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Developing Organometallic Nucleophilic Reagents Via Photoredox Catalysis

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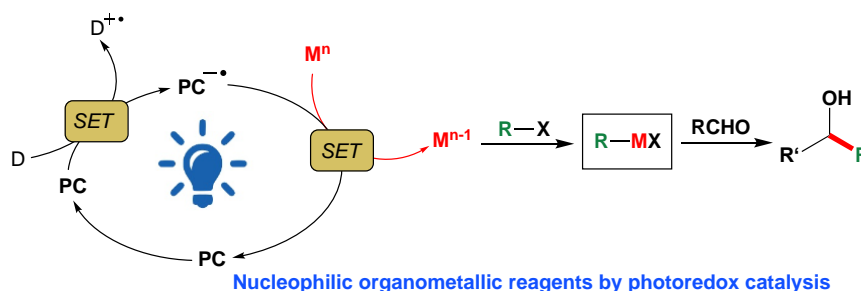
Developing organometallic nucleophilic reagents via photoredox catalysis

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Abstract The addition of organometallic reagents to the carbonyl group represents a key transformation, both in Academia and industry. Most of these transformations rely on a mechanism in which accessible and reactive halides are transformed into the corresponding nucleophilic organometallic reactive compounds through a redox mechanism, using a metal (Cr, Mg, In, etc.) in low oxidation state, by electron transfer. With the advent of photoredox catalysis, the formation of radicals, through oxidation or reduction of suitable and tailored organic precursors, was merged with transition metal catalysis. By radical to polar crossover (RRPCO), a radical metal is combined with an organic radical to produce, via radical-radical trapping, a polar nucleophilic organometallic reagent. Using dual photoredox catalysis (metallaphotoredox catalysis), a reactive organometallic reagent could be prepared, avoiding the use of metals in low oxidation state. Herein, in addition to the description of the results obtained by our group and others' contributions at the connection between carbonyl addition and radical-based photochemistry, we provide a core guiding for further synthetic developments. We anticipate that extending the photoredox dual strategy beyond the Barbier's reactions described here, taming less-activated carbonyls, studying other important electrophiles, will realize important breakthroughs soon.

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Key words Photoredox catalysis; dual catalysis; Radical to polar cross over; Carbonyls electrophiles; Photoredox Nozaki-Hiyama-Kishi; Ti(III) reactions.

1. Introduction

The addition of organometallic reagents to carbonyl compounds to afford alcohols (primary, secondary, or tertiary) is one of the most useful synthetic transformations in organic chemistry.¹ This transformation can be performed using a multitude of organometallic reagents with high levels of diastereo- and enantioselectivity.² Normally, organometallic reagents are obtained by transmetalation from lithium or magnesium reagents³ or they can directly be obtained by employing an oxidative addition to metals in low oxidation state. In the second case the net transformation of a reactive electrophile (halide, tosylate, mesylate, phosphate, or other redox-active functional groups) requires the transfer of two electrons from the metal. Normally, the metal changes its oxidation state by two, and when just one electron is involved, two equivalents of the metals are acting in the reaction with the electrophilic substrates. This chemistry is polar since negative (the organometallic reagents) and positive charges (the electrophile) are formally involved. However, a neutral transformation, in which radicals are formed, and just one electron is donated or removed are rarely considered. In retrosynthetic analysis, the disconnections are based on the insertion of positive or negative formal charges, and chemists are using this mental approach to propose correct strategies and new reagents. When radical reactions became more accessible, radical disconnections were proposed⁴ and, nowadays, thanks to the photoredox strategies⁵ radicals could be generated using mild conditions, with a broad group tolerance.⁶ It is possible to convert carbonyl in radical, forming the persistent ketyl radical,⁷ and perform a selective coupling with transient radicals generated in the reaction media.⁷ Although the generation of ketyl radical with a strong reducing reagent/catalyst is possible, a high reduction potential required⁸ (for example for acetophenone $E^{\text{red}}_{1/2} = -2.11 \text{ V vs. SCE}$)⁸ limits the employment of these conditions. Additionally, generation of not stabilized ketyl radicals is more difficult. However, the generation of these type of radicals and their use in reactions recently become possible with the use of α -acyl halides.⁹ The direct addition of radicals to carbonyl, used as radical acceptor, was recently reintroduced by Glorius and co-workers, with tailored and interesting strategies that makes the formed alkoxy radical, which normally decays directly via C–C β -scission, more stabilized.¹⁰ Interesting photoredox transformations, in which transient radicals are transformed by “radical to polar cross over” (RRPCO)¹¹ in carbanion able to react with carbonyl electrophiles, were reported by Martin (CO_2 as electrophile),¹² Zuo (intramolecular aldol reaction),¹³ Yu (CO_2 as electrophile),¹⁴ and König (carbonyls and CO_2).¹⁵ In all these transformations, the direct formation of a reactive nucleophilic carbon anion was observed.

The generation of organometallic nucleophilic reagents can be performed using the principle of the RRPCO when a C-centered radical is intercepted by the metal complex in low oxidation state. In the past this was routinely accomplished by alkyl halide-derived radicals in reactions with transition metals. A notable example of these accomplishments is the Nozaki-Hiyama-Kishi (NHK) reaction,¹⁶ a classical and important reaction with intriguing feature of selectivity, compatibility of functional group, and accessibility of wide range nucleophiles (allyl, propargyl, alkenyl, alkynyl, and aryl halides, alkenyl triflates, allyl sulfonates, and phosphates). The organochromium intermediates were normally formed by using an excess of Cr(II) as a one-electron donor, with a minimum of 2 mol equivalent of Cr(II) for mol of halide. Shenvi¹⁷ and Baran¹⁸ have recently demonstrated that version of the NHK reaction can be realized via the RRPCO pathway. Shenvi and co-workers reported the generation of a C-radical from a Co(III) complex, able to react with a Cr(II) complex to form a reactive Cr(III) alkyl reagent. Baran employed a redox activated ester (RAE) that is able to generate a C-centered radical upon fragmentation induced by Cr(II). The so-formed radical is then intercepted by another molecule of Cr(II) to give an active and reactive nucleophilic Cr(III) reagent. Clearly, both works demonstrated the ability of Cr(II) to intercept radicals and form the desired nucleophilic organometallic reagents, however both protocols rely on the requirement of stoichiometric chromium salts to obtain the desired reactivity. In addition, Cr(II) is expensive and

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highly oxygen-sensitive, making its handling difficult. The concept of catalytic redox reactions, again with the chromium-based NHK chemistry, was reported by Fürstner in 1996, in his seminal paper.¹⁹ In order to recycle chromium, and allow to perform the catalytic cycle, manganese powder as the stoichiometric reductant and TMSCl as additive were introduced. While manganese acts as terminal reductant for Cr(III) leading the formation of active Cr(II), the TMS acts as scavenger to liberate the Cr(III) from the alkoxide formed after the organometallic addition to the carbonyl. This concept was then extended to an enantioselective variant of the NHK reaction,²⁰ and to other reactions with different metals.²¹ As a main drawback of these protocols is the production of a stoichiometric amount of metal waste, and the need of an additive as a scavenger increases the amount of by-products. Moreover, the presence of a scavenger determines the formation of the product as its corresponding silylated adduct. In the above-mentioned scenario, the necessity of further treatment of the reaction crude to liberate the final desired product is hardly overcome (e.g., treatment of the reaction mixture in basic condition or with stoichiometric amounts of TBAF or analogs). Although electrochemical conditions can be a remarkable solution for the chromium chemistry,²² with the possibility to recycle chromium and adjust properly its oxidation state, the advantages to use photoredox conditions and to apply radical to polar cross over with metal led to considerable developments, here summarized. We have considered the photoredox cycles that allow the practical synthesis of organometallic reagents developed since 2018, after the seminal paper published by Glorius²³ that described the combination of chromium and photoredox catalysis. Up to now chromium, cobalt, titanium, and nickel were preferentially used in photoredox cycles allowing the generation of reactive organometallic reagents.

2. Photoredox catalysis: a survival guide for “photo-curious”

Ciamician in his famous article “*The Photochemistry of the Future*”²⁴ recognized the photons as “*energy in its most concentrated form*” that could be used “*as reactant*”²⁵ for injecting energy in molecules, avoiding thermal methodologies. Molecules by adsorption of photons can reach their excited states.²⁶ The peculiar and multifaced reactivity observed after light absorption is such that an electronically excited molecule is considered as a new molecular entity, different from its ground state. In a photoredox reaction the chemistry is mediated by a species able to absorb light (metal complexes, organic molecule, or material) that we call for sake of simplicity photocatalyst (**PC**), capable to activate substrates that cannot directly absorb light in a specific range of wavelengths, via two possible pathways: single electron transfer (SET) or energy transfer (EnT). In the synergistic use of metals to produce organometallic reagents SET events are predominant, since the oxidation state of metal is modulated by the **PC**. It is possible to alter the ability of the metal to undergoes elementary steps (i.e., reductive elimination) by EnT²⁷ and therefore, EnT is an important and well recognized area of research in photoredox catalysis.²⁸ However, for our scope we will limit our short guide to the SET-induced reactions.

The first important and key factor in photoredox catalysis is that, upon excitation by absorption of light at suitable wavelength, the **PC** is becoming a stronger oxidant and reductant compared to the **PC** molecule in its ground state.²⁹ **PCs** can act as oxidant or reductant in their excited state forming their reduced or oxidized form respectively. These, in turn, will be able to act as reductant or oxidant to restore the photocatalytic cycle. The important and primary step in a photocatalytic process is the adsorption of light. The event is regulated by the laws of quantummechanic²⁹ but can be qualitatively discussed and presented in simplified diagram called Jablonski diagram³⁰ (Figure 1).

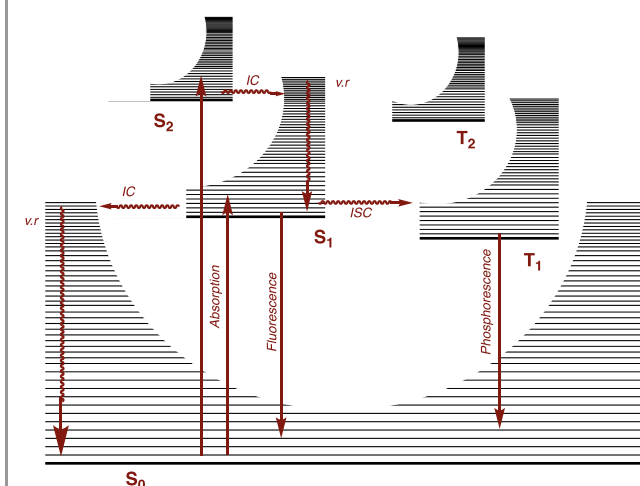


Figure 1 A Jablonski diagram used to depict ground and excited states with indicated photophysical processes.

Electronic states, represented by thick horizontal lines, are arranged to represent relative energies. In organic molecules, the ground state is a singlet state labelled as S_0 (no radicals!). In the diagram are normally depicted only a few states, with the state of different multiplicity separated horizontally. The thin lines sometimes inserted over S_0 , S_1 and T_1 represent vibrational levels. For some key calculation the level $v = 0$ is the lowest and the most important level. Then, the absorption or emission of photons is indicated by straight arrows, ascending (absorption) or descending (emission). However, the deactivation of an excited state can be occurring via a non-radiative phenomenon (dissipation of energy by vibrational relaxation), and these transitions are indicated by wavy lines. It is assumed that the transition $S_0 \rightarrow T_n$ cannot happen because forbidden by spin rules (electron states must have same spin multiplicity). Different excited states (i.e., S_1 and T_1), with same numerical label, are close or large in energy as a function of electrons repulsion. The radiative emission of energy from a S_n state corresponds to the return of the molecule in the ground state and is accompanied by emission of light, called *fluorescence*. The T_1 state, with different spin multiplicity to respect the ground state, can be accessible from the S_1 state by a physical phenomenon called *intersystem crossing* (ISC). Molecules from the T_1 state can return in their ground state by emission of light, indicated in the Jablonski diagram as an arrow line and this emission phenomenon is called *phosphorescence*. This transition is formally forbidden by the selection rules, but it is normally observed thanks to the longer lifetime of T_1 state to respect S_1 state. However, long, and short living states need to be reported to the range of time scale of electronic events, that are normally nanoseconds for S_1 to milliseconds for T_1 . The lifetime of excited state is strongly dependent from the nature of **PC**. The efficiency of all the processes can be measured and referred to quantum yields. If one photon is adsorbed by the molecule and S_1 is reached, then is the T_1 state populated? Is the process 90, 80 or 10% efficient? Or completely efficient? Of course, if deactivation of the excited states happens before the formation of T_1 , the probability to effectively use the excited state in a subsequent SET event is low. In some **PCs** an interesting phenomenon happens when the S_1 and T_1 states are close in energy. The behavior is described as thermally activated delayed fluorescence (TADF). In few words, when the two states (S_1 and T_1) are close in energy, thermal energy could be able to repopulate the higher energy state S_1 from T_1 by a phenomenon called *reverse intersystem crossing* (RISC), from which fluorescence decay can take place. The decay from excited state of this kind of organic dyes can give two different, well distinct, and observable decays, called *prompt fluorescence* and *delayed fluorescence*. As we will see in this review, TADF organic dyes were employed to promote formation of organometallic nucleophilic reagents (based on nickel, titanium, and chromium). The quantity, called E_{00} is crucial for many purposes. This quantity of energy, normally reported in eV is the difference between the lower vibrational levels of the ground and excited state. This energy can be evaluated by the adsorption and emission spectra of the **PC**, or, when not possible, can be estimated. As we have already mentioned, a **PC** is a better oxidant or reductant in its excited state compared to the unexcited form. Is it possible to evaluate its reduction or oxidation potential in excited state?

This estimation is crucial and important, particularly especially for new photocatalysts never reported in the literature. For many PCs, tables³¹ and reviews³² containing photophysical properties are available. The redox potentials of the excited state of a **PC** can be evaluated by the following equations, known as Rehm-Weller formalism (equations 1 and 2).³³

$$E_0(\text{PC}^+/\text{PC}) = E_0(\text{PC}^+/\text{PC}) - E_{00}(*\text{PC}/\text{PC})$$

Equation 1 Estimation of the oxidation potential of the PC in its excited state.

$$E_0(*\text{PC}/\text{PC}^-) = E_0(\text{PC}/\text{PC}^-) + E_{00}(*\text{PC}/\text{PC})$$

Equation 2 Estimation of the reduction potential of the PC in its excited state.

For new reactions, the excited state redox potential values are considered in the selection of **PCs** and are usually compared in the discussion of a reaction pathway, to corroborate a mechanistic picture, as we will discuss for the photoredox processes reported in this review. The interaction between the excited states (S_1 or T_1 , in function of the considered **PC**) and an organic molecule can generate a redox event, the *photoinduced electron transfer* (PET).³⁴ The interaction between an organic molecule and a **PC** in its excited state, indicated as ***PC**, is called *quenching*, and depending on the fate of the **PC**, it could be *oxidative* (the PC is oxidized and it is indicated as PC^{++}) or *reductive* (the PC is reduced and it is indicated as PC^{--}) (figure 2). The excited states populated by the TADF mechanism can also interact with organic molecules, following two distinguishable interactions: one with the S_1 state, populated by direct excitation, and one with the long lived S_1 state, populated by RISC. As function of the redox properties of the ***PC** and the substrate involved, the oxidative or reductive quenching may be possible. If the ***PC** acts as a reductant, a molecule that behave as an Acceptor (A) is necessary.

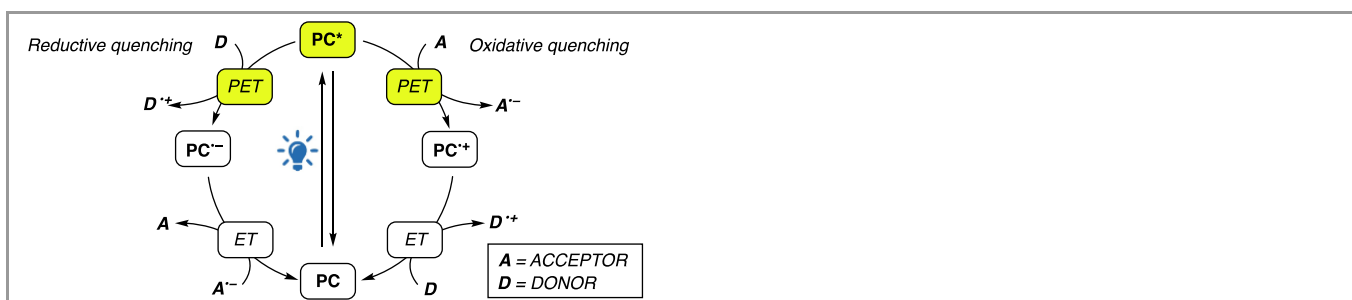


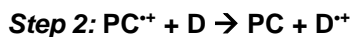
Figure 2 Interaction of photocatalyst in excited state with quenchers.

The PET event will generate the corresponding $\text{A}^{\bullet-}$ and PC^{++} . The property of the oxidized **PC** (PC^{++}) can be assessed by electrochemistry. The value is important, because to restore the catalytic cycle from the PC point of view, another SET event (a reduction) needs to take place. This event will restore the **PC** in its original state ($\text{PC}^{++} + e^- \rightarrow \text{PC}$). In this case, a donor (D), capable to reduce the PC^{++} , needs to be employed. A qualitative estimation of the free energy involved in these steps can give a rough idea if the process could be favored from the energetic point of view. If we consider only the ***PC** in its excited state, we could estimate energies involved in the process by the equations 2 and 3.



$$^*\Delta G_{SET}^0 \simeq E_{ox}(PC^{++}/^*PC) - E_{red}(A/A^{--})$$

$$^*\Delta G_{SET}^0 \simeq E_{ox}(PC^{++}/PC) - E_{red}(A/A^{--}) - E_{0,0}(^*PC/PC^{--})$$



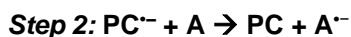
$$\Delta G_{SET}^0 \simeq E_{ox}(D^{++}/D) - E_{red}(PC/PC^{--})$$

Equation 2 Estimation of the free energies involved in a catalytic cycle where an oxidative quenching process is present.



$$\Delta G_{SET}^0 \simeq E_{ox}(D^{++}/D) - E_{red}(^*PC/PC^{--})$$

$$^*\Delta G_{SET}^0 \simeq E_{ox}(D^{++}/D) - E_{red}(PC/PC^{--}) - E_{0,0}(^*PC/PC^{--})$$



$$\Delta G_{SET}^0 \simeq E_{ox}(PC/PC^{--}) - E_{red}(A/A^{--})$$

Equation 3 Estimation of the free energies involved in a catalytic cycle where a reductive quenching process is present.

$E_0(PC^+/^*PC)$ and $E_0(^*PC/PC^-)$ values (in V) are referred to the photocatalyst in its excited state evaluated with the precedent equation, while $E_0(PC/PC^-)$ and $E_0(PC/PC^+)$ are referred to the organic species involved in the ET event in the ground state. If we want to oxidize a substrate D via a PC in its excited state, the value of $E_0(^*PC/PC^-)$ needs to be more positive than $E_0(D^+/D)$. Based on available potentials reported to the same reference electrode (SCE or ferrocene are the most common), we can judge, from the energetic point of view, if the desired SET event will be feasible or not. An experiment, now quite standard in the economy of publications in the photoredox reaction arena, can suggest which event, oxidative or reductive quenching, is effectively happening. This experiment is called Stern-Volmer³⁵ and is about to study how the intensity (when possible, otherwise lifetimes of excited state need to be monitored) of emission (fluorescence or phosphorescence) is altered by increasing the concentration of an organic substrate. If the interaction between the latter and the excited state is taking place, the intensity of emission will be decreased, and the response is normally linear³⁶ with the concentration of the quencher. By performing the Stern-Volmer experiment using all the organic species involved in the reaction, an idea about the main quencher of the *PC can be obtained and by redox potential analysis can be possible to understand if an oxidative or a reductive quenching are active in the PET event. The experiment can help in the construction of a reasonable catalytic cycle, as we will discuss in detail in the examples of this review. When a metal complex is used, in dual photoredox catalysis, almost the involvement of the original metal complex with the *PC could be investigated and, sometimes, direct interaction of the metal complex by ET events can be revealed. Attention needs to be paid to the Stern-Volmer experiments, since complicate phenomena (such as static quenching) can make the experiment difficult to be interpreted,³⁷ and, when TADF is used, both the prompt and the delayed fluorescence are interacting with a possible quencher, making the interpretation of the results complicated.

Finally, another important experiment that can give useful information about the process is the determination of the quantum yields. This could be done by actinometry,³⁸ or by direct measure of the photon flow.³⁹ By the measure of the number of photons interacting with the sample, it is possible to measure the efficiency of the process. How many molecules of product are formed per absorbed photon? If we get more product in respect to

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the number of photons (i.e., quantum yield $\gg 1$) a radical chain mechanism is involved. The reaction can start with a photoredox event, but it is propagated by transfer of radicals.⁴⁰ If the quantum yields ≤ 1 , one photon produces only one molecule of product, but a radical chain mechanism could not be excluded.

$$\Phi_i = \frac{\text{n}^\circ \text{ of molecules undergoing the } i\text{-process}}{\text{n}^\circ \text{ of absorbed photons}}$$

Equation 4 Determination of quantum yield for a photochemical process.

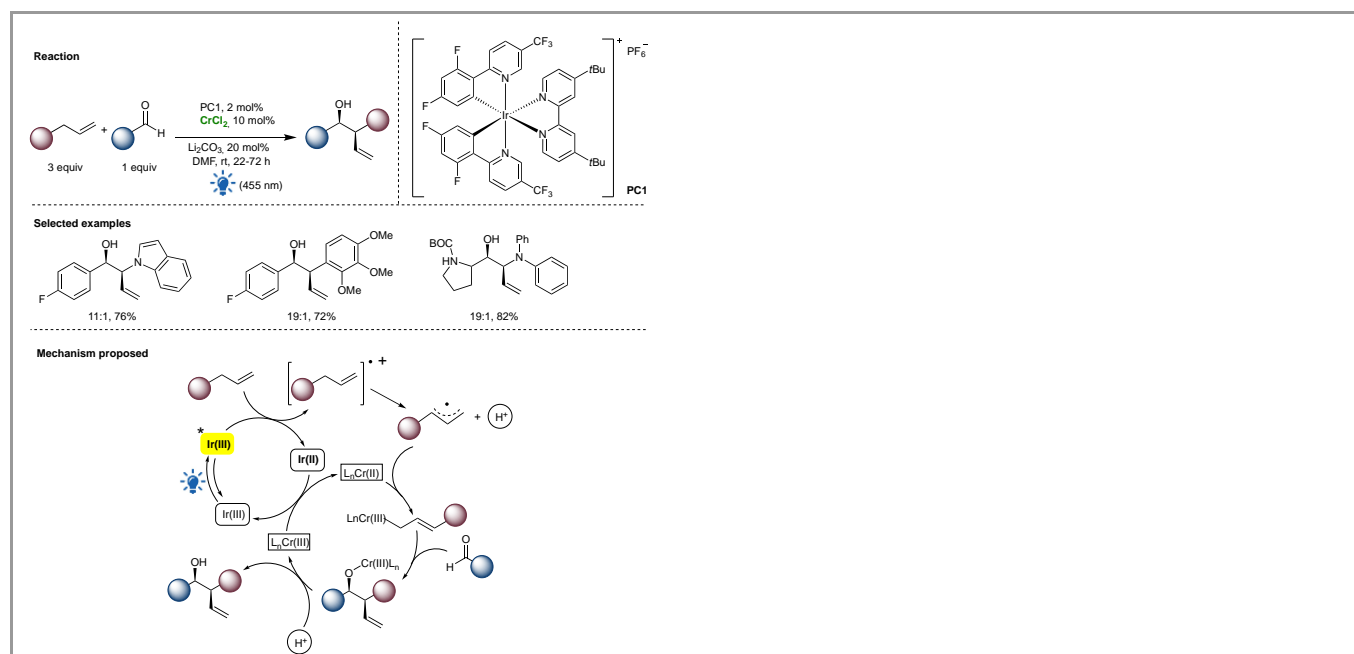
With this “theoretical minimum”⁴¹ of the basic understanding of photoredox catalysis, we can now examine the results reported in formation of nucleophilic organometallic reagents in photoredox conditions.

3. Chromium nucleophilic organometallic reagents

The Nozaki–Hiyama–Kishi (NHK) is a powerful methodology, especially in field of the total synthesis,⁴² due to the broad functional group tolerance. The possibility to use chiral ligands and to control the C–C bond formation in enantioselective and diastereoselective ways, it was recently employed in the preparation of the powerful antitumoral Eribuline mesylate,⁴³ that illustrate all the possibility offered by this synthetic method. In this beautiful example of selectivity and compatibility, the catalytic conditions developed by Fürstner are employed. In diastereoselective construction of C–C bonds manganese powder as the stoichiometric reductant and Cp_2ZrCl_2 as an additive⁴⁴ to cleave the incipient O–Cr bond were employed. One of the major concerns about the employment of chromium, is the historically established “beliefs” that Cr(II) and Cr(III) are toxic and it is better to avoid the use of these reagents. Instead, chromium it is a cheap and non-toxic metal.⁴⁵ A breakthrough realized recently was the application of photoredox conditions to approach chromium organometallic reagents.⁴⁶

3.1. Allylation of aldehydes

As we already mentioned, in 2018 Glorius reported a dual chromium/photoredox catalytic protocol, describing the redox-neutral allylation of aldehydes with electron-rich allyl (hetero-) arenes, β -alkyl styrenes, and allyl-diarylamines (Scheme 1).



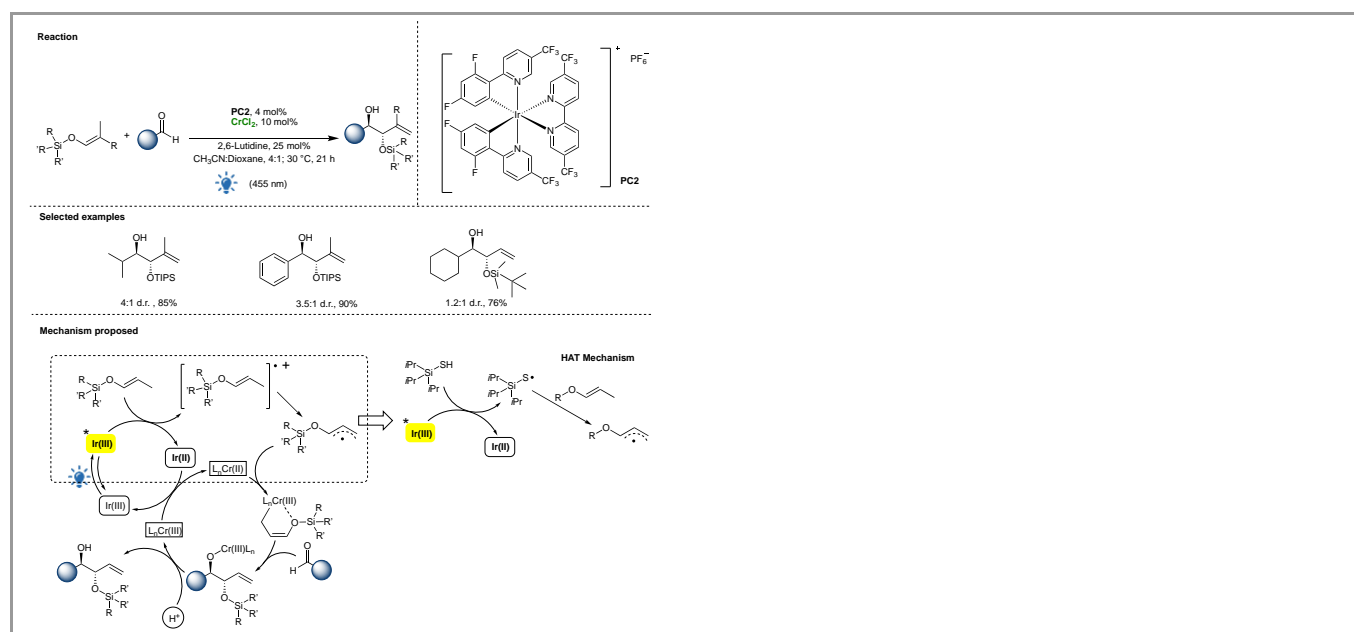
Scheme 1 Dual chromium/photoredox catalytic protocol for the allylation of aldehydes with alkenes.

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The authors used the iridium complex Ir(III) **PC1** as photocatalyst [$E_{1/2}(*\text{Ir(III)}/\text{Ir(II)}) = +1.21 \text{ V vs SCE in MeCN}$]. Stern-Volmer experiment identified allyl-diarylamines and allylindole as quenchers, while aldehydes were not interacting with the ***PC1**. Interestingly, also the products were found to be quenchers of ***PC1**. This behavior explains the excess of starting allylamines used for the reaction. Moreover, experiments for controlling the ability of Cr(II) to quench the **PC1** were not carried out. It was suggested, as a possible alternative mechanism, that ***PC1** was able to quench Cr(III) complex, but no Stern-Volmer studies were realized. Additionally, it seems that Cr(III) salts (that avoid the use of glove box for the setup of the reaction) could not be good as precursor for the metal catalyst. The reaction is peculiar as no ligands were introduced to control the coordination of Cr(II) and, since the reaction is performed in DMF, probably molecules of solvents coordinate the Cr(II). In the proposed catalytic cycle, depicted in Scheme 1, the ***PC1** interacts by a reductive quenching with the allyl (hetero-) arene generating an aryl radical cation. The loss of H^+ by the acidic radical cation species forms the corresponding allyl radical that is intercepted, in a radical polar cross over reaction, by the Cr(II), forming the Cr(III) allyl nucleophile. Kochi reported the rate constants of the reaction between carbon radicals and Cr(II), demonstrating the high rate of the process.⁴⁷ The high diastereoselectivity obtained for the reaction with aldehydes was explained by a Zimmerman–Traxler transition state. The product obtained by the reaction with the aldehyde is a chromium alkoxide. The authors have supposed that the generated proton from radical cation is able to liberate the Cr(III) that is reduced by the Ir(II) complex [$E(\text{Ir(III)}/\text{Ir(II)}) = -1.37 \text{ V vs SCE in MeCN}$]. To this respect, Baran and co-workers, measured the reduction potential of $\text{CrCl}_3 \cdot (\text{THF})_3$ at -0.66 V vs SCE ⁴⁸ and noted a slow electron transfer, that can account with the needed to use Cr(II) for the reaction, compatible with the reduction potential of [Ir(II)].

Similarly, the homoallylic 1,2-diol motif can be accessible by the chemistry described by Glorius (Scheme 2).⁴⁹



Scheme 2 Dual chromium/photoredox catalytic synthesis on monoprotected diols.

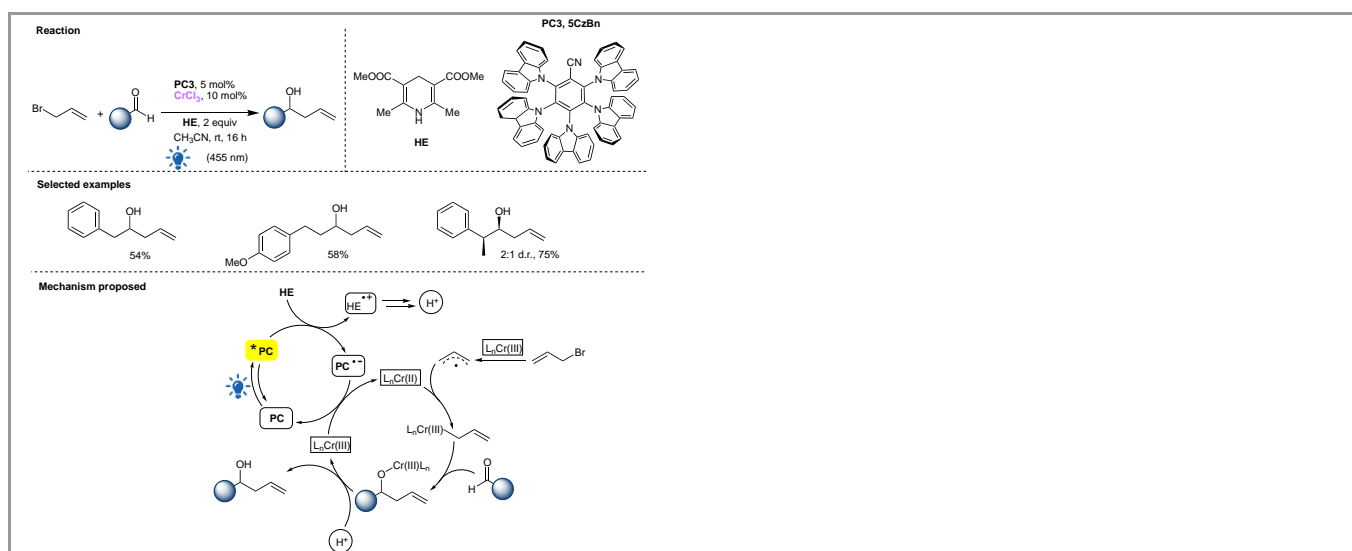
Oxidation of silyl enol ether by the excited state of photocatalyst **PC2** [$E(*\text{Ir(III)}/\text{Ir(II)}) = 1.68 \text{ V vs SCE in MeCN}$ ⁵⁰] was possible. In fact, oxidation potentials of different silyl enol ethers were measured, and they were in the range 1.64–1.96 V vs SCE.⁴⁹ From the Stern Volmer analysis was clear that the different silyl enol ethers studied were able to quench the excited state of the photocatalyst ***PC2**, while the aldehyde does not interact. The base (2,6-lutidine) has the role of accelerating the deprotonation of radical cation, formed by oxidation of the double bond, into the allyl radical. Opposite to the allylation of aldehydes with allyl compounds, the use of air stable CrCl_3 was possible. Similarly, to the catalytic cycle described in the previous example, the [Ir(II)] photocatalyst was able to reduce the Cr(III) species liberated from Cr-alkoxide, recycling the Cr for a further catalytic cycle. The major diastereoisomer obtained was assigned as *anti*, as is expected from a Zimmerman–Traxler type transition state.

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The reaction was applied to a variety of aromatic and aliphatic aldehydes and different silyl groups were also investigated, affording the desired product from good to moderate diastereoselectivities; instead, unsubstituted alkyl enol ethers were completely unreactive. This was not a surprise, as the oxidation potential of unsubstituted alkyl enol ethers, not activated by β -silicon effect nor by hyperconjugation, was close to 2 V and cannot be directly oxidized by the ***PC2**. For this kind of ethers another approach was developed. The reaction was performed in the presence of triisopropylsilanethiol (35 mol%) as Hydrogen Atom Transfer (HAT) catalyst (Scheme 2). Oxidation of the thiol by the photocatalyst formed a thiol radical, this last can abstract a hydrogen radical to the enol ether, affording the formation of the desired allyl radical. The photoredox allylation variant presented above rely on the employment of a strong photooxidant, that after oxidation step and proton lost can generate a radical from a suitable (oxidable) alkene. The formed radical was intercepted by the Cr(II) salt to form the reactive organometallic Cr(III) reagent. The photocatalyst, in its reduced form, could restore the Cr(II), closing both the transition metal and the photocatalytic cycle. The proton deriving from the alkene precursor was the scavenger able to liberate the Cr(III) from the intermediate alkoxide, allowing the use of chromium in catalytic amount. Although redox neutral, these reactions rely in the use of a strong oxidant photocatalysts in their excited states.

Many NHK reactions developed from its discovery employed cheap and available organic halides, as reaction partner. A major advance in chromium mediated photoredox methodology would be the possibility to use organic halides. Furthermore, in many of the reported methods for chromium catalysis, high yields were obtained employing the sensitive Cr(II) that needs a glovebox for its handling, although the use of air stable Cr(III) salts is possible. Cozzi has recently reported a partial success in this direction even if limited to the allylation of aliphatic aldehydes (Scheme 3).⁵¹



Scheme 3 Photoredox catalytic NHK reaction.

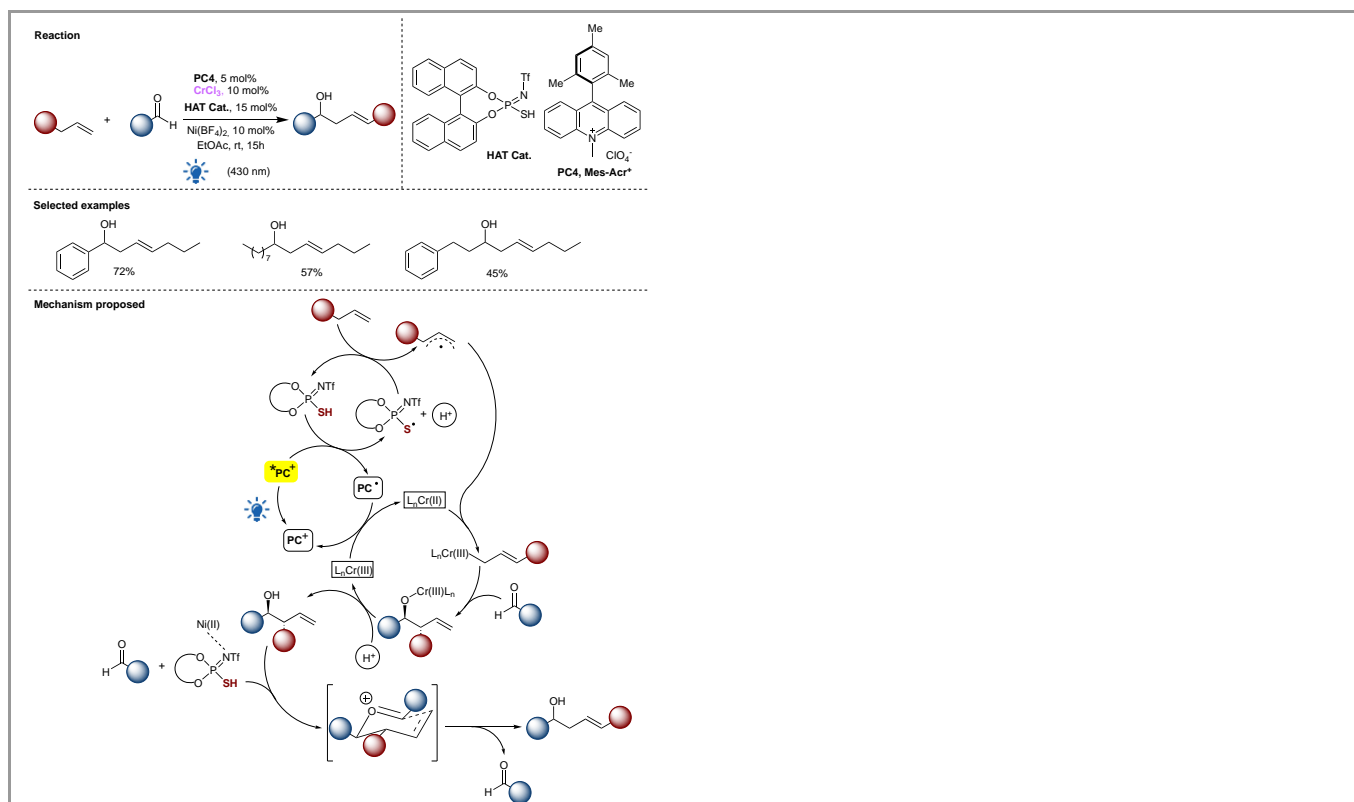
Stable Cr(III) salts were specifically chosen to avoid the use of Cr(II) salts but it was necessary to use the TADF dye 5CzBn (**PC3**) as photocatalyst, a strong reductant in its excited state ($E(\text{PC3}^{*+}/\text{PC3}^{\bullet-}) = -1.42$ V vs SCE) and in its reduced state ($E(\text{PC3}/\text{PC3}^{\bullet-}) = -1.52$ V vs SCE). Unfortunately, using aromatic aldehydes as substrates the reaction conditions were sufficiently reducing to promote pinacol coupling. The sacrificial organic compounds used to restore the photoredox cycle was the Hantzsch ester (**HE**) (Scheme 3). Although aromatic aldehydes used have reduction potential near to -2 V vs SCE, the formation of Brønsted acids during the reaction (for example **HE**⁺⁺) can activate the aldehyde towards the reduction by a proton coupled electron transfer. Although this limitation, it was possible to use allyl bromide for the first time in photoredox chromium reaction, with a variety of aliphatic linear and branched benzylic aldehydes. The presence of functional groups such as alkene, alkynes, protected alcohols, and amines is well tolerated. The Stern-Volmer analysis clarified that both Hantzsch ester (**HE**) and $\text{CrCl}_3 \cdot (\text{THF})_3$ quenched the emission of the photocatalyst, with a better efficiency for the quenching of

HE ester, due to the higher concentration in solution. The reduced form of the photocatalyst, thanks to its high oxidation potential, is then able to reduce the Cr(III) complex. The slow electron transfer kinetic for the reduction of Cr(III) limits the possibility to use photocatalysts in which the transient excited state (***PC**) is quenched by Cr(III) complexes. Instead, the reduced form of the catalyst (**PC⁻**), is relatively stable and has a lifetime long enough to interact and reduce the Cr(III) species. In the cases presented of chromium mediated photoredox methodologies starting from alkene or substituted allyl halides, the branched product is always obtained. The linear product is not favored, as results of a cyclic Zimmerman-Traxler transition state.

It is well known that Lewis acid can induce the formation of an oxonia-Cope rearrangement.⁵² With this idea in mind, Kanai followed a hydrogen atom transfer (HAT) approach, employing an acridinium photoredox catalyst (**PC4⁺**, Mes-Acr⁺), a thiophosphoric imide (TPI, **HAT cat.**) as HAT catalyst and a catalytic amount of chromium complex, in presence of a Lewis acid (Scheme 4).⁵³ As briefly discussed in the previous example, a sulfur-centered radical (**RS[•]**) is generated through single-electron oxidation of TPI by a photo-excited acridinium catalyst. The TPI[•] radical can form an allyl radical by atom hydrogen abstraction, and the allyl radical is intercepted by the Cr(II) complex. Ni(BF₄)₂ as Lewis acid, working via coordination with the phosphoric thioamide, was found suitable for the scope. It is worth mentioning that the selected photocatalyst did not have the reducing power necessary to form nickel in low oxidation state. In addition, other Ni(II) salt were found less suitable for the scope. The reaction was generally investigated with different aromatic and aliphatic aldehydes and the linear product was obtained in good yields. The addition of Ni(BF₄)₂ enhanced the acidity of the phosphoric acid thioamide,⁵⁴ and nickel was a suitable metal, as it enables the coordination with the phosphoric thioamide as demonstrated by the authors by IR and ³¹P NMR studies.

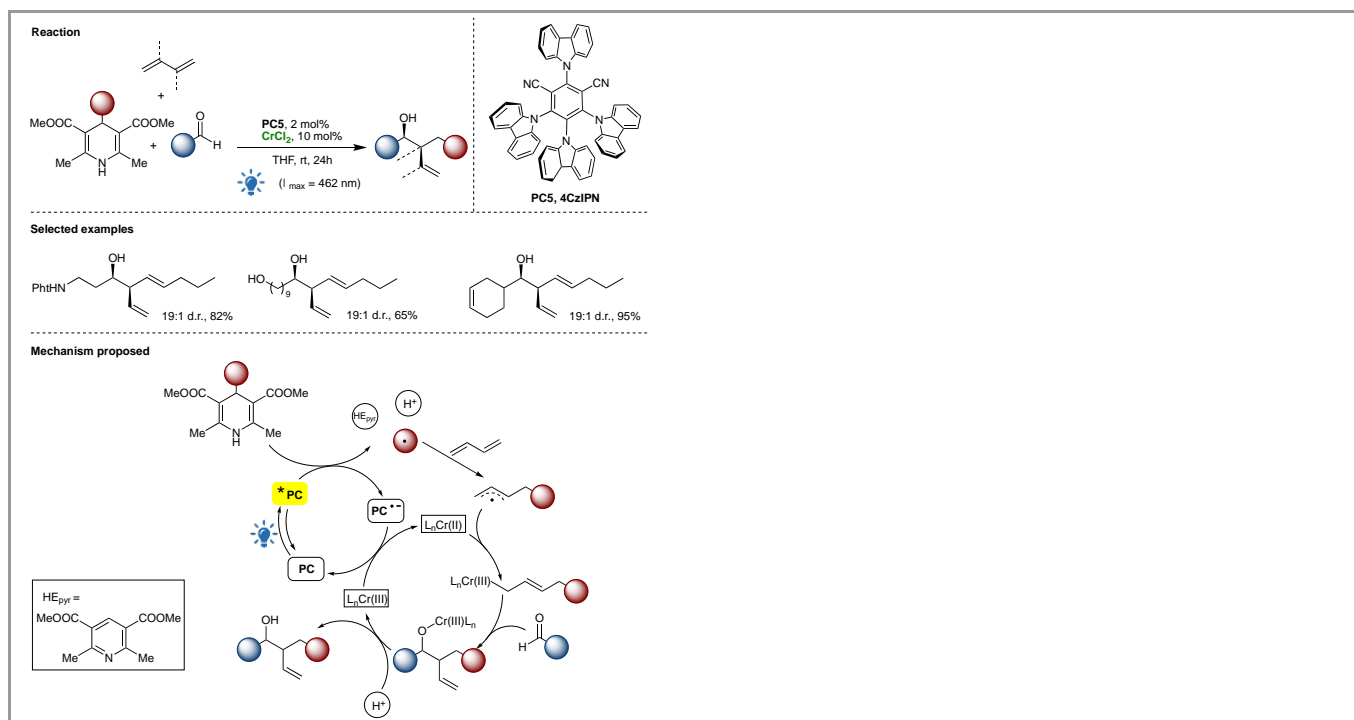
3.2. Allylation of aldehydes via diene

1,3-Dienes are abundant feedstocks, particularly present in many natural products.⁵⁵ Photoredox catalysis offers the possibility to realize a direct conversion of these inexpensive feedstocks into valuable chemical intermediates. The addition of a radical to a 1,3-diene generates an allyl radical. By using the chromium photoredox chemistry would be possible to access to



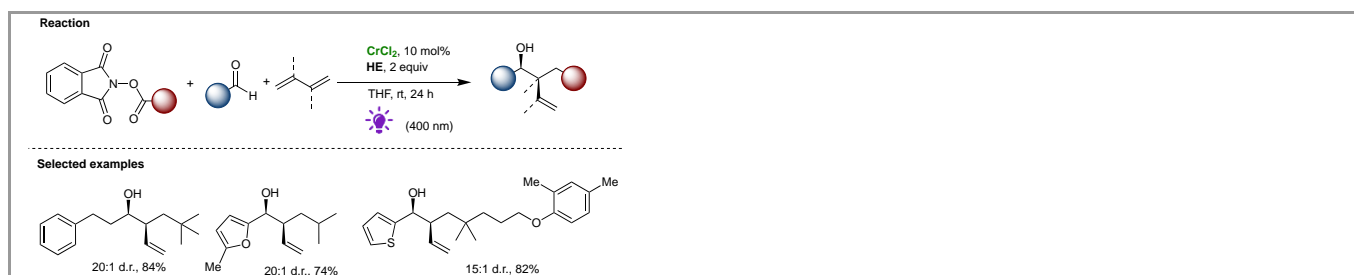
Scheme 4 Photoredox HAT approach to allylation of aldehydes.

a nucleophilic chromium allyl complex from the radical so formed. However, the trapping of the allyl radical by Cr(II) needs to be faster than the trapping of unstabilized alkyl radicals. For this reason, the formation of the allyl radical by addition of alkyl radical species to 1,3-diene needs to be realized by using a molecule capable of releasing alkyl radical through a photoredox oxidation mediated by the ***PC**. The PC^{•-} formed in the first event should be capable to reduce Cr(III) to Cr(II) and the source of radical should release H⁺, that is indispensable for cleaving the O-Cr bond and liberate the Cr(III) for a further reduction. Additionally, an easy to handle and oxidable (by the ***PC**) stable radical source it would be necessary. All these requirements can be met in 4-alkyl Hantzsch's ester,⁵⁶ easy prepared reagents able to give radicals by oxidation. By using 4-alkyl Hantzsch esters, Glorius reported⁵⁷ a practical multicomponent allylation reaction (Scheme 5). Precedent works based on chromium, were reported in literature, although the use of stoichiometric amount of Mn as reductant was required.⁵⁸ The reaction was promoted using the TADF dye 4CzIPN [**PC5**; E_{1/2}(***PC5**/**PC5**^{•-}) = + 1.43 V vs SCE in MeCN, E_{1/2}(**PC5**^{•+}/**PC5**) = +1.49 V vs SCE in MeCN]⁵⁹ as photocatalyst, and CrCl₃ can be employed as well. The reaction also tolerates a broad range of functional groups and the use of aliphatic as well as aromatic aldehydes was possible. Various 4-alkyl Hantzsch's esters were tested in the reaction. Employing tertiary substituted alkyl Hantzsch esters it was necessary to use 3,5-dicyano substituted Hantzsch esters analogous. Moreover, carrying out the reaction on unsymmetrical 1,3-dienes, two regioisomeric 1,2-addition products were obtained, with some selectivity towards the formation of more stable allyl radical. The Stern-Volmer analysis of the reaction confirmed that Hantzsch's esters quench the **PC5** in its excited state.



Scheme 5 Chromium(II) mediated photoredox allylation of aldehydes with dienes.

In 2021, Shi reported a different photoredox methodology using dienes and chromium salts (Scheme 6).⁶⁰



Scheme 6 Three components photoredox allylation of aldehydes.

Instead to employ a photocatalyst, the group has developed a chromium mediated reaction taking advantage by the photoredox properties of the Hantzsch's ester (**HE**).^{56d-i,61} In this case, a UV light source (400 nm) is necessary to excite **HE**. As we will discuss further, Hantzsch's ester is a useful sacrificial agent, able to quench in a reductive manner many photocatalysts employed in photoredox catalysis. In addition, as we have illustrated for alkylated Hantzsch esters, the **HE**^{•+} formed by first ET event is a good reductant, and, upon oxidation, forms a stable pyridine derivative, releasing a proton. The potential of ***HE/HE**^{•+} was estimated to be -2.28 V versus SCE⁶¹ making the reduction of Cr(III) extremely favorable. In this strategy, the formation of allylchromium from diene is obtained taking advantage from the use of a redox-active esters (RAE).⁶² These esters, reintroduced in the practical organic chemistry by Baran,⁶³ can accept an electron via ET event, and by loss of CO₂ and fragmentation, can form radicals. However, years before photoredox catalysis became a hot topic, Okada used RAEs and ruthenium based photocatalyst to achieve radical Michael additions.⁶⁴ RAE can be reduced at ca. -1.2 V vs SCE,⁶⁵ therefore both the excited **HE** and its oxidized product (**HE**^{•+}) are strong reductants for inducing the fragmentation of RAE. In the reaction reported by Shi, stable CrCl₃ could be used as chromium source, but the yield dropped down. It was possible to use primary, secondary, and tertiary alkyls RAE derivatives and the reaction was efficient with aliphatic and aromatic aldehydes. A good diastereoselective ratio, in favor for the *anti*-stereoisomer was obtained, as normally expected by a Zimmerman-Traxler transition state involving allylchromium derivatives. The catalytic

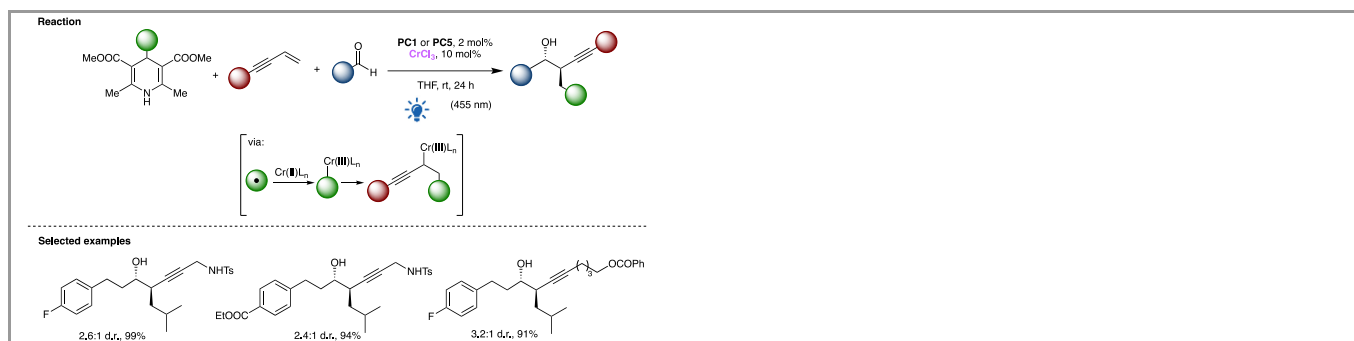
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cycle proposed by the authors suggests a direct reduction of Cr(III), however the scope of the reaction was described with Cr(II), given the better yields obtained. Stern-Volmer quenching experiments were not executed but experimental evidence suggests that RAE can be directly reduced by **HE** via the formation of an electron donor–acceptor (EDA) complex.⁶⁶

3.3. Propargylation of aldehydes via 1,3-enyne

The addition of radical to the double bond of 1,3-enyne can give access to propargylic radicals. By chromium mediated RPCO is possible to have access to nucleophilic chromo-propargyl nucleophiles. The advantage of the chromium promoted reaction is to realize an alternative to the well-established methodologies that rely on polar chemistry.⁶⁷ The use of 1,3-enynes as pronucleophiles in the addition to carbonyl was investigated.⁶⁸ Although 1,3-enynes were employed in reactions affording substituted allenyl (1,4-adducts) or alkynyl (1,2-adducts) derivatives via radicals,⁶⁹ addition to carbonyls using this strategy was not previously reported. In 2021, Glorius described the photoredox generation of propargylic chromium reagents able to react with aldehydes (scheme 7).⁷⁰



Scheme 7 Photoredox propargylation of aldehydes with 1,3-enyne.

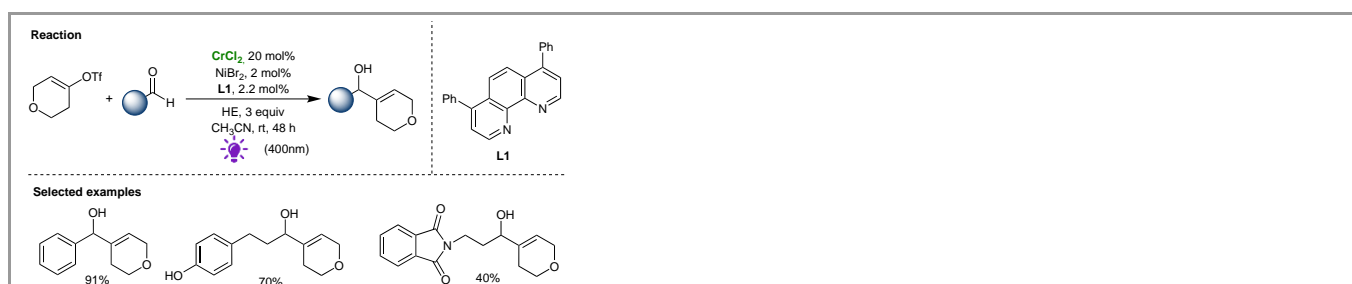
Predictably, the outcome obtained by enyne and diene methodologies are quite similar. However, the most important difference here was the possibility for standard reaction to employ CrCl₃ (10 mol %) as chromium source, that simplify considerably the reaction set-up. The photocatalysts selected for the reaction are **PC1** [$E_{1/2}(*\text{Ir(III)}/\text{Ir(II)}) = 1.21 \text{ V vs. SCE in MeCN}$] or 4CzIPN **PC5** [$E_{1/2}(*\text{PC5}/\text{PC5}^{\bullet-}) = 1.35 \text{ V vs. SCE in MeCN}$]. Both photocatalysts were able to oxidize the 4-substitued Hantzsch's ester [$E(\text{HE}^{\bullet+}/\text{HE}) = 1.10 \text{ V vs. SCE in MeCN}$], that upon fragmentation gave the corresponding alkyl radical. The proton released by the oxidized Hantzsch's ester could protonate the chromium alkoxide, restoring the chromium complex for further reduction. The reaction showed compatibility with many functional groups (phthalimido, free diols, tosylamides, benzyl ethers, esters, heterocycles, alkynes, etc.), and it was also possible to use different aldehydes, even bearing sensitive indole moiety. Regarding the Hantzsch's ester derivatives, broad and versatile arrays of different substituents were examined (different primary and secondary alkyl groups, substituted alkyls), with limitations discovered in the acyl substituents, that were found not reactive, since the acyl radical is not able to interact with the enyne. A detailed mechanistic analysis of the reaction ruled out the formation of ketyl radicals, since the employed photocatalysts were not sufficient reductants to reduce carbonyl. On the other hand, the formation of propargylic radical was established. Finally, by standard Stern-Volmer experiments a reductive quenching of the photocatalysts by the Hantzsch's ester was disclosed. The reduced photocatalysts were enough reductant to reduce Cr(III) to Cr(II). The key step in the transformation was the radical to polar cross over that allowed the formation of the chromium organometallic specie by reaction of the alkyl radical from the **HE**, the 1,3-enyne and the Cr(II) complex. The allenyl- and propargyl chromium are in equilibria⁷¹ and because no traces of allenylic compounds are detected, the allenylic chromium species was more reactive. The collected data supported the proposed catalyst cycle, illustrated in Scheme 5.

3.4 Alkenylation of aldehydes

The formation of allyl- or propargyl chromium compound from halides does not require additives, while a catalytic amount of nickel(II) salts is an essential co-catalyst for the preparation of alkenylchromium species.⁷² In the

fundamental work of Fürstner,¹⁸ about the catalytic version of NHK reaction, the presence of Ni(II) salts made possible to extend the catalytic version to a variety of vinylic reagents. Kishi reported catalytic enantioselective version⁷³ of the reaction, introducing nickel salts, crucial for the observed reactivity.

The photocatalytic alkenylation of aldehydes by chromium organometallic reagents was reported by Shi (Scheme 8).⁷⁴ The reaction was promoted by catalytic amount of CrCl₂, NiBr₂ and 4,7-diphenyl-1,10-phenanthroline **L1** as ligand for nickel,⁴⁷ in the presence of 3 equivalents of the Hantzsch's ester under irradiation of 400 nm LED in CH₃CN. Vinyl triflates were employed as precursor of vinylic chromium reagents. Many different aldehydes were reactive under these conditions, primary or secondary, affording good yields in the desired products. It was also possible to vary the alkenyl triflate with different cyclic or acyclic starting materials.



Scheme 8 photocatalytic alkenylation of aldehydes by chromium organometallic reagents.

As we have already mentioned, the high reduction potential of **HE** in its excited state makes the reduction of Cr(III) and Ni(II) [$E_{1/2}(\text{Ni}^{\text{II}}/\text{Ni}^0) = -1.2 \text{ V vs SCE in DMF}$]⁷⁵ favoured. The high concentration of ***HE** can overcome the very short lifetime of its excited state ($\tau_0 = 320 \text{ ps}$).⁷⁶ Stern Volmer experiments clarified that luminescence of **HE** was quenched by both CrCl₃(THF)₃ and Ni(II) salts, with a slight better efficiency for the quenching of chromium. Since the reaction was developed using Cr(II), the electrochemical studies performed by Baran²² can help to shed light about the mechanism. Cr(II) is able to reduce Ni(II) to Ni(0), and, alternatively, Ni(0) can be obtained from reduction performed by **HE** in its excited state. Oxidative addition of alkenyl triflate to low-valent Ni led to the formation of vinyl nickel compounds that undergoes through a transmetallation by the Cr(III) to give the chromium vinylic reagent.

3.5. Alkylation of aldehydes

Taking inspiration from Steinborn's studies on [(dimethylamino)methyl]chromate(III) complex,⁷⁷ in 2020 Glorius investigated the photoredox preparation of nucleophilic α -aminoalkyl-Cr reagents,⁷⁸ as a direct alternative to the ring-opening of epoxides to prepare 1,2-amino alcohols (Scheme 9).

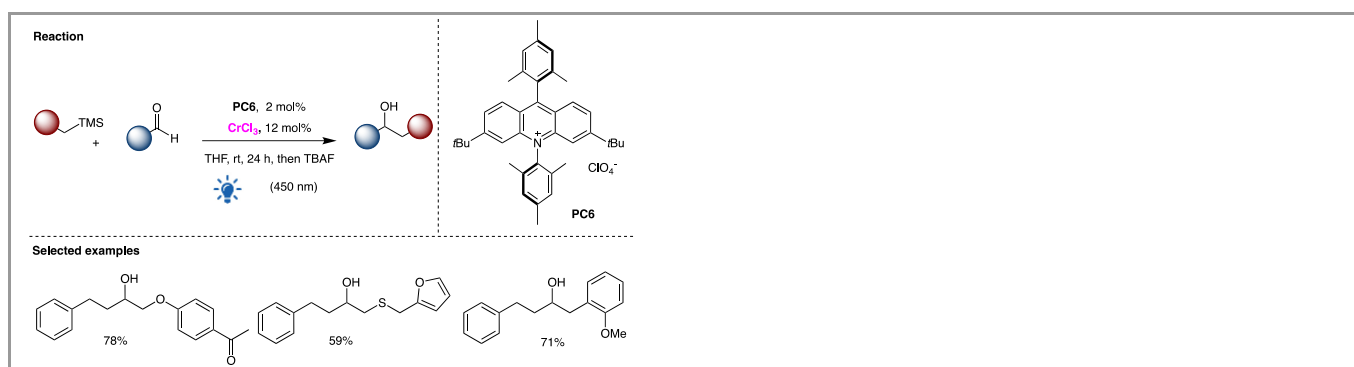


Scheme 9 Synthesis of 1,2-amino alcohols by photoredox alkylation of aldehydes.

To promote the process, Ir(III) **PC1** was used although the process could be also promoted by the TADF catalyst 4CzIPN **PC5**⁷⁹ in slightly reduced efficiency. Interestingly, in this reaction bench stable CrCl₃ could also be

employed as catalyst. Again, Stern–Volmer luminescence quenching studies revealed that both the silyl amine and aldehyde were able to quench the excited state of the $^*Ir(III)$ but the quenching with amine was more efficient (larger quenching constant). With this information in hand, a catalytic cycle in which the amine reduces the $^*Ir(III)$ to $Ir(II)$ was proposed. Since the quantum yield measured for the reaction was 12.5, a chain mechanism was invoked for the reaction: the intermediate $Cr(III)$ alkoxide reacts with the silylamine generating the alkylchromium reagent.

With the aim to expand the alkylation of aldehydes with other chromium reagents, Glorius used a Cr /photoredox system for accessing α -benzylic alcohols, isochromanones, oxy-alcohols and thio-alcohols.⁸⁰ The main idea was to try to generate α -thio⁸¹ and α -oxy radicals⁸² under photoredox conditions and to capture the radicals with chromium in low oxidation state. To facilitate the formation of radical by oxidation, the generation of the respective benzylic, α -thio, and α -oxy radicals by the introduction of alkylsilane was assured (Scheme 10).



Scheme 10 Chromium(III) alkylation of aldehydes with trimethylsilyl derivatives.

In these reactions, the employment of $Cr(II)Cl_2$ gave better yields compared to $Cr(III)Cl_3$ on benzylic substrates, while for alkoxy- and thio-derivatives the employment of the air stable $CrCl_3$ was possible. The photocatalyst employed for the reaction was 3,6-di-*tert*-butyl-9,10-dimesitylacridinium perchlorate **PC6** [$E_{1/2}(\text{PC6}^*/\text{PC6}^{\cdot-}) = +2.0$ V vs SCE in MeCN], a strong oxidant and able to oxidize silyl derivatives. In reactions with aldehydes, the silyl group was found bounded to the oxygen ex-aldehyde, acting as a scavenger able to liberate the chromium alkoxide formed in the organometallic reaction (similarly to NHK reactions). The reaction tolerated various functional groups like pyridine, pyrazoles, esters, and amides in the case of benzylation. Moreover, in the case of α -oxy radical it was possible to vary the precursors. In the case of thio-derivatives was possible to use primary, secondary and tertiary thioalkyl derivatives. Finally, the Stern-Volmer quenching experiments were relevant to suggest a mechanistic picture that confirmed the silyl derivative as quencher of the $^*\text{PC}$, while $\text{PC}^{\cdot-}$ was sufficient to reduce $Cr(III)$ to $Cr(II)$.

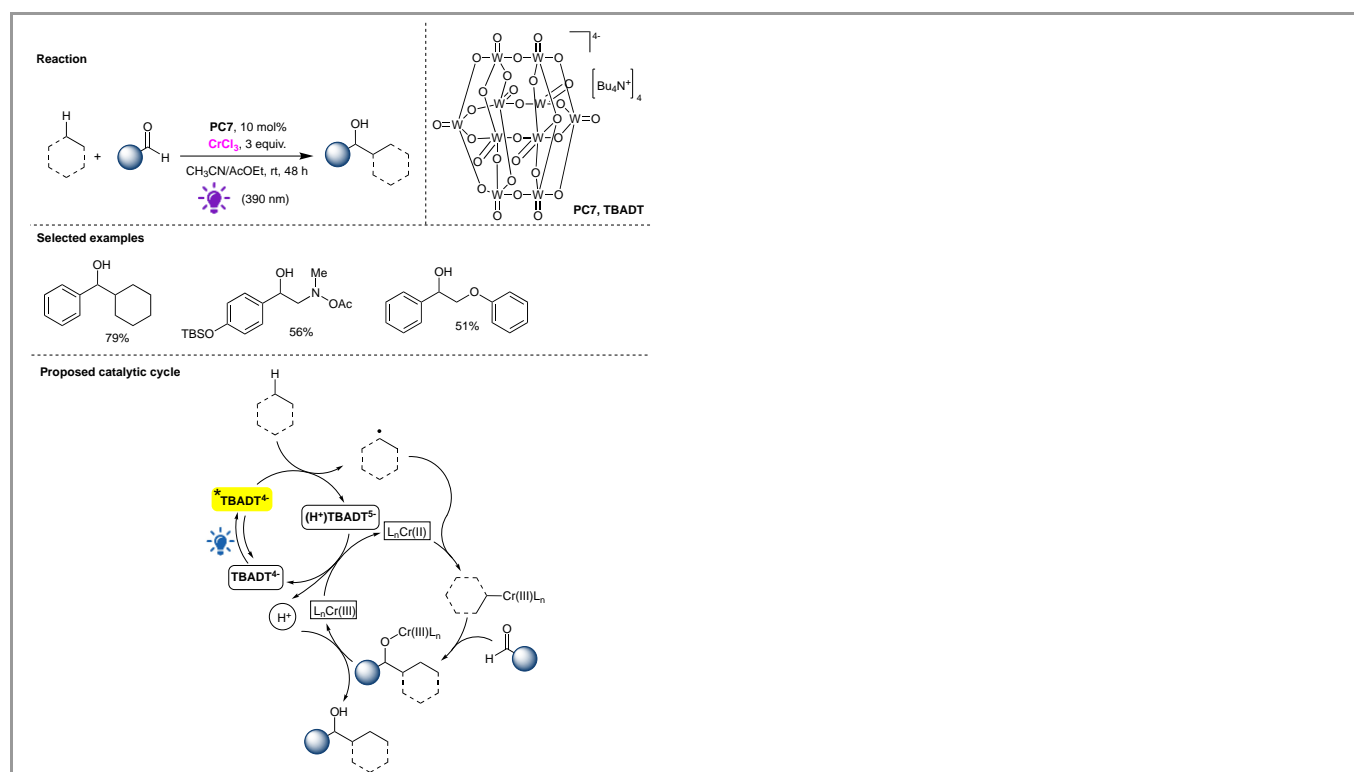
An interesting solution for alkylation of aldehydes using chromium in photoredox conditions was reported by Kanai.⁸³ With the idea to generate the alkyl radical, photolysis of alkylzirconium derivatives,⁸⁴ obtained *in situ* from a wide range of alkenes and Schwartz's reagent, was investigated (Scheme 11).



Scheme 11 Chromium(II) promoted alkylation of aldehyde by photolysis of alkylzirconium derivatives.

Although photochemical investigation to clarify the mechanism of the reaction was not carried out, previous works suggested that zirconium alkyl derivatives are photoactive⁸⁴ and adsorb in the range of light used for the reaction. The reaction proceeded with high functional group tolerance at ambient temperature under visible-light irradiation. In the supposed mechanism was reported the formation of Zr(III), a strong reductant [$E_{1/2}(\text{Cp}_2\text{Zr(IV)}/\text{Cp}_2\text{Zr(III)}) = -1.85 \text{ V vs SCE}$]⁸⁵ able to restore the chromium catalyst in its active state. The alkyl radical generated by homolysis of the C–Zr bond, was intercepted by Cr(II) complex to afford alkylchromium(III), able to alkylate the aldehyde. Since Cp_2ZrCl_2 was used as scavenger in chromium mediated reactions to replace Me_3SiCl , is reasonable to assume that the formation of a stable Zr alkoxide liberates the chromium for a successive reduction.

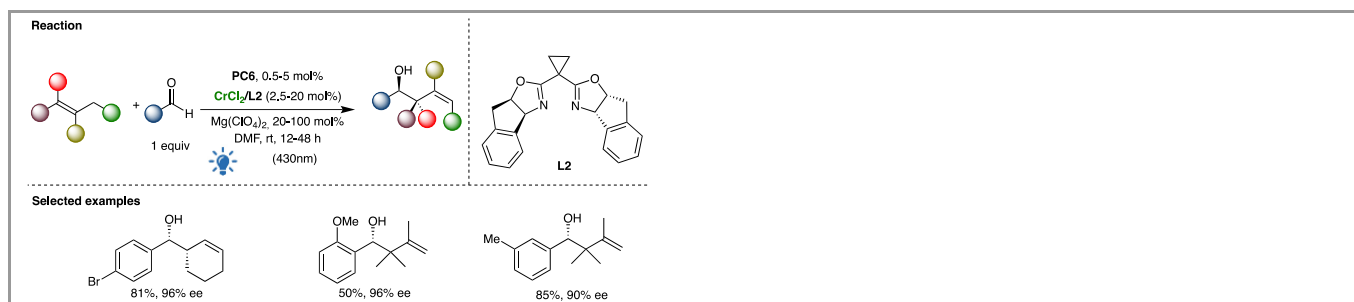
Alkylchromium(III) species were obtained by Yahata and coworkers by a direct $\text{C}(\text{sp}^3)\text{--H}$ activation using unfunctionalized starting material. The key concept used in this work was the employment of a hydrogen atom transfer (HAT) catalyst⁸⁶ in presence of stoichiometric amount of chromium salt (Scheme 12).⁸⁷ The HAT photocatalyst used for the reaction was the tetrabutylammonium decatungstate ($(\text{nBu}_4\text{N})_4[\text{W}_{10}\text{O}_{32}]$) (TBADT, **PC7**), that was capable of generate radicals from alkanes through a HAT event.⁸⁸ The proposed mechanism for the generation of alkyl radical considered the abstraction of hydrogen from alkanes by the photo-excited TBADT raised by absorption of 390 nm LED light. The reduced form of TBADT had a sufficient potential [$E_{1/2}([\text{W}_{10}\text{O}_{32}]^{4-}/[\text{W}_{10}\text{O}_{32}]^{5-}) = -0.97 \text{ V s SCE}$] for reducing Cr(III) to Cr(II). The Cr(II) intercepted the alkyl radical forming the desired alkylchromium(III) species that reacted with aldehydes.



Scheme 12 HAT photoredox alkylation of aldehydes.

3.6. Enantioselective chromium mediated photoredox reactions

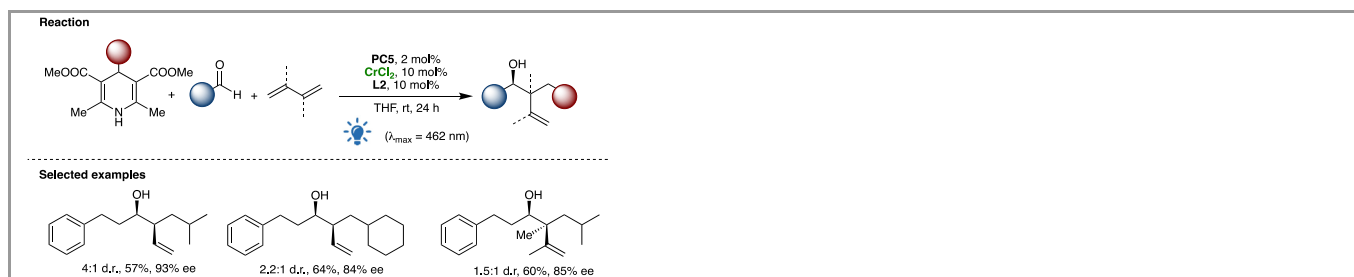
Glorius introduced a breakthrough in the use of chromium mediated nucleophilic photoredox reaction achieving products in stereoselective fashion, even if enantiomeric excess (ee) for the single example reported was only 20%.²³ In 2019, Kanai reported the use of a chiral chromium complex to reach an impressive ee (close to 99%) for several substrates (Scheme 13).



Scheme 13 Enantioselective chromium mediated photoredox allylation of aldehydes with alkenes.

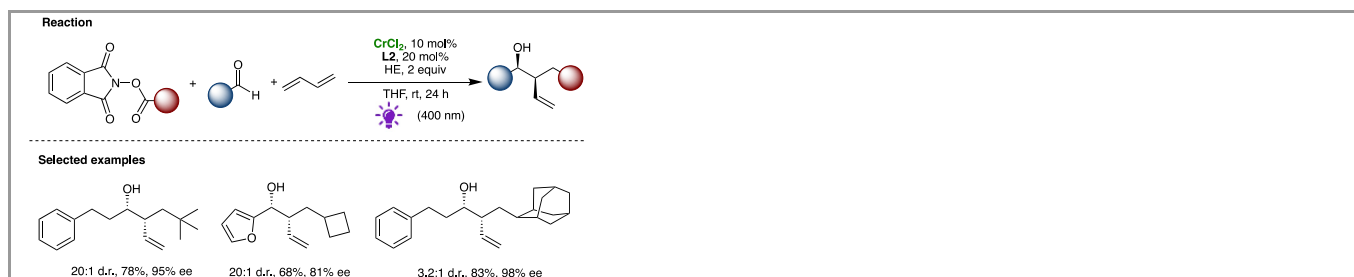
Moreover, he also extended the possibility to use unfunctionalized alkenes by using a stronger oxidant.⁸⁹ Kanai employed the acridinium photocatalyst **PC6** (***PC6**⁺/**PC6**[•] = +2.0 vs SCE) to oxidize alkenes via electron-transfer, giving access, after deprotonation to the allylic radical and subsequent interception by a chiral Cr(II) catalyst, to an alkyl Cr(III) intermediate. Among all the chiral catalyst tested, BOX ligand **L2** was the most adapted for the reaction. On the other hand, many other chiral catalysts that were found useful in classical NHK reactions were completely ineffective in photoredox conditions. This is an interesting remark, since photoredox conditions, although like established reactions, requires their own optimization and studies. In order to use simple alkenes, Lewis acid additives like Mg(ClO₄)₂ were found to increase the concentration of the radical cation specie and increased the enantiomeric excess. The reaction was explored with cyclic (cyclohexene, cyclopentene) and linear alkenes, with different aliphatic and aromatic aldehydes, reaching ee from 85% to 99%. Additionally, sophisticated transient spectroscopical studies were able to detect the electron transfer from the excited state of **PC6** to the alkene.

Using CrCl₂ in presence of the same chiral ligand **L2** and following the same approach reported in Scheme 5, Glorius⁵⁸ gave few examples of enantioselective reactions with aliphatic aldehydes (Scheme 14).



Scheme 14 Enantioselective dual alkylation of diene by chromium and photoredox catalysis.

By a similar strategy, but using RAE as source of radicals, in the supporting information of the work published by Shi,⁶⁰ three examples of enantioselective allylation of aldehydes were reported (Scheme 15). It is worth mentioning that also one challenging example, due to competitive pinacol coupling of aromatic aldehydes induced by the photocatalyst, was reported.



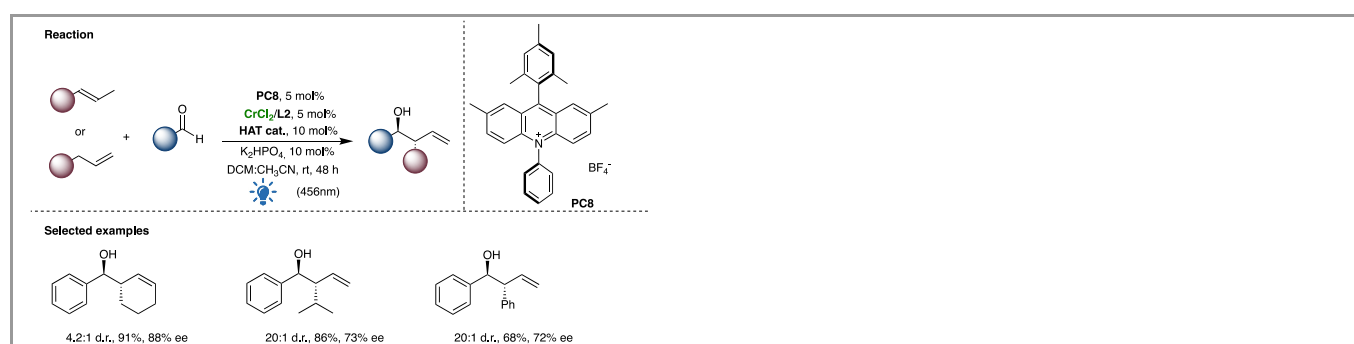
Scheme 15 Enantioselective photoredox chromium dual alkylation of butadiene.

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An interesting improvement of enantioselective allylation methodology was described by Kanai.⁹⁰ The major concern in the described methods was the accessibility of the allylic radical. For example, it was not possible to access the simple alkyl-monosubstituted allyl group by oxidation, due to its high oxidation potential. To produce allyl radical able to be intercepted by radical to polar cross over with chromium, Kanai used a HAT approach (Scheme 16). He designed a thiol thiophosphoric RSH (**HAT cat.**) imide for its ability to activate C–H bond.⁹¹ Starting from a thiolate RS^- , through the oxidation by **PC8** photocatalyst, a RS^\bullet was formed. This RS^\bullet radical can abstract a hydrogen atom from the allylic C–H bond of alkene substrates. The reaction was applied to different simple alkenes, such as 1- and 2-butenes, linear alkenes (1-pentene) and branched alkenes (3-methyl-1-butene) affording the RPCO with a chiral Cr(II) complex by the use of BOX ligand **L2** reported by Kanai in his previous reaction. This enantioselective methodology was also applied to the formation of linear products adding, as discussed in allylation section, $Ni(BF_4)_2$ as a Lewis acid.⁵³

It is worth to mention that this methodology was really an advance in making chromium photoredox reactions suitable to be applied to natural product bearing polyketide structure. However, even in this case the simple allyl moiety was absent.



Scheme 16 Chromium(II) mediated allylation of aldehyde with simple alkenes through a HAT mechanism.

The issue was recently solved by Glorius.⁹² Starting from oxidable allylsilanes,⁹³ it was possible to perform enantioselective photoredox chromium-mediated allylation reactions, in presence of **PC6** as photoredox catalyst and the BOX ligand **L2** previously employed by Kanai (Scheme 17). The reaction gave the possibility to use functionalized allylsilanes, even bearing boron derivatives. In addition, high enantiomeric excesses were generally obtained with aromatic, heterocyclic, and aliphatic aldehydes. Finally, the unsubstituted allylsilane was useful starting material for this chemistry.



Scheme 17 Enantioselective photoredox chromium-mediated allylation of aldehydes with allyl silanes.

The photocatalyzed SET oxidation of the allylsilane, followed by the loss of Me_3Si^+ , produced an allyl radical, differently from the previous example discussed where a deprotonation of the radical cation intermediate was necessary to generate the allyl radical. This highly electrophilic and exophilic specie was involved in coordination of chromium catalyst, as founded by DFT analysis of the reaction, lowering the activation barrier for the formation of a Zimmerman-Traxler transition state. Additionally, Cr(III) was released after the C–C bond formation by the assistance of TMS^+ . As expected, Stern–Volmer quenching studies confirmed that allyl silane was the quencher

of the photocatalyst. Interestingly, the quantum yield measured for the reaction gave a value (6.8 in the presence of chiral ligand) that was indicative of a radical chain mechanism. Since the oxidation potential of Cr(III) was not sufficient to oxidize the silane, the authors supposed the direct generation of the allylchromium(III) species by metathesis of the product with the starting allylsilanes.

4. Titanium photoredox organometallic nucleophilic reagents

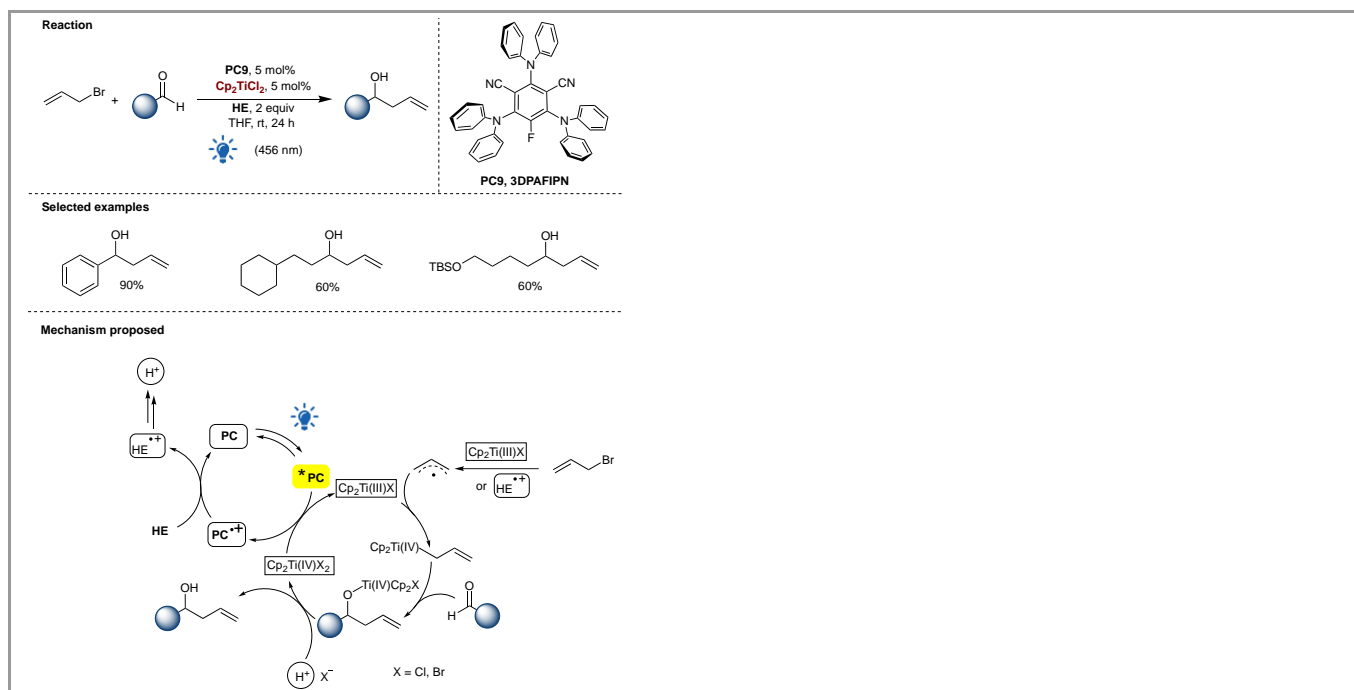
The reductive radical-polar crossover (RPCO) concept can be suitable for titanium.⁹⁴ In fact, the use of $\text{Cp}_2\text{Ti(III)Cl}$, the Nugent–Rajanbabu reagent, in radical mediated reactions was well investigated,⁹⁵ and it is particularly interesting, since titanium is a low toxic and abundant metal.

In the catalytic use of Ti(III),⁹⁶ Fürstner and Gansäuer methodologies were largely employed.⁹⁷ In these methodologies, $\text{Cp}_2\text{Ti(III)Cl}$ was prepared in situ by a metal reductant (Mn) and restored using a scavenger able to liberate the titanium complex from the Ti-O bond. Following these strategies, it was possible to move from a stoichiometric to a catalytic use of Ti(III) complexes.

Gansäuer recently reported the possibility to use Cp_2TiCl_2 in catalytic amount under photoredox conditions, promoting the ring opening of epoxides and trapping the resulting radical with different acceptors.⁹⁸ The conditions developed by Gansäuer used Ir(III) photocatalyst but Shi and co-workers were able, with the employment of 4CzIPN, to extend the results to the opening/spirocyclization of epoxyalkenes.⁹⁹ These preliminary studies open the possibility to employ titanium in photoredox catalysis with the aim to prepare nucleophilic organometallic species.

4.1. Allylation reaction with titanium reagents

A titanium mediated catalytic Barbier-type allylation reaction, settled in the general conditions reported by Fürstner (Mn as stoichiometric reductant, and TMSCl as scavenger) illustrated the possibilities offered by catalytic Ti(III) reactions in the formation of C–C bonds. As for the chromium catalytic reactions, also for titanium the use of stoichiometric metal reductant was essential for recycling the titanium complex. Cozzi and Gualandi were the first to report the possibility to use the concept of photoredox RPCO in the formation of allyl titanium reagents, starting from the low toxic and available Cp_2TiCl_2 .¹⁰⁰ The reaction employed the organic dyes 3DPAFIPN⁵⁹ **PC9** (Scheme 18), another TADF dyes that could be effectively used in photoredox reactions promoted by metals.¹⁰¹ The reaction was possible using Hantzsch's ester as stoichiometric sacrificial reductant.



Scheme 18 Photoredox titanium-mediated allylation of aldehydes.

Respect to the chromium, a decisive role in these reactions was played by the titanium complex concentration. For positive results, the reaction is carried out 0.005 M concentration of titanium complex. The Cp_2TiCl_2 is a red complex, able to absorb visible light and, quite interestingly, it is able to behave as active photoredox catalyst.¹⁰² The strong overlap in the absorbance of the photocatalyst and the titanium complex ($\epsilon_{455\text{nm}} \approx 250 \text{ M}^{-1} \text{ cm}^{-1}$) is deleterious for the reaction, since the titanium complex is used in higher concentration to respect the photocatalyst and it is hampering the dye adsorption. Although Gansäuer showed the effectiveness of tertiary amines in the presence of Ir(III)¹⁰² photocatalysts or by Cp_2TiCl_2 itself to be good quenchers of the excited state, only **HE** ester was effective to promote allylation reactions. The scope of the reaction was broad, with tolerance to various functional groups such as halides, trifluoromethyl, esters, nitriles, and ethers, and with the possibility to use aromatic and aliphatic aldehydes. A peculiar sensitivity for aldehydes containing acid-sensitive indole or pyrrole was revealed, due to the protons derived from the oxidation of the Hantzsch ester. Both **HE** and Cp_2TiCl_2 can quench the emission intensity of the photocatalyst, with the Cp_2TiCl_2 the most efficient quencher. The catalytic cycle, depicted in Scheme 18, illustrates the probable reaction mechanism. Cp_2TiCl_2 is reduced, by the excited state of 3DPAFIPN, to $\text{Cp}_2\text{Ti(III)Cl}$. The formed 3DPAFIPN^{•+} is a strong oxidant [$E(3\text{DPAFIPN}^{\bullet+}/3\text{DPAFIPN}) = +1.30$ vs SCE]⁵⁹ and is reduced by the Hantzsch ester [$E(\text{HE}^{\bullet+}/\text{HE}) = +1.0$ vs SCE]. The reaction produces $\text{HE}^{\bullet+}$ that is a strong reductant and can be active in further electron transfer events. The reaction probably proceeds through the radical coupling between allyl radical, formed by reduction of the allyl bromide in presence of $\text{Cp}_2\text{Ti(III)Cl}$ and second molecule of titanium in low oxidation state. The protonated rearomatized Hantzsch ester is a strong Brønsted acid, and it is capable to restore the catalytic cycle by protonation of the titanium-oxygen bond.

Although Oltra, Cuerva, and Gansäuer have found that the catalytic titanium(III) mediated allylation reactions was suitable also for ketones, the photoredox version of the reaction gave low yields with different ketones tested. However, by using slightly different conditions and photocatalyst, Shi found that the reaction with ketones was effectively promoted (Scheme 19).¹⁰³



Scheme 19 Photoredox titanium-mediated allylation of ketones.

The quenching studies identified the Cp₂TiCl₂ titanium complex as the quencher of the excited state of 4CzIPN also in these reactions, with the same mechanism suggested for allylation of aldehydes.

4.2. Propargylation reaction with titanium reagents

In the paper reported by Shi, where 4CzIPN was used as photocatalyst, an isolate example of propargylation reaction was included, but the scope of the reaction was not examined. A full study of propargylation of aldehydes in presence of Cp₂TiCl₂ was recently published.¹⁰⁴ While in the case of chromium methodology,⁷⁰ the formation of propargylic radical was induced by the employment of 1,3-enynes as radical precursor; with the employment of titanium catalysis, the direct use of propargylic halides is possible. The reaction worked employing the general conditions applied for allylation, with 3DPAFIPN as photocatalyst and **HE** as stoichiometric reducing agent (Scheme 20).

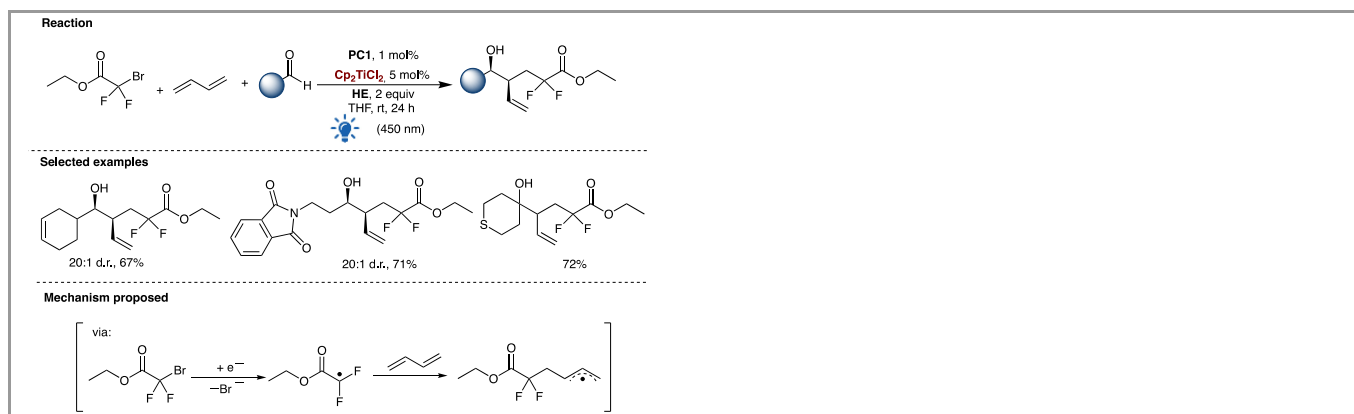


Scheme 20 Photoredox mediated propargylation of aldehydes promoted by Cp₂TiCl₂.

Moreover, propargylation scope was broad applying the general conditions to variously substituted aromatic and aliphatic aldehydes. Quenching studies supported the previously discussed mechanism.

4.3. Allylation reaction via dienes

Extending the strategy reported by Glorius in the preparation of allyl radical from dienes,¹⁰⁵ Shi used Cp₂TiCl₂ to intercept the allyl radicals, forming functionalized allylating reagents in convenient conditions (Scheme 21).¹⁰⁶

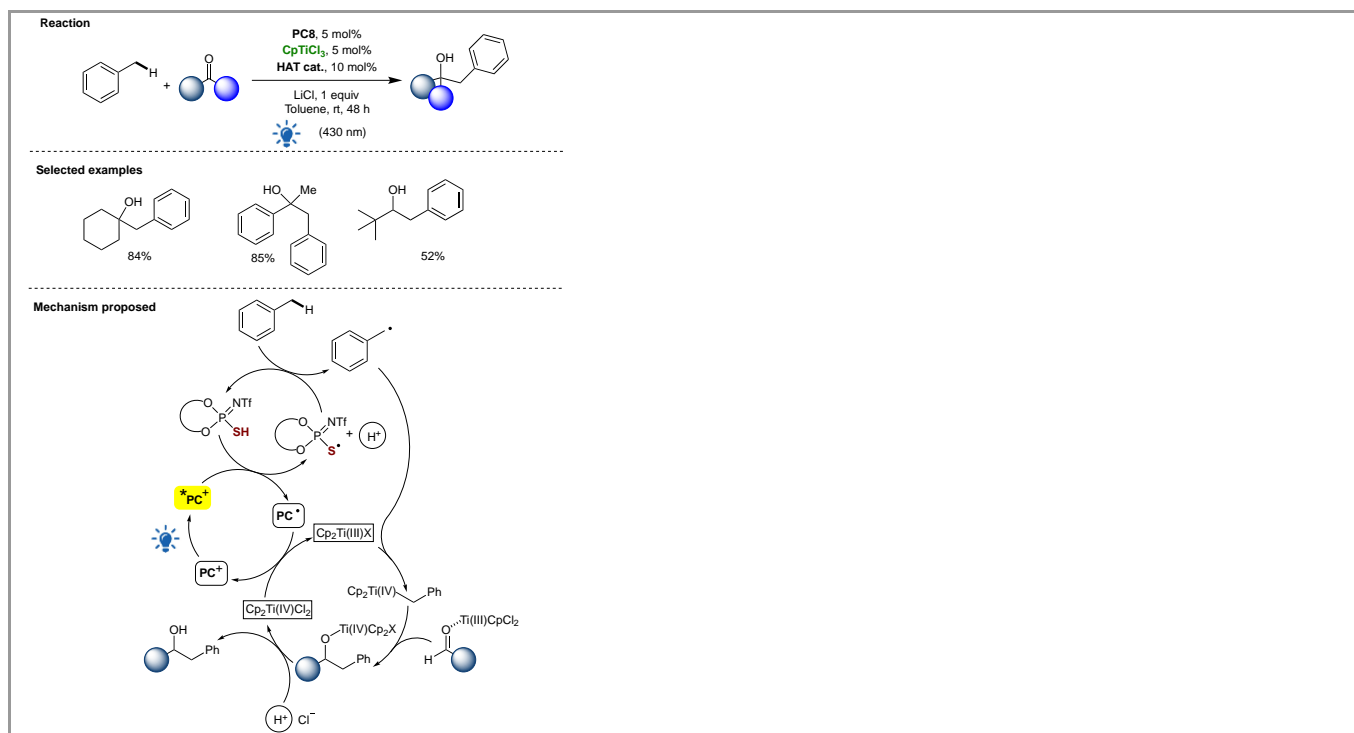


Scheme 21 Dual photoredox alkylation of dienes mediated by titanium.

The reaction was promoted using Cp_2TiCl_2 , iridium complex **PC1** as the photocatalyst and Hantzsch's ester as stoichiometric reductant. It was also possible, although in diminishing yields, to employ 4CzIPN as photocatalyst. Differently from the work reported by Glorius with chromium, the source of the first radical was a halide with an appropriate reduction potential to generate a persistent radical in the reaction conditions (i.e., ethyl bromodifluoroacetate). Aliphatic and aromatic aldehydes were reactive partners and, importantly, also aliphatic, and aromatic ketones. The reaction was also performed with various heteroarenes, such as furan, thiophene, benzothiophene, and benzofuran. As previously discussed, pyrrole and indole carbonyls form products that are susceptible to acidic conditions and, therefore, not suitable substrates when **HE** is used as sacrificial reductant. The reaction is also tolerant to different functional groups as phenols, ethers, and alkenes. Aromatic reducible groups containing iodine are also tolerated. Mechanistic investigations suggest the formation of a radical to polar cross over between the allylic radical and titanium. The bromodifluoro acetate is reduced by the Ir(III) photocatalyst to give a transient radical that reacts with the diene to form the allylic radical intercepted by the $\text{Cp}_2\text{Ti(III)Cl}$.

4.4. Alkylation reaction with titanium reagents: benzylation

The possibility to use benzylic halides in photoredox addition of alkyl titanium reagents to aldehydes was mentioned by Gualandi and Cozzi¹⁰⁰ and reported by Shi in just one example.¹⁰³ However, only Kanai reported in a full account the benzylation of ketones in photoredox conditions (Scheme 22).¹⁰⁷

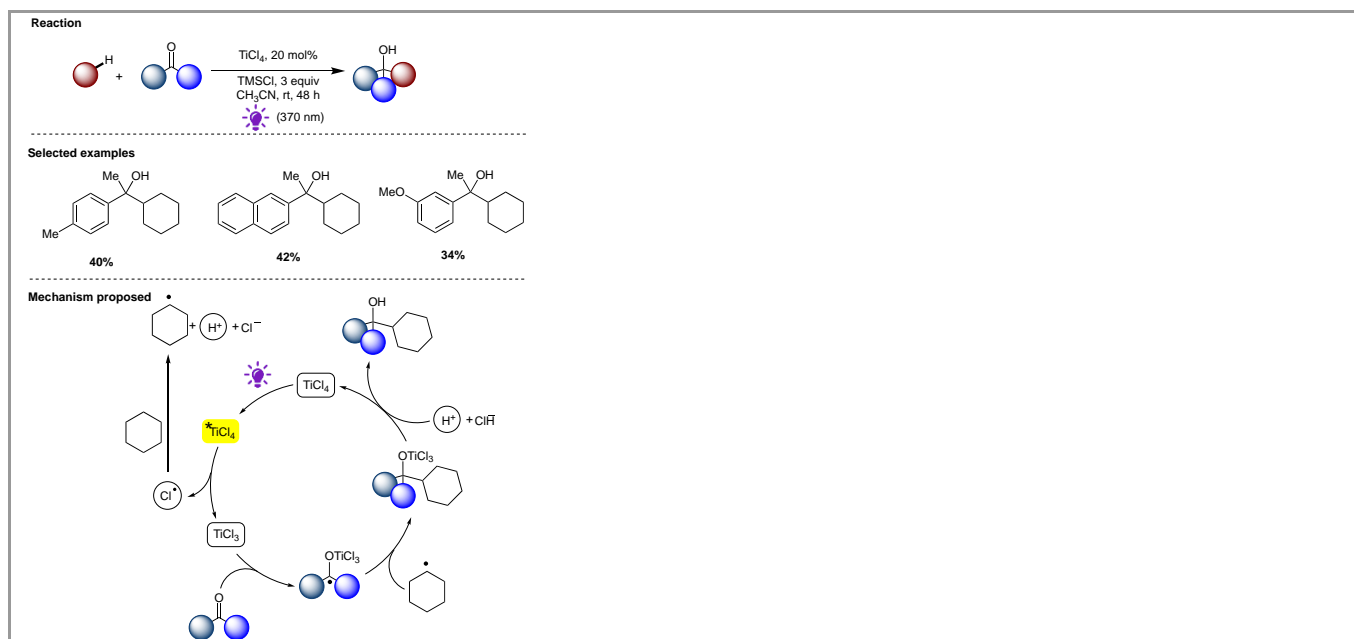


Scheme 22 Benzylation of ketones under HAT photoredox conditions.

To generate benzylic radicals the thiophosphoric imide (**HAT cat.**) was employed (20 mol%) in presence of the acridinium catalyst **PC8**. For this reaction, CpTiCl_3 was found to be the best catalyst and the reaction was performed in the presence of LiCl as additive, in a toluene/dichloromethane mixture as solvent. The LiCl was assumed to regenerate the CpTiCl_3 from the formed titanium alkoxide. Different aldehydes, and aromatic and aliphatic ketones were found reactive under the optimized conditions affording the desired products in good to moderate yields. The reaction was tolerant to various functional groups including esters, amides, halides, and was also applied to drugs molecules such as pentoxifylline, an anti-inflammatory drug, zaltoprofen, and iodometacin. Regarding the mechanism, the authors excluded the formation of benzylic anion¹⁵ since the reduction potential of the photocatalyst [$E_{1/2}(\text{PC8}^{\bullet}/\text{PC8}^+) = -0.58 \text{ V vs SCE}$] is unable to reduce a benzylic radical [$E_{1/2}(\text{PhCH}_2^{\bullet}/\text{PhCH}_2^-) = -1.45 \text{ V vs SCE}$].¹⁰⁸ The formation of Ti(IV) complexes with the thioamides was also excluded since isolated complexes were much less active under the optimized conditions. Stern-Volmer studies confirmed that thioamide was the effective quencher, and the mechanism follows the same pathway that was described for the chromium enantioselective allylation reaction. The generated thioamide radical (S^{\bullet}) can abstract a H^{\bullet} from solvent (toluene) forming the benzyl radical. The reduced photocatalyst **PC8**[•] [$E_{1/2}(\text{PC8}^{\bullet}/\text{PC8}^+) = -0.58 \text{ V vs SCE}$] is able to reduce the titanium complex CpTiCl_3 [$E_{\text{red}}(\text{Ti(IV)/Ti(III)}) = -0.35 \text{ V vs SCE}$] forming the Ti(III) species. The authors suggested that benzyl radical reacts with the ketyl radical formed by interaction of Ti(III) with ketone. Finally, the protonolysis is possible by the proton released by the HAT catalyst.

4.5. Alkylation reaction via titanium

Although titanium mediated alkylation of carbonyl compound would represent a very important reaction, alkyl titanocene derivatives are not sufficient nucleophilic. Interestingly, an isolate example of such reactivity, in photoredox conditions, was reported by Kanai using the cheap and available TiCl_4 (Scheme 23).¹⁰⁹



Scheme 23 Photocatalytic titanium mediated alkylation of ketones.

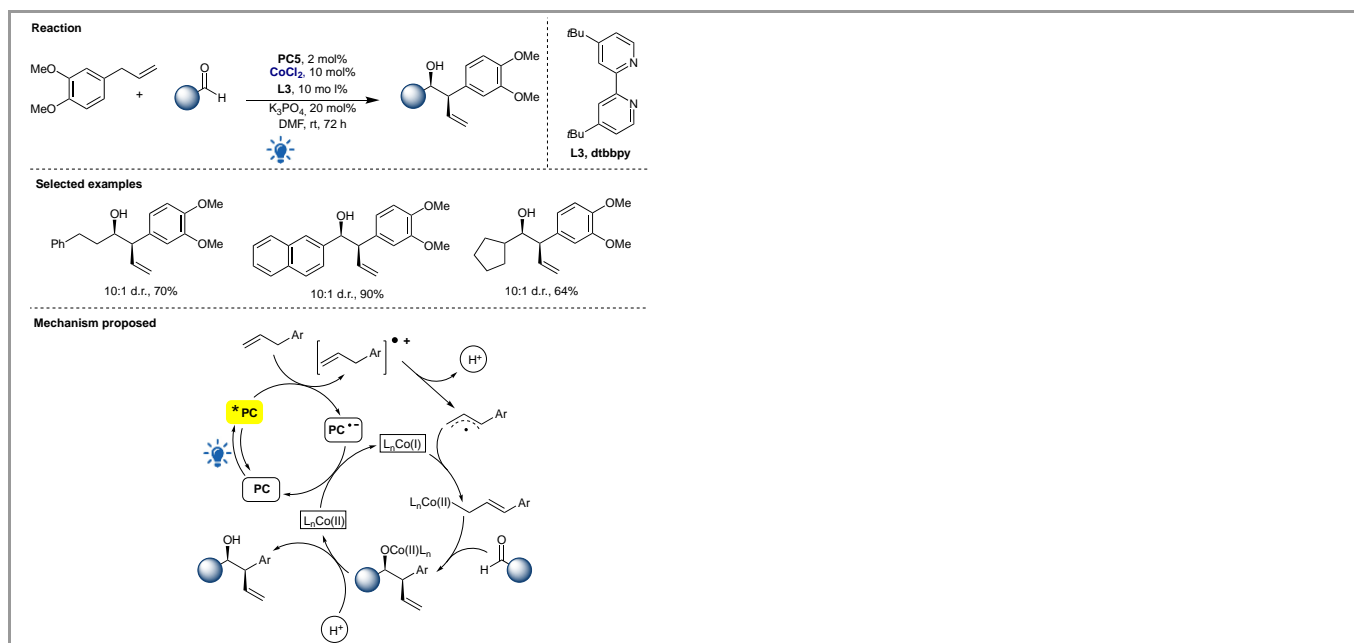
Operating with a light of 365 nm, TiCl_4 was photolyzed to Ti(III)Cl_3 with the formation of the corresponding Cl^\bullet , able to abstract H^\bullet from alkanes. Then, TiCl_3 was involved in the formation of ketyl radical intermediate, allowing to the C–C bond construction via radical coupling. To close the catalytic cycle and improve yields, TMSCl as additive was used. Although quite interesting, the scope was limited to simple aromatic ketones with cyclohexane or cycloheptane as radical sources.

5. Cobalt mediated reactions

Cobalt is an Earth-abundant, low toxic, and inexpensive metal,¹¹⁰ with useful oxidation state.¹¹¹ Cobalt is a key metal in many industrial processes, like Fischer-Tropsch,¹¹² and in many modern cross-coupling applications based on C–H activation and hydrogenation reactions.¹¹³ Photoredox allylation reactions based on cobalt were successfully described, independently, by Cozzi, Kleij, and Shi¹¹⁴ groups. However, in all these methodologies the allylating species were obtained by oxidative addition of a suitable precursor to $\text{L}_n\text{Co(I)}$ complexes (L = bidentate nitrogen-based ligands). Then, the resulting Co(III) allyl complexes underwent to electron transfer processes, mediated by reducing species present in solution, to give the nucleophilic reactive $\text{L}_n\text{Co(II)Allyl}$ complexes.¹¹⁵ These processes are not based on a radical to polar cross over.

5.1. Cobalt allylation reaction

However, very recently, Shi reported that the formation of a reactive allyl cobalt by photoredox catalysis under the framework of radical to polar cross over is possible (Scheme 24).^{116,117}



Scheme 24 Dual cobalt photoredox allylation of aldehyde with electron rich allyl alkene.

They have investigated the possibility to use the redox neutral system employed by Glorius and Kanai, based on the formation of the allyl radical by oxidation of C=C and deprotonation. Since the reduction potential of the cobalt complexes are lower compared to chromium, this limits the selection of the suitable photoredox complexes for the reaction. The photocatalyst needs to be an oxidant in its excited state, capable to oxidize an electron rich allyl alkene, while in its reduced state needs to be a strong reductant the generation of cobalt in low oxidation state. The reaction was successfully performed using 1,2-dimethoxy-4-allylarenes or *N*-allyl-diarylamine in the presence of CoCl₂, 4,4'-di-*tert*-butylbipyridine (**L3**, dtbbpy) as effective ligand for cobalt, and 4CzIPN as photocatalyst in the presence of K₃PO₄ in DMF, under irradiation with a blue LED. The reaction was applied to primary and secondary aliphatic aldehydes, and on aromatic aldehydes bearing various substituents. In all cases, the *anti* diastereoisomer was the favored one, with diastereoisomeric ratios from moderate (3:1) to quite good (13:1). Stern-Volmer analysis shown that the cobalt catalyst and the allyl substrates are effective quenchers for the excited state of the photocatalyst, but the quenching of the allyl substrates, due to the higher concentration, was more efficient. The 4CzIPN in its excited state is a good oxidant [$E_{1/2}(*4CzIPN/4CzIPN^{\cdot-}) = 1.35$ V vs SCE] and can form the corresponding radical cation of the allylic compounds, that are rapidly deprotonated by the base present in solution to form the corresponding allylic radical. The allylic radical is then intercepted by the L_nCo(I), formed by the reduction of the corresponding L_nCo^{II} complex mediated by the 4CzIPN^{•-} [$E_{1/2}(4CzIPN/4CzIPN^{\cdot-}) = -1.21$ V vs SCE]. The allylic Co(II) complex is the reactive nucleophilic species and reacts with the aldehydes by a Zimmerman-Traxler transition state affording the observed products.

6. Conclusion

The preparation and practical use of organometallic reagents generated in photoredox conditions, together with the use friendly conditions, such as the absence of metal reductant, will allow to reduce waste. The expansion of the number of the transformation, particularly in the case of titanium, could be predictable.¹¹⁸ In addition, enantioselective titanium mediated photoredox transformations are quite challenging¹¹⁹ and efforts to develop enantioselective addition to carbonyls will be certainly focus of future research. Finally, in all the described methods based on chromium, titanium, and cobalt, the use of electrophiles was limited to carbonyls, while imines and epoxides reactions were not explored. The employment of these electrophiles requires to adjust conditions and photocatalysts. Moreover, to move these methodologies towards the large scale or industrial applications, deep attention in the use of more penetrating lights (green or red lights) needs to be considered, readjusting reaction conditions to new catalysts. Certainly, the exploration to include challenging metals for producing

organometallic reagents in photoredox will continue, expanding the knowledge and the applicability of photoredox catalysis area.

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Conflict of Interest

The authors declare no conflict of interest.

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