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Cp₂TiCl₂-Catalyzed Photoredox Allylation of Aldehydes with Visible Light / Gualandi A.; Calogero F.; Mazzarini M.; Guazzi S.; Fermi A.; Bergamini G.; Cozzi P.G.. - In: ACS CATALYSIS. - ISSN 2155-5435. - ELETTRONICO. - 10:6(2020), pp. 3857-3863. [10.1021/acscatal.0c00348]

Availability:

This version is available at: <https://hdl.handle.net/11585/753892> since: 2020-04-06

Published:

DOI: <http://doi.org/10.1021/acscatal.0c00348>

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This document is the Accepted Manuscript version of a Published Work that appeared in final form in *ACS Catalysis*:

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ACS Catal. 2020, 10, 6, 3857-3863

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To access the final edited and published work see:

<https://doi.org/10.1021/acscatal.0c00348>

Cp₂TiCl₂-CATALYZED PHOTOREDOX

ALLYLATION OF ALDEHYDES WITH VISIBLE LIGHT

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KEYWORDS Titanium • allylation • photoredox catalysis • aldehydes • Hantzsch Ester

ABSTRACT A Barbier-type Cp₂TiCl₂-mediated (10 mol%) photoredox allylation of aldehydes under irradiation with visible light (blue LEDs, 450 nm) and in the presence of an organic dye (3DPAFIPN, 5 mol%) with allylbromides is described.

Allylation of carbonyls is a key strategy for the preparation of functionalized building blocks in the total synthesis of natural products.¹ In particular, allylation reaction realized under Barbier conditions can give access to transient organometallic reactive allylating species.² Normally,

over-stoichiometric amount of sacrificial reductant such as metallic manganese or zinc, in the presence of an active redox metal complex is necessary. In Barbier type allylation performed with catalytic amount of titanium³ or chromium⁴ (Nozaki-Hiyama-Kishi reaction),⁵ the use of a scavenger able to liberate the active metal from the organic product is mandatory for sustaining the catalytic cycle. Pioneering studies reported by Fürstner⁶ and Gansäuer⁷ have introduced the practice of catalytic redox cycle in Organic Synthesis, further developed into interesting stereoselective variants.⁸

Photoredox catalysis, by the use of metal complexes, dyes, or semiconductors, can give interesting approaches to radical species by electron transfer (ET) or energy transfer.⁹ The combination of photoredox catalytic cycle with other catalytic cycles, working cooperatively, opens the way to new reaction pathways.¹⁰ Metallaphotoredox catalysis, i.e. metal catalysis merged with photoredox catalysis, is a new and rapidly growing research area.¹¹ Now, photoredox catalysis is starting to explore the possibility to use a clean and rapid access to radicals for generating nucleophilic reagents.¹² This concept, that combines radical and polar chemistry, in a so-called reductive radical-polar crossover (RRPC) was recently reviewed.¹³ In this approach, a suitable alkyl radical is converted into a nucleophile by reduction or by capture with a suitable transition metal complex. These so formed nucleophilic species can then react with electrophiles such as carbonyls or imines.

Glorius and Kanai have recently reported RRPC photoredox allylation methodologies based on chromium (Figure 1).¹⁴ In these radical reactions, photogenerated allyl radicals are converted into a traditional nucleophilic Cr(III)allyl reagents by means of a single electron reduction carried out by the Cr(II) present in the reaction mixture. The Cr(II) used in catalytic amount was re-

generated by the photocatalytic cycle. Importantly, these new transformations are still in their infancy, although high enantiomeric excesses can be obtained.^{14b,c}

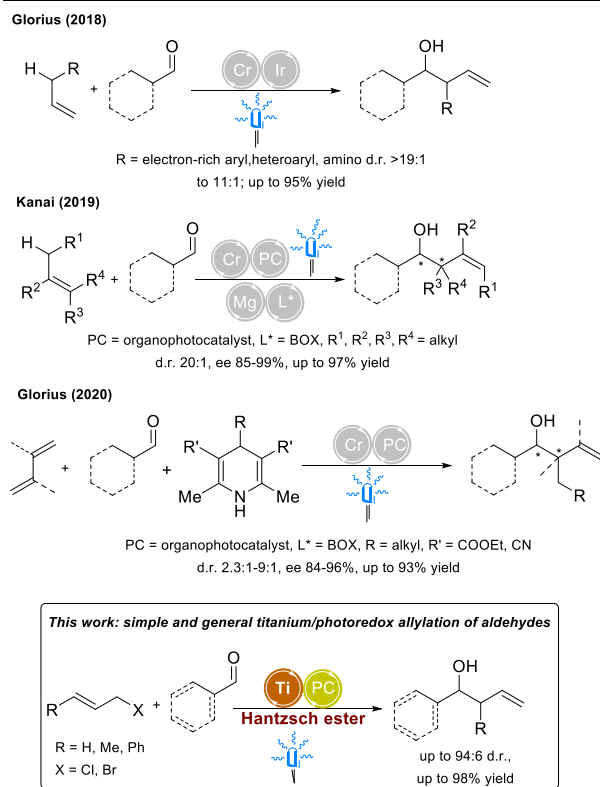


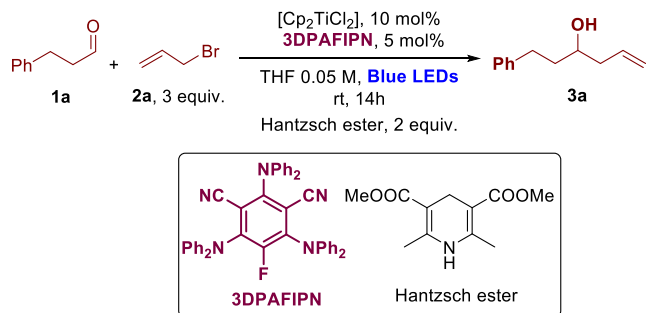
Figure 1. Photoredox synergistic allylations of aldehydes.

In this paper, we report a practical and straightforward radical-polar crossover photoredox allylation of aldehydes mediated by titanium complexes, that give access to a wide range of homoallylic alcohols in high yields. Moreover, the reaction uses 1,3-dicyano-5-fluoro-2,4,6-tris(diphenylamino)-benzene (3DPAFIPN) as the photocatalyst,¹⁵ a cheap and easily prepared organic dye, in the presence of the readily available Hantzsch's ester as sacrificial reductant and scavenger for the titanium complexes.

Recently, we have reported a nickel based dual photoredox approach in the allylation of aldehydes, with a broad scope and functional groups compatibility, by the use of commercially

available or easily prepared allylacetates.¹⁶ However, we want to explore the use of affordable green metals and mild reaction conditions. In particular, the use of Cp₂Ti(III)Cl, the Nugent-Rajanbabu reagent,¹⁸ in Barbier-type allylation reactions,¹⁸ is particularly attractive, as titanium is considered non-toxic, environmentally friendly, and abundant.¹⁹

Methodologies based on the employment of Cp₂(III)TiCl in catalytic conditions, in the presence of stoichiometric amounts of active metals (Mn) and in combination with 2,4,6-collidine and Me₃SiCl added more interest in this chemistry, leading to the discover of new transformations.²⁰ In addition, recently Gansäuer reported an interesting study on the photoredox titanium mediated reactions of epoxides, combining Cp₂Ti(III)Cl catalysis with photoredox catalysis bypassing the requirement of metallic reductants and stoichiometric acidic additives.²¹ Shi and co-workers have recently reported another synergistic utilization of titanocene/photoredox dual catalysis in the radical opening/spirocyclization of epoxyalkynes in the presence of 2,4,5,6-tetra(9H-carbazol-9-yl)isophthalonitrile (4CzIPN) as a photocatalyst and Hantzsch's ester.²² Based on our, Gansäuer and Shi studies, we have settled a new photoredox allylation of aldehydes mediated by catalytic amount of titanium complex, and in Table 1 some key observations about the reaction conditions are reported.

Table 1. Allylation reaction and variation of some reaction parameters.

Entry	Deviations from standard conditions	Yield (%) ^b
1	none	>99 (98) ^c
2	40W Kessil [®] lamp 456 nm, 6 h	>99 (98) ^c
3	40W Kessil [®] lamp 456 nm, 14 h, 0.7 mmol scale	>99 (97) ^c
4 ^d	40W Kessil [®] lamp 456 nm, 48 h, 5 mmol scale	>99 (96) ^c
5	4CzIPN instead then 3DPAFIPN	45
6 ^e	{Ir[dF(CF ₃)ppy] ₂ (dtbbpy)}(PF ₆) instead of 3DPAFIPN	96
7 ^e	[Ru(bpy) ₃]Cl ₂ instead of 3DPAFIPN	0
8	No Hantzsch ester	0
9	Allylchloride instead of allylbromide	92
10	No [Cp ₂ TiCl ₂]	0
11	No light	0
12	No degassed solvent	0
13	No photocatalyst, with irradiation at 380 nm	0
14	Toluene instead of THF	60

^a Reactions performed on 0.1 mmol scale. ^b Determined by ¹H-NMR analysis. ^c Isolated yield after chromatographic purification. ^d The reaction was performed using 8 mol% of Cp₂TiCl₂ and 3 mol % of 3DPAFIPN. ^e 1% of the photocatalyst was used.

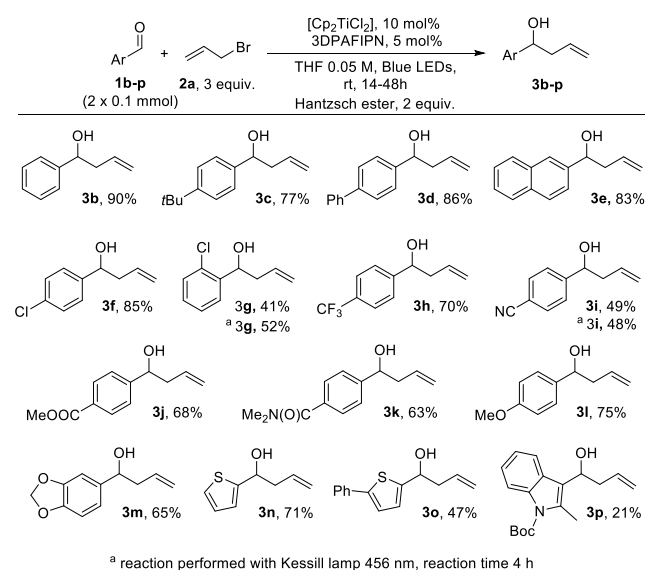
Hydrocinnamic aldehyde (**1a**) was used in the model reaction, and in general it was found that the reaction was promoted by various photocatalysts (entries 5-7 Table 1, and Table S7), LED

sources (entries 1-2, Table 1), with the organic dyes 3DPAFIPN¹⁵ affording good conversions and extremely clean reactions. Other organic dyes were found to be less efficient in promoting the transformation. Different titanium complexes and salts were employed (see Table S3), demonstrating their inferior ability to promote the reaction compared to the cheap and available Cp₂TiCl₂. Reaction conditions were carefully optimized bringing out that THF with a substrate concentration of 0.05 M was crucial. It is also important the role played by the Hantzsch's ester since a series of different sacrificial reductants were found not suitable for the reaction (see Table S5). In this regard, we firstly checked the stability of Cp₂TiCl₂ in the presence of different amines (See Figure S15). The addition of 1,3-dimethyl-2-phenyl-2,3-dihydro-1H-benzo[d]imidazole (BIH), quinuclidine and other aliphatic amines to a mM solution of Cp₂TiCl₂ causes changes in the absorption spectrum attributable to ligand exchange. The bulky triphenylamine (TPA) did not interact with the titanium complex in the ground state, but absorption changes have been observed under visible light irradiation. However, addition of amines was found deleterious, giving practically no conversion (see Table S6). From a practical point of view, the reaction was quite sensitive to traces of oxygen and water. It is worth noting that the photocatalyst does not decompose during the photoreaction and can be easily recovered at the end of the reaction by flash chromatography. By the use of a Kessil® LED lamp at 456 nm (40 W, for 6 hours, Table 1 entry 2), it was possible to considerably reduce the reaction time and to scale the reaction up to 5 mmol without observing lower conversion and yield (Table 1 entry 3 and 4).

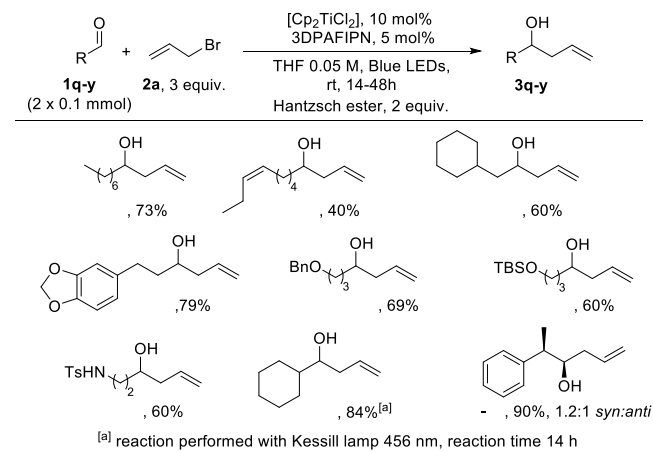
The wide applicability of our initial finding was confirmed with a variety of aromatic and aliphatic aldehydes, and Schemes 1 and 2 illustrate the salient results obtained. As evident by the data reported in Scheme 1, aromatic, and heteroaromatic aldehydes are suitable substrates for the

reaction. Yields are good to moderate as a function of the presence of electron-withdrawing groups, that have an impact on the isolated yields. As the Hantzsch ester is oxidized under the reaction conditions to the corresponding protonated pyridinium salt, with concomitant formation of H^+ , acid sensitive substrates such as pyrrole or indole gave lower yields due to decomposition promoted by the presence of Brønsted acids.

Scheme 1. Synergistic allylation reaction of aromatic aldehydes.

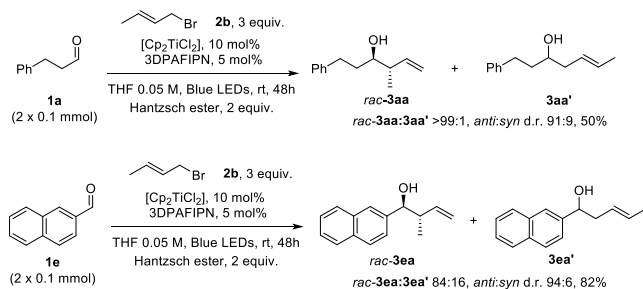


Hindered aromatic substrates were found less reactive. In comparison to the published titanium mediated allylation reaction, a minor percentage of titanium (10 vs 20 mol%) it is necessary. No further scavengers or bases are necessary for the titanium as the proton derived from the oxidation of the Hantzsch's ester is able to restore the catalytic cycle acting as a scavenger. Differently substituted linear aliphatic aldehydes are quite suitable substrates as illustrated in Scheme 2 (see Scheme S2 for further substrates studied).

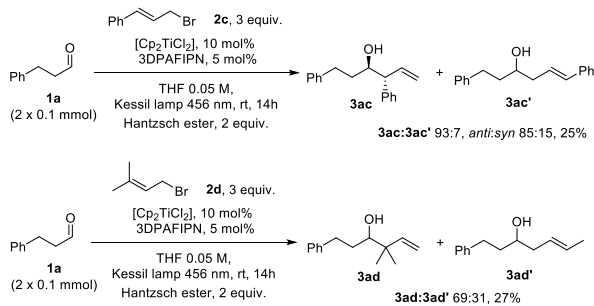
Scheme 2. Synergistic allylation reaction of aliphatic aldehydes.

Hindered aromatic substrates were found less reactive. In comparison to the published titanium irradiation with powerful Kessil® lamp is necessary for hindered cyclohexane carboxaldehyde. In the case of pyvalic aldehyde, the reaction gave only low yields (see Scheme S2). Reaction with chiral aldehydes **1y** gave quite moderate diastereoisomeric ratio, in favor of a Felkin-controlled allylation product. The reaction is quite tolerant to functional groups including halides, CF_3 , esters, nitriles, ethers. Interestingly, acidic NH groups were also tolerated although aliphatic or aromatic amines cannot be used.

Allyl bromide bearing substituents in three position can be employed with good regioselectivity in favour of the branched products and with moderate to good yields (Schemes 3).

Scheme 3. Synergistic allylation reaction with crotyl bromoderivative.

Allyl substituted reagents are in general less reactive to respect allylbromide under our photoredox condition, as indicated by the preliminary results obtained (Scheme 4) with cinnamyl bromide (**2c**) and in the presence of prenyl bromide (**2d**).

Scheme 4. Synergistic allylation reaction with substituted allyl bromoderivatives.

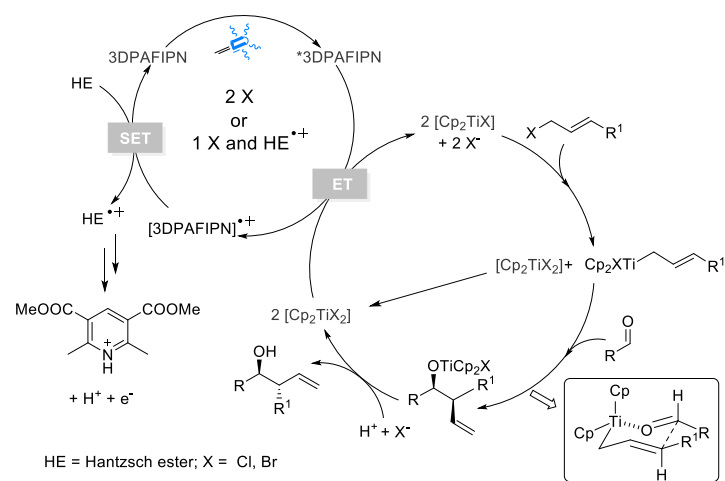
Ketones showed a quite reduced reactivity in this reaction compared to aldehydes, and the corresponding products were isolated in low yields, even using Kessil® lamp (see Scheme S2).

In order to evaluate the photoinduced mechanism of the reaction we investigated the quenching of the photocatalyst's luminescence by each of the components of the reaction (see SI). As observed for similar substituted isophthalonitriles,^{15,23} 3DPAFIPN is particularly suitable in photocatalysis because possesses a very long emission lifetime in degassed solutions at room temperature (0.130 ms in THF at λ_{em} 520 nm, see SI for details). Interestingly, no change in the intensity and decay of the 3DPAFIPN emission was observed upon addition of the allyl bromide

and hydrocinnamic aldehyde (at the same concentrations used to perform the reaction). On the other hand, the addition of Hantzsch's ester and Cp_2TiCl_2 induces strong changes in the emission intensity of the photocatalyst. In particular, the quenching constants, determined from Stern-Volmer experiments, are $1.5 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ for the Hantzsch's ester and $5.2 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ for the Ti complex in degassed solutions (as in the employed photoreaction conditions described above). It is worth noting that the two Stern-Volmer plots have been obtained using the ratio of the lifetime (τ_0/τ) for the quenching relative to Ti, because it re-absorbs the light emitted by 3DPAFIPN, and the ratio of the emission intensity (I_0/I) in the case of Hantzsch's ester because of the superposition of its emission with pulsed laser source at 405 nm (see SI). To evaluate a possible role of the pyridine, produced by the oxidation of the Hantzsch's ester, in the photoinduced processes,²⁴ we also test the quenching of 3DPAFIPN emission by this compound. No quenching of the excited state of 3DPAFIPN was measured at any concentration of pyridine added (Figure S20). The optimized reaction conditions are in line with the photophysical observation, because the amount of 3DPAFIPN should be enough to absorb significant blue photons to promote the photo induced electron transfer. However, the cost, availability and sustainability of these two players, make the present approach extremely competitive for large scale application. The determination of the quantum yield carried out gave a value of 1.3 % (see SI for full details). Based on the results of the photophysical investigation, and although we cannot exclude short radical chains, the tentative catalytic cycle is depicted in Figure 2. The oxidative quenching of 3DPAFIPN induces the formation of $\text{Cp}_2\text{Ti(III)Cl}$. The 3DPAFIPN $^{\bullet+}$ is a strong oxidant ($E_{3\text{DPAFIPN}^{\bullet+}/3\text{DPAFIPN}} = + 1.30 \text{ vs SCE}$)¹⁵ and is reduced by the Hantzsch's ester ($E_{\text{HE}^{\bullet+}/\text{HE}} = +1.0 \text{ vs SCE}$).²⁵ The reaction produces $\text{HE}^{\bullet+}$ that can participate in further electron transfer events²⁵ and is a strong reductant. As suggested by Cuerva and Oltra,³ two molecules of $\text{Cp}_2\text{Ti(III)Cl}$ are

necessary for the formation of the allyl titanium specie. Two possible scenarios could be envisioned. The two molecules of $\text{Cp}_2\text{Ti(III)Cl}$ are generated by two oxidative quenching of two molecules of $^*3\text{DPAFIPN}$. On the other hand, one molecule of Cp_2TiCl_2 is reduced by $^*3\text{DPAFIPN}$ and another by the formed $\text{HE}^{\bullet+}$. In experiments carried out with crotyl, cinnamyl, and prenyl reagents (Schemes 3 and 4) we have observed a prevalent γ -regioselectivity. It is well-known that both crotyl-Ti(IV) and prenyl-Ti(IV) reagents react with carbonyl favoring the γ -position.²⁶ As is illustrated in Figure 2, the reaction is probably proceeding through the radical coupling between allyl radicals and $\text{Cp}_2\text{Ti(III)Cl}$, that forms the allylating Ti(IV) reagents. The protonated re-aromatized Hantzsch ester possesses a low pKa (see Scheme S3 for reactions induced by this Brønsted acid), compared to other reagents used as scavengers in the catalytic redox reaction promoted by titanium chemistry (such as collidine and Me_3SiCl), and it is efficient in restoring the catalytic cycle by protonation of the titanium-alkoxy bond.

Figure 2. Proposed mechanism for the reaction.



In summary, we have reported a novel allylation photoredox methodology based on the use of Cp_2TiCl_2 complex. From the point of view of a green chemistry perspective, the abundance and low toxicity of titanium make the procedure attractive for organic synthesis.^{20,27} Careful

mechanistic studies has shed light of the application on 3DPAFIPN or parent organic dyes in accessing $\text{Cp}_2\text{Ti(III)Cl}$ reagent, avoiding the use of stoichiometric metal, such as Mn or Zn. The Hantzsch's ester used as stoichiometric reductant is unique for the titanium(III) chemistry, and its oxidized and protonated form is beneficial for the turn-over of the titanium catalyst. Further studies to expand these radical-polar crossover reaction²⁸ and to use other redox reactive metals are in progress and will be reported in due time.

Supporting Information. The following files are available free of charge.

Reaction optimization studies. Synthetic procedures for allylation reaction and preparation of substrates and photocatalysts. Spectroscopic data for new compounds, and copies of NMR spectra. Photophysical studies for the model reaction and Stern-Volmer plot.

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Author Contributions

A.G., G. B. and P. G. C. conceived the study. Photoredox reactions were carried out by A. G., F. C, and M. M.. S. G and A. F. carried out the photophysical investigations, supervised by G. B..

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding Sources

National project (PRIN 2017 ID: 20174SYJAF) SURSUMCAT "Raising up Catalysis for Innovative Developments" is acknowledged for financial support of this research.

ACKNOWLEDGMENT

Prof. P. Ceroni and Dr. M. Marchini are acknowledged for helpful discussions.

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