, Cp₂Ti^{III}Cl is usually generated *in situ* by the reduction of Cp₂Ti^{IV}Cl₂ by metallic zinc, manganese or magnesium (Figure 2, path *a*). Nevertheless, the catalytically active Cp₂Ti^{III}Cl can be also analogously generated electrochemically from Cp₂Ti^{IV}Cl₂ (Figure 2, path *b*). Reduction at the electrode interface avoids, in principle, the use of harsh chemical reductants and the activation of undesirable side reaction involving molecular species containing highly electron-deficient functional groups. The electrocatalytic chemistry of Cp₂Ti^{IV}Cl₂ was taken into account for the ring-opening and consequent reduction of epoxides^[59] and for reductive dehalogenation of organic halides.^[60] In addition, it was recently demonstrated that the dehalogenation equilibrium involving the [Cp₂Ti^{IV}Cl₂]^{•−} radical anion has critical consequences in the electrocatalytic radical arylation of epoxides.^[61]

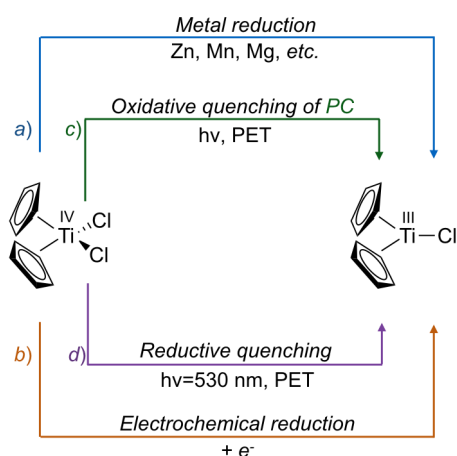


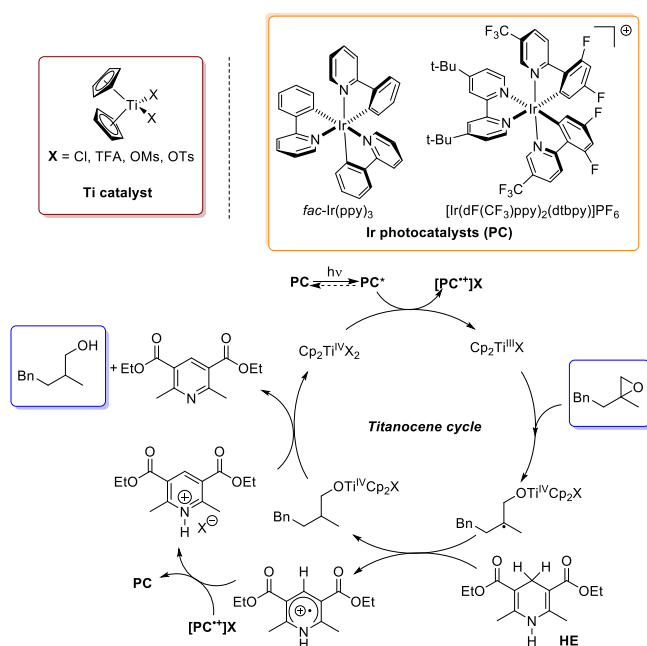
Figure 2. Strategies for the formation of Cp₂Ti^{III}Cl: *a*) metal reduction; *b*) electrochemical reduction; *c*) oxidative quenching of a photocatalyst at excited state *via* PET; *d*) reductive quenching of Cp₂Ti^{IV}Cl₂ at the excited state *via* PET from an electron-donor.

It is worth underlining that, in order to obtain synthetically useful chemical transformations mediated by organic radicals, an efficient initiation is a prime requirement. Recent examples have displayed that under carefully controlled conditions, efficient and highly selective catalytic reactions based on titanocenes can be developed by the selective excitation of a photoredox partner or of the titanium complex itself, using commonly available and affordable visible light sources. In the next section we will therefore introduce the capability of titanocenes to encounter photoinduced single electron transfer (PET, Figure 2, paths *c* and *d*) in order to activate the $\text{Ti}^{\text{IV/III}}$ redox chemistry.

4. Titanocenes in metallaphotoredox catalytic reactions

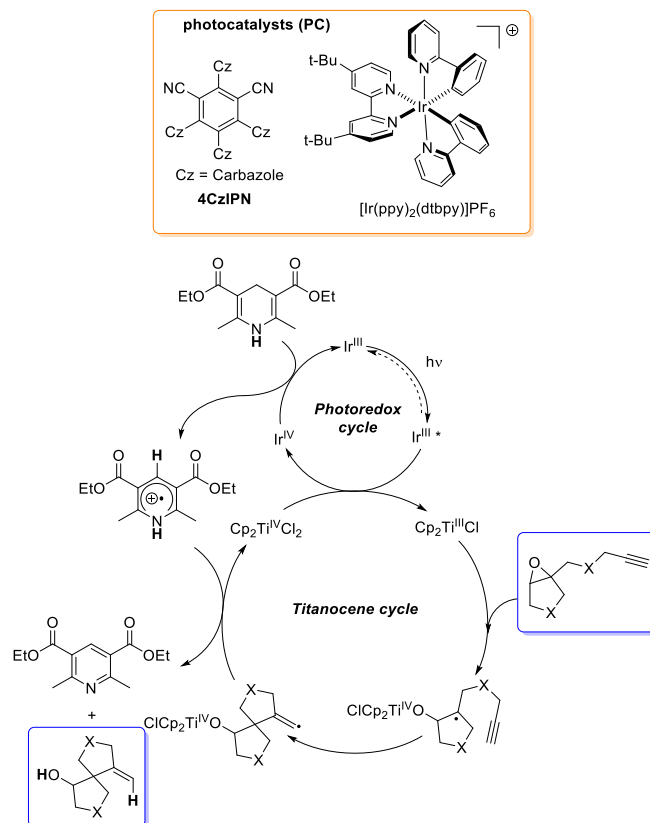
The combination of Ti^{IV} species with other transition metal complexes (based on Cr,^[62] Ni^[63,64] and Ir^[65]) in thermal catalysis was recently reported, displaying the isomerization of epoxides to allylic alcohols afforded by a bimetallic redox-relay mechanism.^[66]

On the other hand, the suitability of the merger of photoredox and $\text{Ti}^{\text{IV/III}}$ catalysis was recently demonstrated by the group of Gansäuer in a pertinent work.^[67] By irradiating with visible light solutions containing a polypyridyl complex (either Ir^{III} or Ru^{II}) as a photocatalyst (PC), $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ and an epoxide, the authors demonstrated the reductive ring opening of the latter to the corresponding alcohol *via* a radical mechanism supported by the Ti metal center. The mechanism relies on the presence of a sacrificial hydrogen-atom donor (Hantzsch ester, HE; $E_{\text{ox}} \approx 0.89$ V vs. SCE in DMF^[68]) able to donate a hydrogen atom to the C-centered radical generated upon the SET from the Ti^{III} species coordinate to the epoxide (Scheme 8). In the proposed mechanism, the role of the photoredox-active chromophore is twofold: *i*) its excited state is able to promote a PET to $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$, producing the Ti^{III} reactive center and its corresponding radical cation $[\text{PC}]^{+\bullet}$, which is in turn *ii*) able to oxidize radical Hantzsch ester intermediate to the corresponding pyridinium ion. Due to the strong acidity of the latter, it can act as the scavenger necessary for the release of the product from the Ti^{IV} center. Furthermore, this reaction scheme supports the intramolecular cyclization of aromatic epoxides, displaying the proficiency of this approach in the conversion of more electron-deficient substrates. The study reports a screening as well of several Ti^{IV} precatalysts with different ligands which slightly modify the reduction potential.



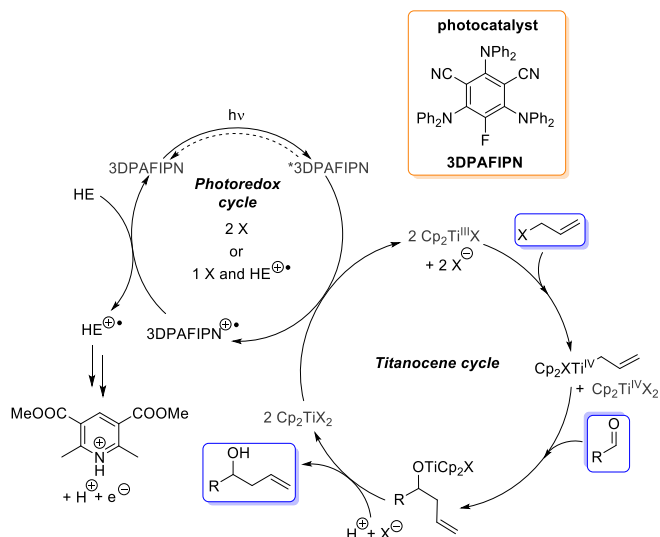
Scheme 8. Reductive ring-opening of epoxides *via* $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ -mediated metallaphotoredox catalysis under visible light irradiation.

In an analogous example,^[69] Shi and coworkers expanded the use of the photoredox-active species to the organic chromophore **4CzIPN** ($E_{00,S} \approx 2.67$ eV; $E^*_{\text{ox},S} \approx -1.18$ V vs. SCE in CH_3CN ^[70]). Its relatively and inexpensive easy preparation represent desirable requisites for its employment as photocatalysts. In this example, **4CzIPN** is able to promote, in combination with titanocene dichloride, for the photoactivated production of synthetically demanding spirocycles, which represent attractive targets in pharmaceutical chemistry (Scheme 9). In addition, iridium complex $[\text{Ir}(\text{dtbbpy})(\text{ppy})_2]\text{PF}_6$ is a compelling photocatalyst in this transformation and the authors performed an interesting spectroscopic investigation on the transient radical species with this complex. The studies evidenced that the reduction of $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ to the corresponding Ti^{III} center – provided by the photocatalyst in its excited state – is accompanied by a color change of the solution from orange to yellow, with the lowest energy absorption LMCT band of $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ rapidly decreasing its intensity. The low oxidation state titanium complex starts the radical cascade to the exocyclic vinyl radical. Hydrogen and proton transfer from the oxidized Hantzsch ester to this radical intermediate provides the desired product.



Scheme 9. Radical opening/spirocyclization of epoxyalkynes *via* $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ metallaphotoredox catalysis under visible light irradiation.

In another recent report,^[71] we employed another isophthalonitrile derivative (**3DPAFIPN**, $E_{0,0.5} \approx 2.68$ eV; $E^*_{\text{ox},5} \approx -1.38$ V vs. SCE in CH_3CN ^[70]) for the photoactivation of $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ in a Barbier-type allylation of aldehydes (Scheme 10), thus expanding the scope of photoassisted $\text{Ti}^{\text{IV/III}}$ catalysis to intermolecular C-C bond formations. In the proposed mechanism, the electron transfer between the $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ and the excited state of the photocatalyst and/or from the oxidized form of the Hantzsch ester generates the $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ active catalyst. Allyl derivatives react with two molecules of $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ to generate allyl titanium complex that act as nucleophile through carbonyl compounds. Hantzsch ester and its protonated rearomatized form restore the catalytic cycle by reduction of the **3DPAFIPN**⁺⁺ and protonation of the titanium-alkoxy bond, respectively. From the perspective of the oxidative quenching event necessary for triggering the Ti-center redox cascade, the article displays how to take advantage of the remarkable photophysical properties of this class of organic dyes. By virtue of their thermally-activated delayed fluorescence, this class of chromophores shows long-lived excited states (up to 10^2 μs in deoxygenated solutions at r.t.) that allow efficient quenching dynamics towards both reductants and oxidants. In addition, their electron-deficient aromatic core permits facile substitution by different electron-donors allowing a wide range of modulation of the photophysical and redox properties.^[70]

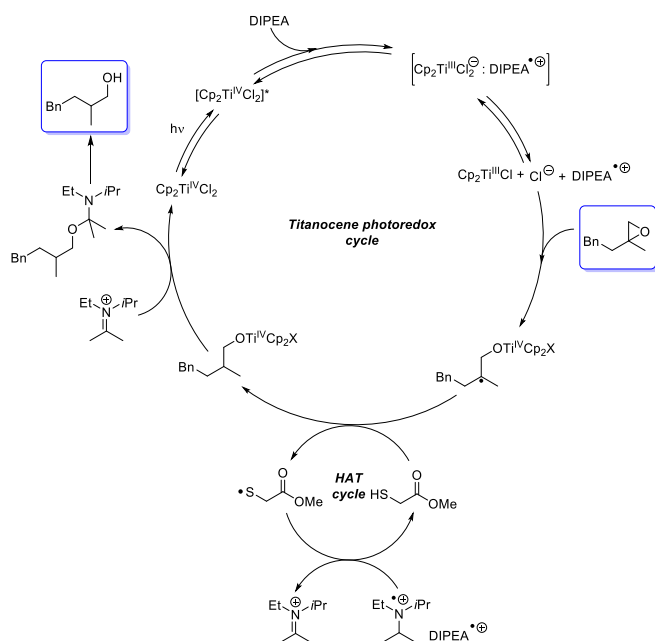


Scheme 10. Titanium catalyzed photoredox allylation of aldehydes with visible light.

These findings prompted further developments in photocatalyzed C-C bond formations, merging the peculiar chemistry of titanocenes with conventional metal catalysis triggered by photoinduced electron transfer. Doyle and coworkers^[72] recently employed the merger of nickel, titanium, and organic photoredox catalysis for coupling reactions between three different class of epoxides and aryl iodides. For each subset of epoxides, the authors identified distinct ligands for the Ni^0 metal center able to suppress undesired homocoupling and rearrangements. Furthermore, through comprehensive mechanistic investigations, the authors demonstrated that the photoreduction *via* PET to $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ is crucial to initiate the reactivity by means of the epoxide ring-opening.

The photochemical properties of titanocenes and related Ti^{IV} complexes have been extensively employed in several applications, especially in photoinitiated polymerizations.^[73,74] The irradiation of the mixtures containing $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ and Zn^0 at UV or visible wavelengths can promote the reactivity of this single-electron transfer agent for the reduction of organic halides.^[75]

The groups of Gansäuer and Flowers lately reported the use of $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ as the sole photoactive species in the reductive opening of aliphatic epoxides (Scheme 11).^[76] Relying on the analysis of the bimolecular quenching, the authors showed that the excited triplet state of $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ ($E_{0,0,\text{T}} \approx 2.14$ eV; $E_{\text{red,T}}^* \approx 1.39$ V vs. SCE), produced upon excitation of its low-energy lying LMCT transition, is effectively quenched in the presence of *N,N*-diisopropylethylamine (DIPEA), leading to the corresponding transient ion pair which eventually evolves in the Ti^{III} redox-active species. The carbon center radical formed performs a hydrogen atom transfer (HAT) process with methyl thioglycolate to give the corresponding Ti^{IV} -alkoxy species. The HAT cycle is sustained by the radical cation $\text{DIPEA}^{*\oplus}$, whereas the titanocene redox cycle is closed by the interaction with the iminium ion of DIPEA, which serves as scavenger for the Ti^{IV} species. The authors proposed the formation of a hemiaminal as initial reaction product that after hydrolysis affords the corresponding alcohol.

**Scheme 11.** Titanocene as photocatalyst in the reductive ring opening of epoxides.

5. Titanocenes: photophysics and electrochemistry

The merger of Ti catalysis with photoredox catalysis allows the redox cycling, and will be certainly investigated more in the future. However, for the design of new processes and to better understand the requirements of each reaction partner, we illustrate the photophysical and electrochemical properties of titanocenes.

$\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ is a red solid, thus showing a bundle of peculiar absorption bands in the visible spectrum when dissolved in a suitable solvent. Due to its formal $3d^0$ electronic configuration, the lowest energy absorption band ($\lambda_{\text{abs}}=530$ nm in CH_3CN) is assigned to a combination of ligand-to-metal charge-transfer (LMCT) transitions from peripheral cyclopentadienyl and chloride ligands to the Ti center (Figure 3A).^[77,78] The complex is not luminescent in aerated solutions at room temperature, while an easily detectable phosphorescence ($\lambda_{\text{max,ph}} = 660$ nm, Figure 3A, inset) is observed in transparent frozen matrices. Under the same experimental conditions, the phosphorescence decay has been determined in the order of *ca.* 700 μs , thus demonstrating the sensitivity of the triplet excited state to the presence of oxygen in solutions at room temperature.

In solution and upon irradiation $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ itself can undergo a number of degradations, resulting from the photolysis of the Ti-ligand bonds. Depending on the experimental conditions employed^[78–81] (e.g., solvent nature, irradiation wavelength, concentration, etc.) $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ can convert either in $[\text{CpTi}^{\text{III}}\text{Cl}_2]^*$ through the unimolecular homolysis of the Cp– Ti^{IV} bond or $\text{CpTi}^{\text{IV}}\text{Cl}_3$, following the halogen abstraction from a solvent molecule. It is noteworthy that the photodegradation of $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ can take place at the wavelengths and in the conditions in which metallophotoredox catalysis usually operates. So, the nature of the real active species in these processes can no longer be uniquely identified.

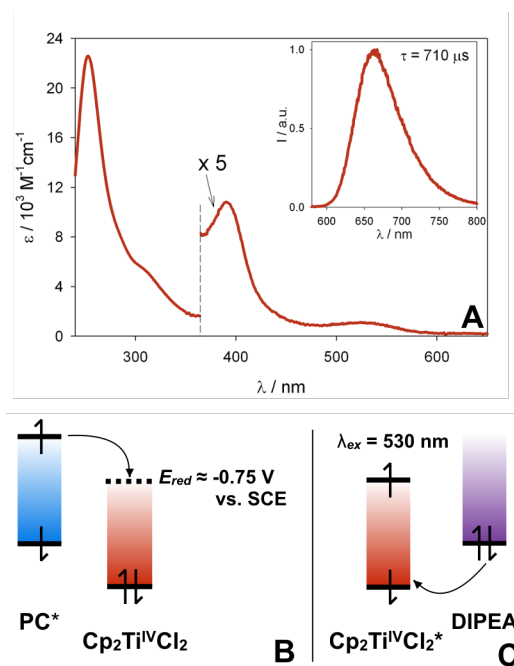


Figure 3. (A) Absorption spectrum of $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ in CH_3CN solution at room temperature). Inset: normalized phosphorescence spectrum of $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ in $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ (1:1 v/v) rigid matrix at 77 K. $\lambda_{\text{ex}} = 520$ nm. (B) Generation of $[\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}_2]^-$ via PET: oxidative quenching from an excited photocatalyst (PC). (C) Reductive quenching of $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ (C).

The redox potential of $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ is also decisive for the determination of the thermodynamic feasibility of the reductive quenching. In THF Cp_2TiCl_2 shows a quasi-reversible reduction wave at ca. -0.75 V vs. SCE,^[82,83] while the chemical reversibility decreases in analogous $\text{Cp}_2\text{Ti}^{\text{IV}}\text{X}_2$ as the halogen X is changed from Cl to Br and I, following the decrease of the bond dissociation energies between metal center and peripheral halogen. Hence, in this perspective, the generation of reactive Ti^{III} -based species is in principle most promising in the cases of $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Br}_2$ and $\text{Cp}_2\text{Ti}^{\text{IV}}\text{I}_2$. However, concerning $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$, the resulting radical anion $[\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2]^{\bullet-}$ can encounter a cascade of redox and cleavage reactions that have been also adequately reported in literature^[84] and display the role of the dehalogenated Ti^{III} metal center. The bulk electrolysis of red solutions $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$, when performed in deoxygenated solvents, generally leads to the development of green solutions of the dimeric $\text{Cp}_2\text{Ti}^{\text{III}}(\mu\text{-Cl})_2$, which eventually can be cleaved by coordinating solvent molecules (e.g., CH_3CN) giving rise to a deep-blue color.^[83,85,86] The presence of molecular oxygen is often detrimental for the stability of the Ti^{III} species: when those are exposed to O_2 , solutions tend to be swiftly bleached to the corresponding yellow Ti^{IV} derivatives.^[87] Due to the rapid chloride ion dissociation,^[88] the presence of H_2O in $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ solutions is often also undesirable for the redox chemistry of the corresponding Ti^{III} -based species. Nevertheless, it has been reported that the strong affinity of H_2O for Ti^{III} complexes can drive the efficient reduction of carbon-centered radicals of diverse nature via a HAT process.^[89,90]

As described for conventional chromophores^[91] and metal complexes,^[92] both optical and electrochemical properties of titanocenes can be reasonably controlled, making those complexes even more attractive catalysts for the development of new radical-triggered transformations in which the photoredox properties of a chromophores match those of titanocenes.^[93–95]

Based on these grounds, one might identify suitable chromophores with given excited state properties (i.e. energy, deactivation kinetics and redox potentials) able to perform oxidative PET to reduce $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ (figure 3 B). On the other hand, considering the triplet excited state of $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$, the reductive PET from an electron donor, e.g. a tertiary amine, represents a viable way to produce $[\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2]^{\bullet-}$ (figure 3 C).

The thermodynamic feasibility of the oxidative PET process is strictly connected to the oxidation potentials of a given chromophore in its excited state (E^*_{ox} , either singlet or triplet multiplicity) and to the reduction potential of ground state $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$. In principle, chromophores with $E^*_{\text{ox}} < -0.75$ V vs. SCE should be able to promote a single electron injection to $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ by means of an exoergonic PET ($\Delta G_{\text{PET}} < 0$ eV). Although thermodynamic parameters are crucial to design this process, they are not sufficient to indicate whether a PET will efficiently occur, as one should also consider the kinetic aspects of a given quenching process: the analysis of Stern-Volmer kinetics ultimately defines whether the PET process takes place at a fast rate. In the case of $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$, several hindrances might arise for the correct determination of the quenching rate: among them, in case of high concentrations of $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$, an overestimation of the Stern-Volmer constant (k_{SV}) can occur, due to the reabsorption of emitted photons from the chromophore. This condition is often encountered in the visible region – where a chromophore usually emits most of its photons – if one considers the moderate molar absorptivity of $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ between 400 and 600 nm. On the other hand, a viable alternative in the evaluation of k_{SV} is represented by the determination of the dye's luminescence lifetime, which is usually not affected by reabsorption or inner filter concerns.

In many photocatalytic reactions the electron and mass balances dictated by the mechanism require the presences of electron or hydrogen donors in sacrificial condition, i.e. at high concentrations and leading to their corresponding irreversible consumptions and accumulation of the subsequent side products while the reaction proceeds. The unique properties of titanocenes make them prone to interact electronically with those partners, which are present in the reaction medium since the beginning of the catalytic transformation. For a designed catalytic cycle involving Ti^{IV} species, it is therefore essential to take into consideration that possible reactions may take place in the presence of strong reductants, bases and complexing agents both at the ground and at the excited state. Tertiary amines or Hantzsch ester (HE) are typical

examples of electron- and H-donors extensively used for the purpose. As shown in Figure 4A,^[71] it is clear that the presence of *N,N*-diisopropylethylamine (DIPEA) in high concentrations in air-equilibrated CH₃CN provokes the decrease of the bands corresponding to the absorption spectrum of Cp₂Ti^{IV}Cl₂ even without irradiation (ground state reaction of the Ti^{IV} complex). The presence of **HE** in air-equilibrated THF does not dramatically affect the concentration of Cp₂Ti^{IV}Cl₂ when the solution is kept over time in the dark, while it decreases significantly when the same solution is irradiated with visible light (Figure 4B). Thus, kinetic effects must also be considered in order to correctly assess the intervention of the redox-active species in a proposed catalytic mechanism.

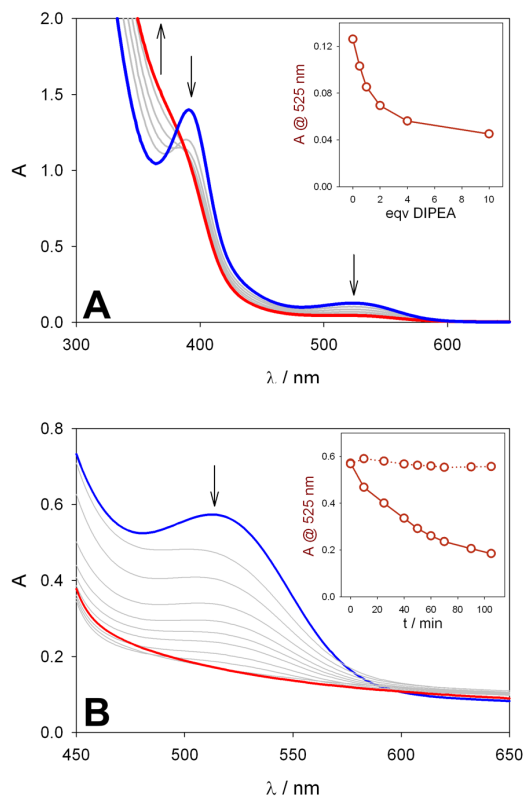


Figure 4: (A) evolution of the absorption spectra of a solution of Cp₂Ti^{IV}Cl₂ (ca. 0.72 mM, blue line) in air-equilibrated CH₃CN solution at r.t. recorded upon addition of increasing amounts of DIPEA (0 to 10 equiv.). (B): evolution of absorption spectra recorded from a solution containing Cp₂Ti^{IV}Cl₂ and **HE** (dimethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate; ca. 2.5 mM and 45 mM, respectively; blue line) in air-equilibrated THF at r.t. upon irradiation with a blue-emitting LED strip (λ_{ex} = 460 nm). Inset: evolution in time of the absorbance at λ=525 nm (solid line); the dotted line corresponds to changes in absorption for the same solution kept in the dark.

6. Perspective and conclusions

The tremendous recent developments in photoredox-mediated chemical reactions have focused the attention on the role of photoinduced electron injection/removal to/from chromophores at their excited state and the related feasibility of the redox activation of organic substrates.^[96] Metallaphotoredox processes demonstrated how the merging of two catalytic cycles (one *photoinduced*, combined with a *thermal*) can broaden the scope and the perspective in the design of synthetic protocols hardly viable in fully thermal conditions.

Being typically a prerogative of heavier metal centers such as chrome, cobalt, nickel or copper, metallaphotoredox reactions can face considerable advances if implemented with environmentally benign metals. From a green chemistry perspective, the abundance and low toxicity of titanium-related compounds make their use attractive for organic synthesis. More specifically, the light-activation of catalysts such as Cp₂Ti^{IV}Cl₂ has been documented to prevent the use of aggressive metal reductants in stoichiometric amounts and, at the same time, it opens interesting perspectives in novel and greener organic transformations. The possibility to use different classes of titanium complexes in metallaphotoredox catalysis will open new ways to efficient transformations.

Keywords: titanium • radicals • photochemistry • metallaphotoredox catalysis • epoxides