

Cp₂Ti^{III}Cl Catalysis in a New Light

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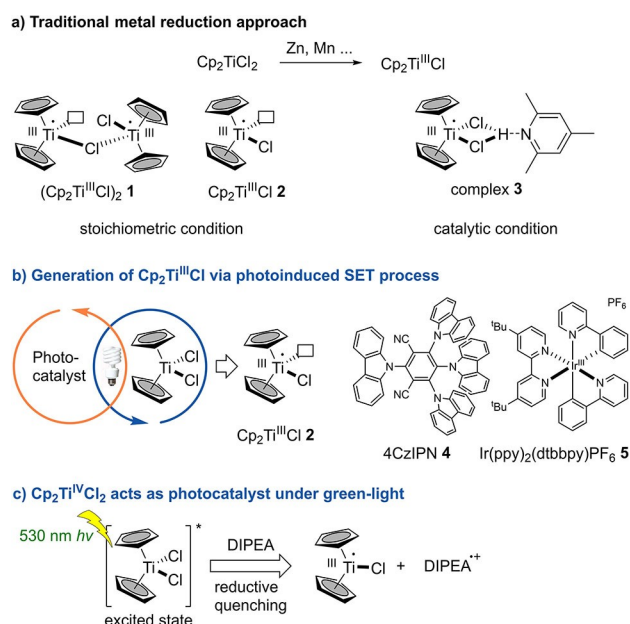
Visible-light-mediated photogeneration of Cp₂Ti^{III}Cl has opened new avenues for titanium catalysis. The synergistic utilization of dual photoredox and Cp₂Ti^{III}Cl catalysis uses Hantzsch ester (HE) as an electron donor instead of traditional super-stoichiometric metallic reductants. This new paradigm has found numerous applications in synthetic organic chemistry. The highly efficient

photoinduced electron transfer process between light-sensitive Cp₂TiCl₂ and an excited photocatalyst is the key to the success of such a photocatalytic system and ensures overall catalyst turnover. Comparisons between the metal reduction approach and photo reduction approach have been made.

Introduction

In recent years, metallaphotoredox catalysis, transition-metal catalysis merged with photocatalysis, has become a versatile tool in organic synthesis.^[1] Under visible-light conditions, photoredox processes can directly modulate the oxidation state of metals such as Ni, Pd, Cu, Au, Ru, Rh, Co, Cr, and Ce via photoinduced electron transfer (PET) with a photocatalyst.^[2–7] This approach expands the synthetic utility of visible light in modern organic synthesis and has successfully led to the discovery of numerous novel reaction modes under eco-friendly conditions. Despite these significant advances, exploiting the rich reactivity of titanium under light conditions for the organic transformations is highly appealing yet less reported.^[8]

Titanium, the seventh most abundant metal on earth, is one of the cheapest transitional metals and in general nontoxic and environmentally friendly.^[9,10] In the seminal works reported by Nugent and RajanBabu, Cp₂Ti^{III}Cl was first used as a stoichiometric single-electron-transfer (SET) reagent capable of generating a radical from an epoxide.^[11,12] Soon afterwards, the Gansäuer's group reported a catalytic variant which enabled asymmetric reactions using chiral ligand.^[13–15] With these inspiring works, Cp₂Ti^{III}Cl has become a powerful tool for the development of new, highly enabling synthetic methodologies in contemporary radical chemistry.^[16–21] In general, this reagent has been generated via chemical reduction of Cp₂TiCl₂ with stoichiometric reductive metals such as metallic manganese or zinc and can be obtained as a green crystalline powder. The structure of Cp₂Ti^{III}Cl in solution was studied and proposed to be the equilibrium of dinuclear **1** and mononuclear **2** species.^[22] Under catalytic conditions, Ti^{III} species are mainly present as complex **3** in the presence of excess collidine-HCl (Scheme 1,



Scheme 1. Generation of Cp₂Ti^{III}Cl.

a).^[23] Cp₂Ti^{III}Cl can also be synthesized via electrochemical reduction of Cp₂TiCl₂.^[24]

Recently, a novel photogeneration of Cp₂Ti^{III}Cl with the aid of a photocatalyst was reported by the Gansäuer group and Shi group (Scheme 1, b).^[25,26] This approach is highly attractive because such an environmentally benign process uses organic electron donors instead of super-stoichiometric metallic reductants. However, it can be surprising at first glance because Cp₂TiCl₂ is well-known for its intrinsic instability under visible light and decomposes with losing a cyclopentadienyl ligand. A hint to solve this challenge lies in our preliminary discovery that Cp₂Ti^{III}Cl is stable under photo conditions. Therefore, the key to success of this photocatalytic system requires the photocatalyst to reduce Cp₂TiCl₂ to Cp₂Ti^{III}Cl as fast as possible before its decomposition. Fortunately, the PET process between a light-sensitive Cp₂TiCl₂ and an excited photocatalyst, such as Ir-complex **5** ($E_{1/2}^{0\text{ IV/III}} = -0.96\text{ V vs. SCE in MeCN}$), is highly efficient as fluorescence quenching experiments exhibit Stern–Volmer kinetics with a rate of $3.8 \times 10^9\text{ L} \cdot \text{M}^{-1} \cdot \text{s}^{-1}$

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(Scheme 1, b). Recently, the Gansäuer group reported that Cp_2TiCl_2 itself can act as a photoredox catalyst under green-light irradiation (Scheme 1, c).^[27] In the presence of a reductive quencher, such as *N,N*-diisopropyl ethyl amine (DIPEA), short-life photoexcited Cp_2TiCl_2 could be directly reduced to $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ without the aid of additional photocatalysts. The bimolecular quenching constant for photoexcited Cp_2TiCl_2 and DIPEA was determined to be $1 \times 10^4 \text{ L} \cdot \text{M}^{-1} \cdot \text{s}^{-1}$ by Stern–Volmer analysis. The use of green light and the titanium photocatalyst/reagent may overcome the limitations involved in the scaling-up process.

Cp_2TiCl_2 is known to undergo homolysis of the Cp-metal bond with irradiation to generate $\text{CpTi}^{\text{III}}\text{Cl}_2$ and a cyclopentadienyl radical. Thus, it is necessary to elucidate the Ti^{III} species under current photo reduction conditions. Cyclic voltammetry (CV) studies have revealed that the main oxidation wave appearing at -0.22 V (vs SCE) corresponds to the $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ 2 monomer (Figure 1). This is different from the traditional metal reduction approach, where the Ti^{3+} species exists as the equilibrium of $(\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl})_2$ 1 dimer and $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ 2 monomer or the complex 3 (Scheme 1, a). Furthermore, it was found that this oxidation wave (-0.22 V vs SCE) does not change with increasing irradiation time, indicating that the $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ 2 species is light-stable. This is an important prerequisite for the realization of $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ 2 catalysis under photo conditions.

The concept of dual $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ and photoredox catalysis has found various synthetic applications in organic chemistry. Radical cascade cyclization reactions of epoxides have featured in numerous elegant total syntheses of natural products. Importantly, the synthesis of spirocyclic molecules bearing a quaternary carbon stereocentre is currently of great interest because these molecules exhibit a broad spectrum of biological and pharmacological activities. In this respect, the Shi group developed 5-*exo* and 6-*exo* spirocyclizations of epoxyalkynes for the rapid construction of a series of spirocycles with different spiro-ring fused systems. Interestingly, compared with

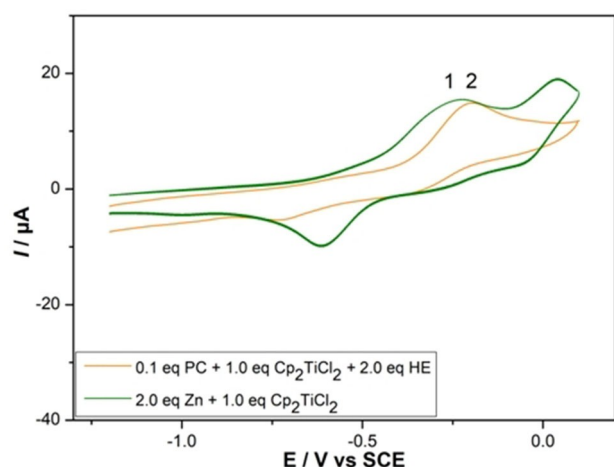


Figure 1. CV of 2 mM $\text{Cp}_2\text{TiCl}_2/\text{Zn}$ (green line) and 2 mM $\text{Cp}_2\text{TiCl}_2/[\text{Ir}(\text{dtbbpy})(\text{ppy})_2]\text{PF}_6/\text{HE}$ (orange line) recorded at a glassy carbon disk electrode with $\nu = 0.1 \text{ V s}^{-1}$ in 0.2 M $\text{Bu}_4\text{NPF}_6/\text{THF}$. The values are given in V vs SCE and can be converted to V vs Fc^+/Fc by subtracting 0.52 V.

the metal reduction approach, the current photocatalytic approach exhibited exceptionally reactivity with less titanium loading (5.0 mol%), shorter reaction time, and higher yield. The proposed mechanism is shown in Figure 2. First, photogeneration of $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ by an excited Ir^{III} complex 5 promotes the reductive opening of the epoxides. The resulting carbon radical intramolecularly adds to the pendant alkyne to construct the spirocyclic structure. The catalytic cycles are closed via SET from the excited Ir^{III} to $\text{Ti}(\text{IV})$ using Hantzsch ester ($E_{\text{HE}^{\bullet+}/\text{HE}} = +1.0 \text{ vs SCE}$) as the terminal reductant. In principle, reductive opening of epoxides undergoes SET process with $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ through an inner-sphere pathway. However, titanium complex 3 (Scheme 1, a) formed under metal reduction conditions has less free coordination due to the presence of excess collidine-HCl. On the other hand, $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ 2 generated under photocatalytic conditions has a coordination site which is occupied by an easily displaceable THF ligand. This feature allows the oxygen atom of the epoxide to efficiently perform a SET process, particularly for the sterically hindered epoxides. These results highlight the unique advantage of the current photocatalytic approach.

It should be noted that the HE used as a terminal reductant is crucial for $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ catalysis.^[28] Its oxidized form (HE radical

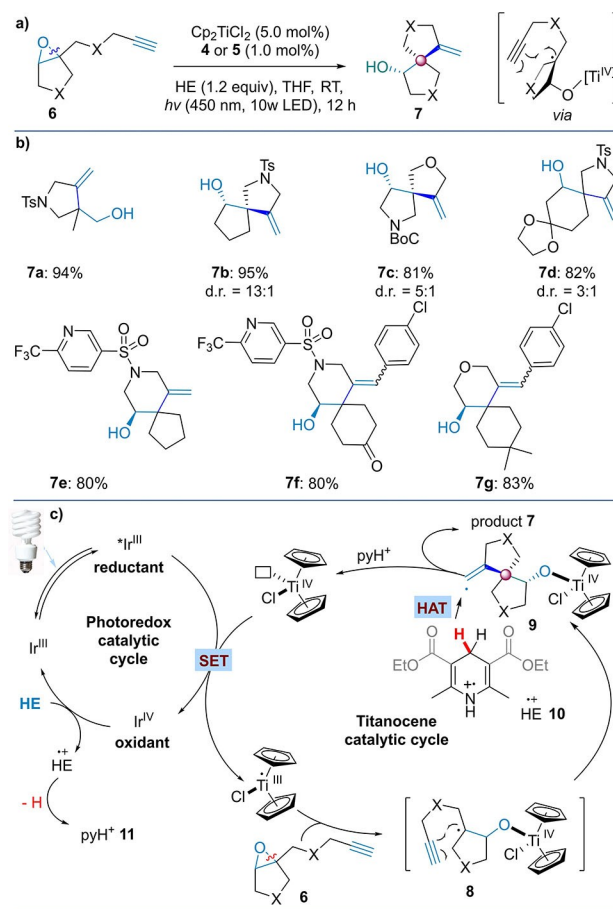


Figure 2. a) Spirocyclization of epoxyalkynes. The photocatalytic reactions were performed on WATTCAS Parallel Light Reactor (WP-TEC-1020SL) with blue COB LED. b) Selected products. c) Proposed catalytic mechanism.

cation, $\text{HE}^{\bullet+}$ **10**) and Hantzsch pyridine cation (pyH^+ **11**) are beneficial for the turnover of $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ (Figure 3). First, the pyH^+ plays a key role in the protonation of *in situ*-generated strong Ti^{IV} -alkoxy bonds under photocatalytic conditions. This contrasts with the metal reduction approach that usually requires additional collidine-HCl as the proton source. Acidity and structural similarity of the pyH^+ **11** and collidine-HCl suggests HE also acts as the proton source. Actually, the reactions are strongly inhibited by the addition of Na_2CO_3 or using triethylamine as a reductant. Secondly, $\text{HE}^{\bullet+}$ **10** has a low homolytic bond-dissociation free energy for the C4-H bond (this energy requirement is $31.4 \text{ kcal mol}^{-1}$ for acetonitrile), thus enabling a thermodynamically favorable transfer of hydrogen atom ($\text{H}^{\bullet}$) to vinyl radical **9**.

The generality of dual $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ and photoredox catalysis can be further demonstrated by a related hydrogen transfer of epoxides reaction (Figure 4). This approach could provide anti-

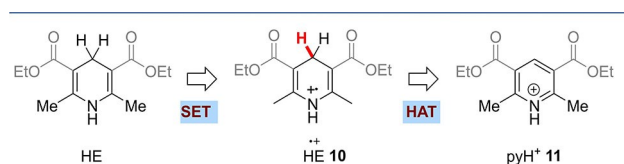


Figure 3. Role of Hantzsch ester.

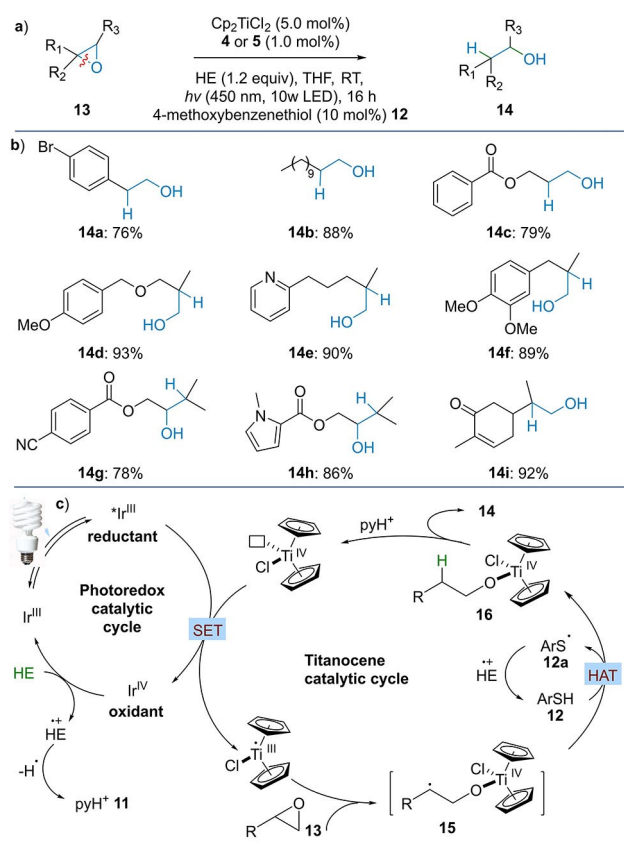


Figure 4. a) Reductive opening of epoxides. The photocatalytic reactions were performed on a WATTCAS Parallel Light Reactor (WP-TEC-1020SL) with blue COB LED. b) Selected products. c) Proposed catalytic mechanism.

Markovnikov alcohols exclusively from a board range of epoxides. In general, various mono-, bi- and tri-substituted epoxides afforded the alcohols in excellent yields.

The mechanism is similar to that of the cyclization reaction. However, in this case, a catalytic concentration of 4-methoxybenzenethiol as a HAT catalyst is necessary for high yields. First, the photogeneration of $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ with a vacant site allows the oxygen atom of epoxide **13** to perform a SET through an inner-sphere mechanism. The resulting β -titanoxy radical **15** can abstract H atoms from 4-methoxybenzenethiol **12** and give intermediate **16**. The resulting thiyl radical **12a** abstracts an H atom from $\text{HE}^{\bullet+}$ to yield the pyH^+ . *In situ*-formed, strong Ti-oxygen bonds of **16** can be protonated by pyH^+ and release Ti^{IV} and reduction product **14**. In the absence of 4-methoxybenzenethiol **12**, radical **15** can react with another equivalent of $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$, and its subsequent elimination affords an alkene, which is a common problem in traditional metal reduction approaches.

The *in situ* formed carbon-centered radical **15** can participate in $\text{C}(\text{sp}^2)\text{--C}(\text{sp}^3)$ bonds coupling reactions in the presence of a suitable transition metal catalyst and a coupling partner. On the basis of previous Weix's works, recently Doyle and coworkers developed a nice triple Ti/Ni/photoredox catalysis for the cross-electrophile coupling of epoxides and (hetero)aryl iodides (Figure 5).^[29] After careful selection of different nitrogen-based ligands for Ni, this highly regioselective coupling reaction accommodates three distinct classes of epoxides including styrenyl-, cyclic-, and terminal aliphatic epoxides in conjunction with a broad scope of coupling partners under the identical conditions. The mechanism is proposed as following (Figure 5, c). Photoexcited 4CzIPN^* undergoes oxidative quenching with Ti^{IV} to generate Ti^{III} which engages epoxide reductive opening and produce radical **15**. Capture of radical

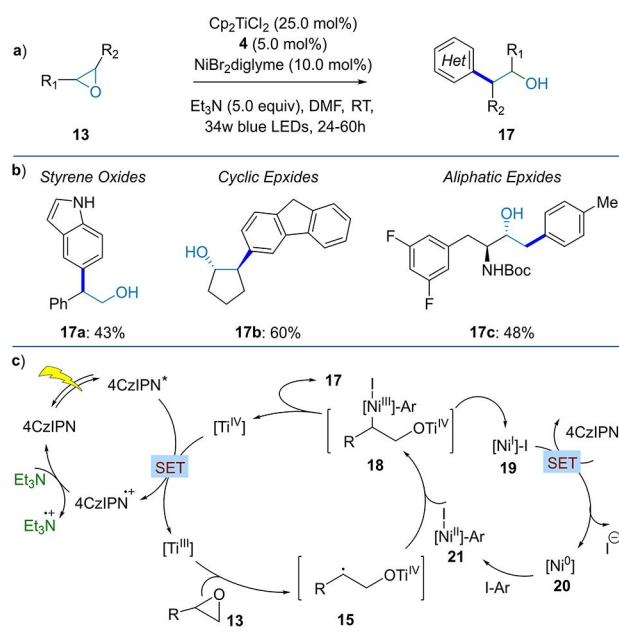


Figure 5. a) Reductive coupling of epoxides and (hetero)aryl iodides. b) Selected products. c) Proposed catalytic mechanism.

15 by Ni^{II} complex **21** forms Ni^{III} intermediate **18** followed by reductive elimination that results in coupling products **17** and Ni^{I} intermediate **19**. This Ni^{I} **19** can be reduced to Ni^0 **20** by $4\text{CzIPN}^{\bullet-}$, which was generated via reductive quenching of 4CzIPN with triethylamine.

The concept of dual $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ and photoredox catalysis was also extended to Barbier-type allylation reactions (Figure 6). These reaction types are important tools for the synthesis of homoallylic alcohols. Normally, an over-stoichiometric amount of the sacrificial reductant in the presence of an active redox metal complex is necessary. The dual $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ and photoredox provide a new platform for this classical transformation in a more environmentally friendly manner. In this regard, Gualandi, Bergamini, Cozzi and coworkers reported a Cp_2TiCl_2 -catalyzed allylation of aldehydes using 1,3-dicyano-5-fluoro-2,4,6-tris(diphenylamino)-benzene (3DPAFIPN) as the photocatalyst.^[30] This novel photocatalytic Barbier-type allylation enables various aromatic and aliphatic aldehydes with allyl bromide for the synthesis of secondary homoallylic alcohols. The proposed catalytic cycle is shown in Figure 6 c. First, Cp_2TiCl_2 is reduced to $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ by a photoexcited 3DPAFIPN*. The strong oxidant $3\text{DPAFIPN}^{\bullet+}$ species ($E_{3\text{DPAFIPN}^{\bullet+}/3\text{DPAFIPN}} = +1.30$ vs SCE) is then reduced by HE. $3\text{DPAFIPN}^{\bullet+}$ species can also oxidize the HE radical generated *in situ* and produce pyH^+ . The allyl bromide can react with two $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ reagents to yield an allyl-Ti complex **23**. The reaction of allyl-Ti **23** with the carbonyl group forms the new C–C bond in the alkoxytitanium product **22**. Protonation of the Ti-oxygen bond by the pyH^+ acting as a

proton source releases Ti^{IV} and an alcohol product. Finally, 4CzIPN can regenerate $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ for the next catalytic cycle.

Conclusions

The photogeneration of $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ represents significant advances in metallaphotoredox catalysis. As the 7th most abundant metal on earth, titanium is one of the cheapest transitional metals and, generally, non-toxic and environmentally friendly. Compared with other transition metals, such low toxicity makes titanium especially attractive for medical purposes and organic synthesis. Complementary to traditional metal reduction approaches, this new environmentally benign photoredox process employs readily available organic HE as the electron donor, H atom donor, and proton source bypassing additional additives and stoichiometric reductive metals. A wide range of synthetically important transformations, including reductive opening of epoxides, cyclization of epoxyalkynes, reductive coupling, and Barbier-type allylation, can then be realized by the combination of $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ and photochemistry. Mechanistic studies suggest that in photocatalytic conditions, Ti^{III} is present as a highly reactive $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ **2**. As expected, the photocatalytic catalysis showed exceptionally high reactivity with lower Ti catalyst loading, shorter reaction time, high yield, and excellent functional group compatibility. With these significant advances, we hope that this article will stimulate more interest and exploration in the chemistry of $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$. Novel synthetic transformations are expected to be rationally designed based on the dual $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ and photoredox catalysis in the near future.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: allylation • dual catalysis • epoxide • photoredox • titanocene

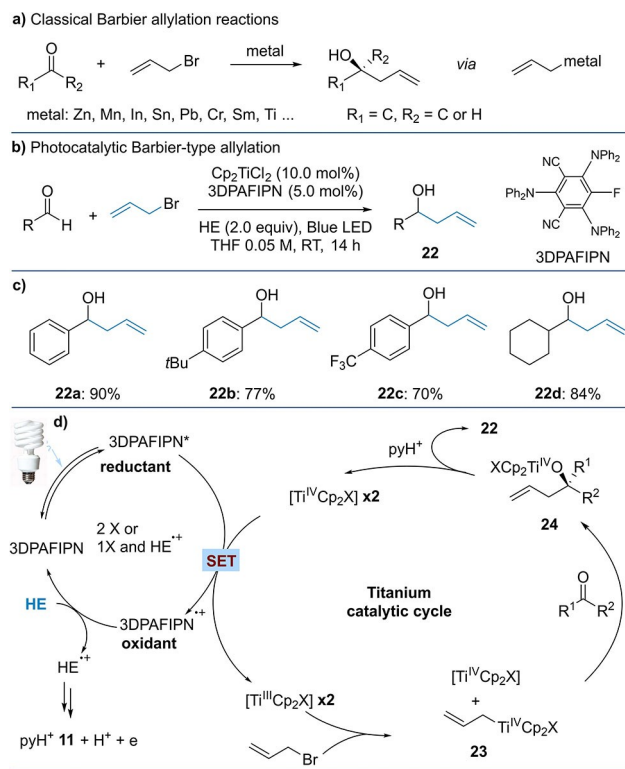


Figure 6. a) Barbier allylation. b) Photocatalytic Barbier-type allylation. c) Selected products. d) Proposed catalytic mechanism.

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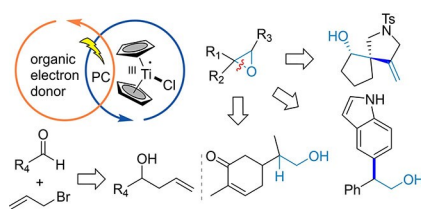
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CONCEPTS

Visible-light-mediated photogeneration of $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ has opened new avenues for titanium catalysis. The synergistic utilization of dual photoredox and $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ catalysis has found numerous applications in synthetic organic chemistry, including reductive opening of epoxides, cyclization of epoxyalkynes, reductive coupling, and Barbier-type allylation. The highly efficient photoinduced electron-transfer process between light-sensitive Cp_2TiCl_2 and an excited photocatalyst is the key to the success of such a photocatalytic system.



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