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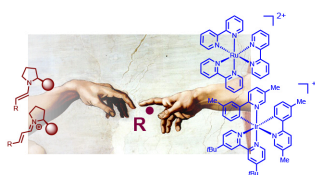
# Stereoselective synergistic organo photoredox catalysis with enamines and iminiums

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## Abstract:

Application of small chiral organic molecules in catalysis has been dominated by formation of chiral enamines or iminium ions. Nucleophiles – electrophiles reactivity has been exploited in many papers. Now, the possibility to combine organocatalysis with photochemistry open new "exciting" possibilities and opportunities, in reactions that are mediated by radicals.




**Keywords:** photoredox catalysis, organocatalysis, stereoselective reactions, enamine catalysis, iminium catalysis  
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## 1 Introduction

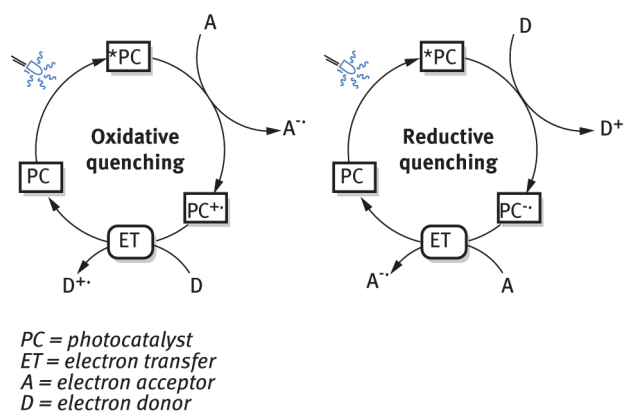
Photoredox catalysis has grown in recent years as an important field in organic chemistry [1]. New photocatalysts (PCs) [2], reactions [3], devices [4] and technical solutions for large scale synthesis [5], have developed rapidly giving rise to new directions and improvements. However, one peculiar aspect of photoredox catalysis is the possibility to merge the photoredox process with other activation mode [6]. The application of synergistic photoredox catalysis, where one or more catalytic cycles work cooperatively with the photoredox cycle enables new interesting transformations. These multiple catalytic systems provide effective control of selectivity, and more importantly, of stereoselectivity. In fact, though enantioselective photoredox catalysis can also be controlled by chiral photoredox metal complexes [7], the employment of a synergistic activation mode can give excellent solutions to this challenge. The possibility to merge different activation modes with photoredox catalysis relies on the quite peculiar way in which the PCs are activated, using visible light irradiation, normally functional groups present in organic molecules do not absorb photons in this wavelength region (380–700 nm). In addition, Lewis acids, Lewis bases and many solvents do not dramatically influence the absorption of light by the PCs. In many cases, when organometallic photoredox catalysts are employed, they are coordinatively saturated and stable avoiding any ligand exchange with reaction partners. Finally, organic molecules used as PCs are quite robust to many reaction conditions [8]. In this chapter, we will discuss the application of photoredox catalysis when merged with stereoselective organocatalysis. Two distinct and particular methodologies will be discussed. The common methodologies, using a synergistic combination, are based on well-established and previously discussed enamine or iminium catalysis combined with the generation of radicals through photocatalytic cycles [9]. Another quite interesting and intriguing possibility of organocatalytic photoredox catalysis is based on the absorption of the intermediates (again iminium or enamines), generated by the reaction of an organocatalyst with the substrate. These intermediates are able to trigger photoredox events that takes place in a stereocontrolled manner. These two distinct methodologies will be discussed, with the prevalent catalysts used and the chemistry developed in recent years. A short introduction regarding properties and behavior of excited states precedes the discussion, for readers unfamiliar with these concepts. It is important to stress that an interdisciplinary combination of expertise is required to provide a clear view of this field of chemistry.

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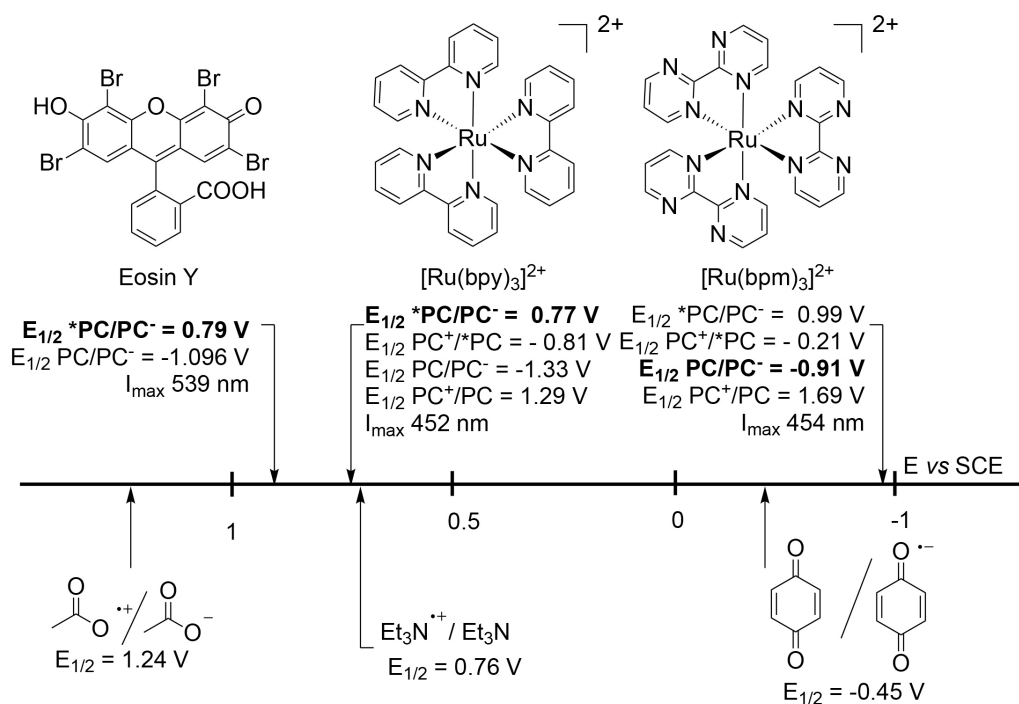
## 2 Photophysical and photochemical properties of organic photoredox catalysis: a guide for dummies

Photochemistry and photophysics of organic molecules are well-established fields, with dedicated journals, books and more than 100 years of investigations. Many applications of photoredox catalysis in organic chemistry have been reported, also in total synthesis. However, the field was addressed mainly to specialists, and common organic laboratories seldomly employed these interesting methods, hampered by technical problems. The renaissance of these studies in synthetic organic chemistry started in 2008, when MacMillan [10] and Yoon [11] reported the possibility to use a well-known coordination compound,  $[\text{Ru}(\text{bpy})_3]^{2+}$  (bpy = bipyridine) in promoting interesting transformations. In the same period, Stephenson [12] was also reporting the use of  $[\text{Ru}(\text{bpy})_3]^{2+}$  in another kind of reaction. Researchers soon realized the key role played by  $[\text{Ru}(\text{bpy})_3]^{2+}$  as a PC. Since then many other metal complexes, dyes, quantum dots, semiconductors were exploited taking advantage of their properties [13]. The ability of a PC to absorb light and reach a relatively stable excited state (\*PC) is required to engage in different processes with present substrates: (a) by single electron transfer (SET), in which radicals are formed, or (b) energy transfer (ET), in which other excited states are generated by direct energy transfer from the PC to other molecules. Both these two modes create a starting event that requires a precise design in order to observe a successful reaction. Another important aspect is that the PC needs to absorb light, preferable visible light, at wavelengths where other species present in solution do not absorb light. Furthermore, the quantum yield of the PC should be as close to one as possible, where the quantum yield of luminescence is defined as the ratio of the number of photons emitted to the number of photons absorbed. In addition, the excited state, once efficiently reached, needs to exist long enough time to permit the exchange of electrons or energy with other species present. It is important to realize immediately, that the PC in excited state can donate (behaving as a reductant) or receive (behaving as an oxidant) one electron easily compared to the PC in the ground state (Figure 1).



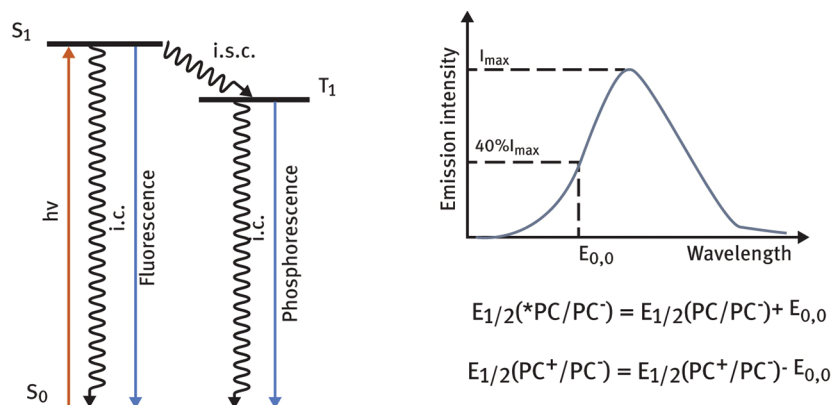
**Figure 1:** Quenching of excited states of a photocatalyst.

Therefore, the excited state of the PC is a stronger oxidant or reductant compared to the ground state of the PCs. This realization has led to a breakthrough in synergistic photoredox catalysis. The obtainment of reactive species is possible by the active role played by PC and by its extra energy gained after the absorption of light. After the electron transfer process, the PC is reduced or oxidized, and the ability to undergo successive electron transfer, can be evaluated by the ground state potential of the new species produced. Oxidation and reduction potentials of many PC are well known [14] or can be determined by cyclic voltammetry. In organometallic complexes, such as  $[\text{Ru}(\text{bpy})_3]^{2+}$ , oxidations and reductions are producing stable species, while other PC might produce quite unstable species. In other words, oxidation or reduction can be irreversible. Nevertheless, also molecules, for which the ground state potential is irreversible, can successfully engage in photoredox reactions. As the redox potentials of the excited state and ground state are known, it would be possible to establish if the reaction with the species present in solution is exothermic or weakly endothermic. Since redox potentials of organic species are known and were recently re-evaluated [15], it is also possible, using well-known concepts of electrochemistry, to quite firmly establish if the reaction is favored or not (Figure 2). It is also important to mention that redox potentials are always referred to a reference electrode, or redox couple (i. e. saturated calomel electrode [SCE] and ferrocenium/ferrocene). It is crucial to compare redox potentials using the same reference electrode, as it may sometimes happen that the potentials are compared using different references leading to wrong conclusions.



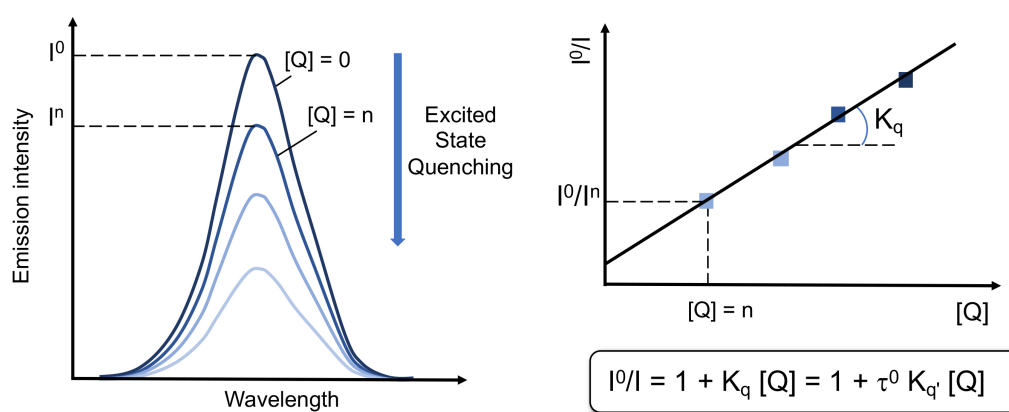
**Figure 2:** Electrochemical series of photocatalyst and organic compounds.

However, as many potentials used in these calculations are irreversible, care needs to be taken, and only experimental confirmation can ultimately give a direct assessment on the feasibility of a new reaction. In metal complexes a strong absorption maximum is observed near the 425 nm region. This region is known as the MLCT (metal to ligand charge transfer) region, in which electron transfer from a  $d$  orbital of the metal to a  $\pi^*$  of the ligand (bpy in the case of  $[\text{Ru}(\text{bpy})_3]^{2+}$ ) occurs. Excited states have their own terminology and energy, and we suggest reading more comprehensive and exhaustive texts for more detailed explanations [16]. In case of  $[\text{Ru}(\text{bpy})_3]^{2+}$ , following excitation, a new state called  $^3[\text{MLCT}]$  is quite rapidly reached. The symbol 3 indicates the coupling between the single electrons in the two semi-occupied states that formed after absorption of light. This state can relax back, through different pathways. Photophysicists describe these phenomena with rate constants  $k$ . The  $^3\text{MLCT}$  can return to the ground state by emitting light (radiative process) with rate constant indicated as  $k_r$ , or by emitting heat (not radiative process) with a rate constant indicated as  $k_{\text{nr}}$ . By definition,  $k_o$  observed ( $k_o$ ) is the sum of  $k_r + k_{\text{nr}}$ . The observed quantum yield ( $\phi_0$ ) of the excited state can also be expressed by a ratio between rate constants of the two emission processes and, in this case,  $\phi_0 = k_r / (k_r + k_{\text{nr}})$ . It is important to realize that the light emitted by the  $[\text{Ru}(\text{bpy})_3]^{2+}$  is observed at a different wavelength with respect to the MLCT state, due to dissipation of energy. The emission maximum of the  $^3\text{MLCT}$  is used to evaluate an important value, the  $E_{0,0}$  energy, which is the energy difference between the  $^3\text{MLCT}$  state and the ground state. This is the gained energy that the PC can exchange in electron transfer. As shown in in Figure 3, this energy value is measured in eV, and can be directly used for having, as first approximation, the values of the excited states potential [16].



**Figure 3:** Jablonski diagram for a generic photocatalyst and evaluation of electrochemical potentials of its excited states.

This formalism is known as the Rehm–Weller equation and it needs to be stressed that other energy terms, important in some cases, are neglected. Anyway, by direct experiments, or by tabulated values, ground state potential and  $E_{00}$  can be used to establish the series of the four redox potentials available for a PC in ground or excited states (Figure 2). At this point, another piece of information is missing. Which is the right potential that needs to be considered? Of course, many aspects as evaluation of organic species present in solutions with their redox potential and the excited or ground state potentials of the PC, need to be evaluated for understanding the kind of electron transfer process (reduction or oxidation) and the involved species. However, experimental data can give an indication if the excited states of the PC are involved. The simplest experiment that can be performed, called the Stern–Volmer quenching study [17], determines if a bimolecular reaction (electron or energy transfer) is occurring between the PC and an organic molecule present in the reaction mixture. The PC is excited with a laser light in the presence of one of the reaction partners in a measured concentration, and the emission of the PC is monitored at increased concentration of the reaction partners. If the emission of the PC is altered by the presence of the reaction partner, this partner is defined as quencher of the excited state. In other words, as electrons or energy are transferred between the quenchers and the PC in the excited state, the concentration of the excited state will be reduced, and, consequently, the intensity of the emitted light. Therefore, it is possible to monitor the phenomenon by plotting the measured intensity of the emitting light [18] in function of the quencher concentrations (Figure 4).



**Figure 4:** The Stern–Volmer experiment: determination of the effective quencher.

The Stern–Volmer experiment is also able to show which is the organic species in solution that is interfering with the excited state, providing the PC in its ground state by SET or energy transfer. At this point we have all the information necessary in order to understand the use of PC in stereoselective organic catalysis. It is important to mention that the PC needs to return in its original state, and therefore, if an electron transfer event (oxidation or reduction) is occurring, another complementary electron transfer through the species in the solution needs to restore the catalysts. Therefore, also this step needs to be exoergonic, or thermodynamically favored. This needs to be coupled with another possible event in which redox potentials are matched in the way that the thermodynamic of the process is favored. The Stern–Volmer experiment is also useful in evaluating energy transfer processes, which are only now starting to be considered in photocatalysis [18]. In the examples discussed in this chapter, only electron transfer events seem to be operative, and a further description of energy transfer will not be presented here.

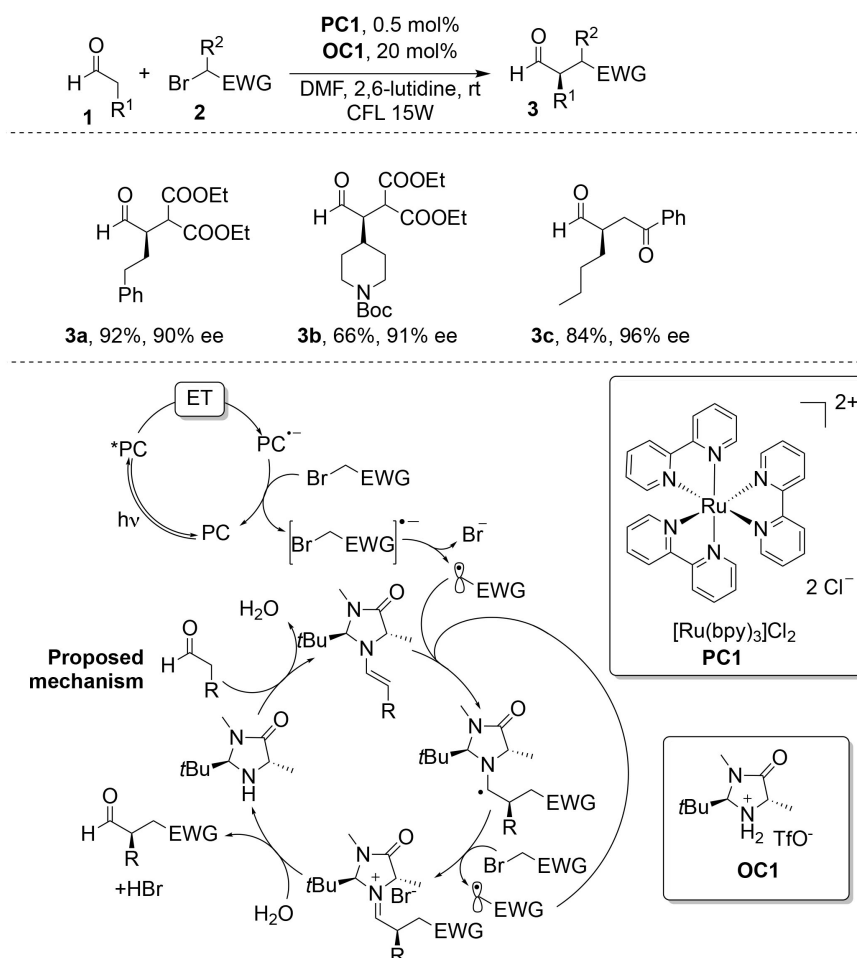
### 3 Stereoselective alkylation of enamines through dual catalysis

As previously mentioned, the pioneering work published by MacMillan in 2008 reopened the field of photoredox catalysis. This work is based on merging enamine catalysis with photoredox catalysis. Enamine catalysis is recognized as a powerful activation mode [19] in organocatalysis [20]. Enamines of aldehydes and ketones are strong nucleophiles [21] activating the  $\alpha$ -position of the aldehydes and ketones towards reaction with compatible electrophiles. As nucleophilicity of enamines is quantified by the Mayr scale [22], it is possible to predict if the reaction with electrophiles is successful if the Mayr relation ( $\log k = S_N[N + E]$ , where  $k$  is the rate constant of the reaction,  $S_N$  is the nucleophile-specific sensitivity parameter,  $E$  and  $N$  are the electrophilicity and nucleophilicity parameters) is satisfied [23]. In particular, if  $E + N > -5$  it will be possible to observe the reaction to proceed in reasonable time (5–24 h). As enamine catalysis can be conducted in the presence of water, and water is produced by the formation of enamines, the presence of water needs to be considered when designing a

catalytic cycle. The ability of enamines to react through radicals, generated by oxidation, in so called SOMO (Single Occupied Molecular Orbitals) catalysis, proved a crucial observation to establish the photoredox cycle [24].

### 3.1 Ruthenium stereoselective alkylation of enamines

Radicals were found compatible with enamine catalysis, and in 2008 MacMillan reported a way to generate radicals and solve one decisive problem in enamine catalysis, the  $\alpha$ -alkylation of aldehydes **1** (Figure 5) [10].



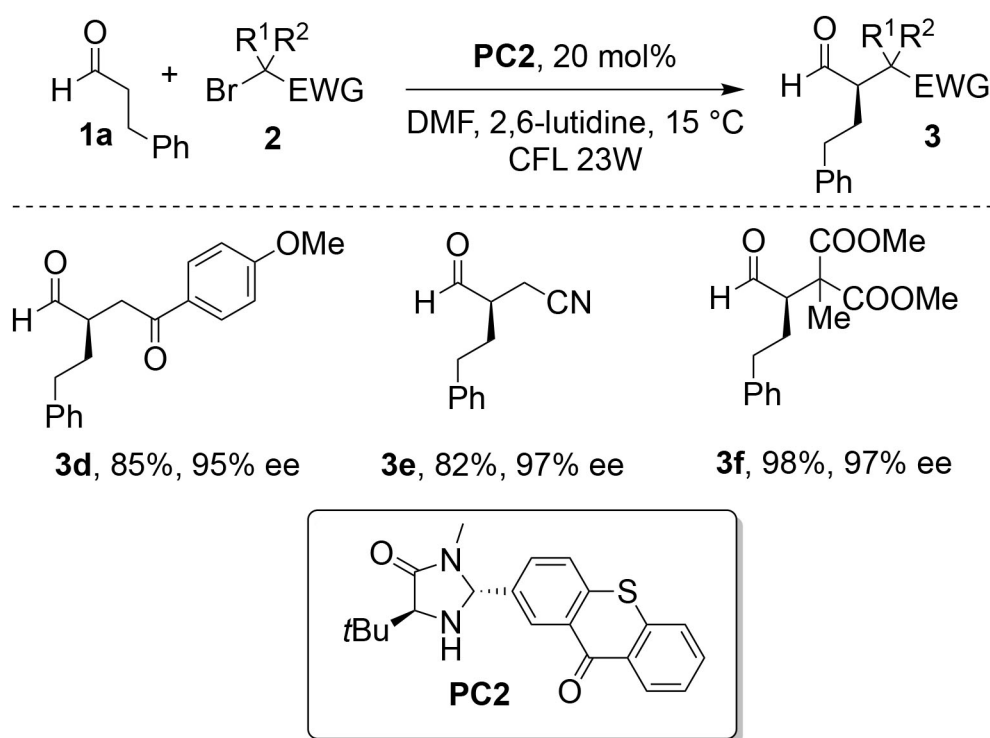
**Figure 5:** Photocatalytic stereoselective alkylation of aldehydes promoted by ruthenium(II) catalyst.

Enamines are electron rich compounds and can be reacted with electron poor radicals. In Figure 5 the proposed catalytic cycle is reported, requiring the presence and action of two distinct cycles, one controlled by the PC and one by the enamine. The PC used in this reaction was the [Ru(bpy)<sub>3</sub>]<sup>2+</sup> discussed above. In order to elucidate the reaction mechanism, Stern–Volmer experiments were carried out, indicating that the enamine was able to quench the excited state of ruthenium and not the aldehydes, or, more importantly, the bromo derivative. As enamines get oxidized, from the reported redox potential it is possible to propose that enamines are able to reduce the ruthenium complex to form a ruthenium(I) species. This part of the catalytic cycle is not shown in Figure 5 and is the starting event that allows the production of active [Ru(bpy)<sub>2</sub>]<sup>•+</sup>. This intermediate is a strong reductant ( $E_{1/2}[\text{Ru}^{2+}/\text{Ru}^+] = -1.33$  V vs. SCE), and the irreversible reduction of bromo derivatives substituted with an electron-withdrawing group is favored. Bromo derivatives **2**, described in the article, have reduction potentials between  $-0.49$  and  $-0.9$  V, and as mentioned, the formation of stabilized alkyl radicals is irreversible process and proceeds with elimination of bromide. The radicals formed react with the enamine giving rise to the formation of  $\alpha$ -amine radicals. These are quite unstable and reactive with low reduction potential ( $-1.12$  V vs. SCE) and are easily oxidized by an oxidant. Which species behaves as the oxidant? The excited state of [Ru(bpy)<sub>3</sub>]<sup>2+</sup>, as reported in Figure 2, has the calculated potential of  $E_{1/2}[*\text{Ru}^{2+}/\text{Ru}^+] = 0.77$  V and is able to oxidize this species. A sacrificial enamine starts the event producing sufficient quantities of Ru<sup>+</sup> that is then able to reduce the bromo derivatives present in solution forming Ru<sup>2+</sup>. As soon as radicals are formed,

they react with enamines producing the  $\alpha$ -amine radical, the species that is able to restart the catalytic cycle by reducing the  $^*\text{Ru}^{2+}$ . The stereoselective process is controlled by the attack of the generated radical to the accessible face of the chiral enamine that depends from the chiral secondary amine used. It is quite important to mention that, among all the enamine catalysts described by the MacMillan group, the *trans* imidazolidinone **OC1** was the most effective catalyst. This catalyst is reasonable instable in solution and tends to equilibrate to the less effective *cis* form. Probably, other imidazolidinones, bearing benzylic groups in  $\alpha$ -positions, can suffer from the generation of radicals, or formation of benzylic stabilized radicals. As the key event in this cycle is the formation of the stabilized radicals from bromo species, another PC able to form a strong reducing intermediate can be used. This strong reductant can be either formed by a PC in its excited state or can be obtained as an intermediate after the reductive quenching of the excited state.

### 3.2 Organic dyes in stereoselective alkylation of enamines

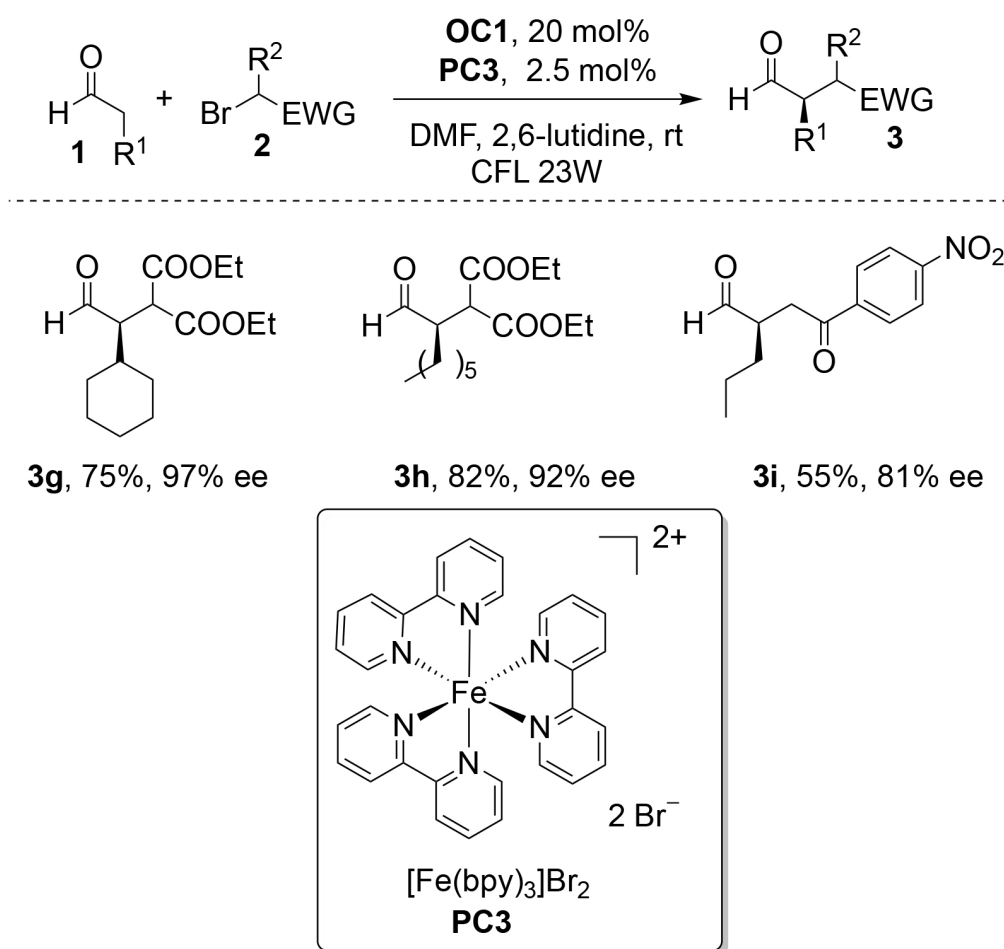
König and Zeitler reported the use of eosin Y (Figure 2) as PC for promoting the same reaction described by MacMillan in 2008, with similar substrate scope [25]. In the proposed mechanistic cycle of this reaction, the authors assumed that eosin Y acts as a photoredox catalyst after its excitation with visible light. Eosin Y acts as a reductant, and similarly to the ruthenium case, the sacrificial oxidation of a catalytic amount of the enamine as the initial event is assumed. The use of organic dyes in a MacMillan's imidazolidinones mediated photocatalytic alkylation was recently reported by Aleman (Figure 6) [26], employing the bifunctional photoaminocatalyst based on an imidazolidinone bearing a thioxanthone group **PC2**.



**Figure 6:** Photocatalytic stereoselective alkylation of aldehydes promoted by a imidazolidinone conjugated with an organo-photocatalyst.

The preparation of these catalysts is quite straightforward. Good enantiomeric excesses and yields were obtained for the examined transformation. Contrary to the previous two examples, careful mechanistic analysis was carried out, indicating that the catalyst can work under visible light conditions. Laser flash photolysis experiments showed that the intramolecular quenching of the excited state (singlet or triplet) of the thioxanthone moiety, by the amino group in the bifunctional catalyst, is reduced after enamine formation. The thioxanthone is then able to directly reduce the bromo derivatives by ET, forming a cationic species. The radical cation is then reduced by the radical intermediates formed by addition of the radical to the enamines, resulting in formation of the iminium intermediate. The calculated potential  $E_{1/2}^{\text{ox}}$  and  $E_{1/2}^{\text{red}}$  for the designed catalysts are very interesting. The high reduction potentials allowed the use of bromonitrile species (bromoacetonitrile,  $E^{\text{red}} = -1.23$  V vs. SCE in  $\text{CH}_3\text{CN}$ ). A simple calculation of the energy ( $\Delta G_{\text{PET}} = -2.3$  kcal/mol) guarantees the thermodynamic

driving force of the process, and in fact, the reaction with nitriles was observed in high yields and excellent enantioselectivities. However, this reaction is also possible with the combination of organocatalysis and  $[\text{Ru}(\text{bpy})_3]^{2+}$  [27] as the Ru(I) species, obtained by sacrificial oxidation of enamine, has a reduction potential sufficient to induce the generation of radicals from bromonitriles. Again, the available values of potentials can give a rough idea on the thermodynamic driving force. Another strong organic reductant, a coumarin derivative that can reach  $E^{\text{red}} = -1.9 \text{ V}$  (vs. SCE in  $\text{CH}_3\text{CN}$ ) was recently reported as a PC for the alkylation of aldehydes [28]. Also in this case, the coumarin PC directly acts as the reductant of the bromo derivative and no sacrificial enamine starts the catalytic cycle. Yoon, measuring the quantum yield (molecules of product formed/number of photons absorbed) of ruthenium catalyzed process [29] obtained a value of 18. Although the photocatalytic cycle was proposed as a key feature of the reaction, the value obtained by Yoon is not compatible with cycles controlled by the PCs, indeed 18 molecules of products were formed per photon absorbed. Radical chain reactions seem to be a relevant issue in many photocatalytic processes. Careful and precise measurement of the quantum yield can give some indications to whether the process is effectively promoted by a PC. For an interesting discussion on radical chains and radicals produced under photoredox conditions, a font of inspiration can be found in a review published in *Angewandte Chemie* by Curran and Studer [30]. Furthermore, a recent theoretical investigation into the origin of enantioselectivity in asymmetric radical additions to the MacMillan imidazolidinone enamines was reported [31]. Interestingly, this calculation can shed some light on the role played by the *E-cis* enamine in enantiocontrol of the reaction.



**Figure 7:** Photocatalytic stereoselective alkylation of aldehydes promoted by  $[\text{Fe}(\text{bpy})_3\text{Br}_2]$  catalyst.

### 3.3 Use of semiconductors and Earth abundant metals

The direct stereoselective  $\alpha$ -alkylation of aldehydes with  $\alpha$ -bromocarbonyl compounds can be obtained by using semiconductors, such as bismuth-based materials ( $\text{Bi}_2\text{O}_3$ ) as low-band-gap PCs [32], in the presence of imidazolidinone **OC1** used for the above described processes. The authors did not conduct a deep photophysical analysis of the results and the suggested catalytic cycle is believed to occur via direct oxidation (oxidative quenching, Figure 1) of the semiconductor, that is able to directly transfer electrons from the conduction band

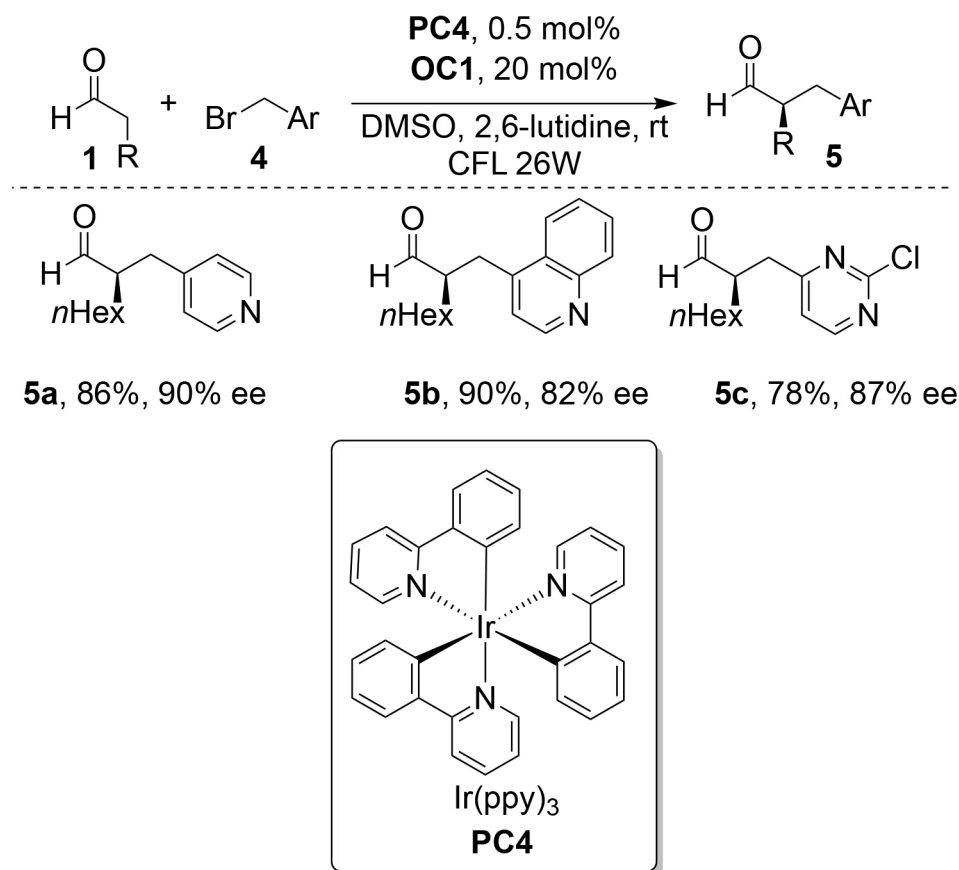
to the bromo derivative. The low abundance and high cost of iridium and ruthenium as well as their use in many electronic devices, demands for new and effective PCs. Well-structured and characterized complexes of abundant earth metals can behave effectively as PC, as many of these complexes have excited-states reachable by visible light irradiation and with lifetimes between 10 ps and 1 ms in solution. New PCs based on Cr, Mn, Fe, Co, Ni, Cu, Zn, Zr, Mo, W and Ce in various oxidation states surrounded with diverse ligands, have been recently studied and applied to established photoredox processes [33]. As iron is an abundant metal, cheap and that presents low toxicity, the search for PCs based on Fe(II) complexes as  $3d^6$  analogues of the emissive  $(\text{Ru}[\alpha\text{-diimine}]_3)^{2+}$  compounds is a hot topic. The principal problems related to iron complexes are due to the non-emissive character and low lifetime of its excited state. For example, the lifetime of excited  $[\text{Fe}(\text{bpy})_3]^{2+}$  is about hundreds of picoseconds [34]. Surprisingly,  $[\text{Fe}(\text{bpy})_3]^{2+}$  is an effective and compelling PC for  $\alpha$ -alkylation of aldehydes, in the presence of the imidazolidinone **OC1** (Figure 7) [35].

Visible light and  $[\text{Fe}(\text{bpy})_3]\text{Br}_2$  were both necessary to drive the reaction to completion. EPR studies with a radical trap evidenced the formation of alkyl radicals from bromo derivatives used in the reaction. A series of compounds was obtained with yields and enantiomeric excesses comparable to those obtained with the before mentioned methodologies. Furthermore, the method was applied to the synthesis of (–)-isodehydroxypodophyllotoxin. A radical chain mechanism was proposed for the reaction, with the iron photosensitizer capable of promoting, upon excitation, a chain radical reaction in which the photochemical event is only the starting step. The photophysical process was studied carefully by femtosecond laser absorption spectroscopy, showing the lifetime of the excited states to be around 600 ps. By evidence obtained with Stern–Volmer experiments, the  $[\text{Fe}(\text{bpy})_3]\text{Br}_2$  photosensitizer acts as a reductant for initiating the chain mechanism. Remarkably, although similar, the iron based PC is substantially different from the ruthenium cases reported, as the PC in the excited state is able to directly generate the radical species from bromo derivative, without the assistance of the enamine to generate the catalytic active species. However, the quite short life of the PC-excited state poses an intriguing problem, as it is significantly shorter than the diffusion rate, which is the limit in encountering processes in solution. Probably, further work is necessary in order to better understand the potential of these PCs, investigating if other processes induced by light (spin transitions) are responsible for the observed reactivity. In addition to the use of abundant iron complexes, commercially available aluminum based luminescent complexes are also quite effective PC for the catalytic reactions [36].

### 3.4 Iridium complexes in alkylation of enamines

One of the problems associated with this example of synergistic catalysis is the limited scope of the reaction. In fact, just to mention, benzyl bromides were found completely unreactive. This is not surprising, as the limitation is determined by the redox potential of the PC in its excited or reduced states. In the case of  $[\text{Ru}(\text{bpy})_3]^{2+}$ , the produced Ru(I) is able to reduce organic molecules that have a potential greater or equal to ca.  $-1.3$  V. In order to favor the reaction a stronger photoreductant is necessary. MacMillan was able to show that the alkylation of aldehydes with benzylic bromides is possible using iridium complexes. These complexes are cyclometallated iridium(ppy) (III), (ppy = 2-phenylpyridine) based and are commonly used as green triplet emitters in OLEDs. Their excited states are readily reached by visible light to generate the strong reductant specie *fac*-\*Ir(ppy)<sub>3</sub> ( $E_{1/2} = -1.73$  V vs SCE in  $\text{CH}_3\text{CN}$ ). Unfortunately, the reaction was ineffective with benzyl bromide and, only the introduction of EWG to lower the reduction potential, allowed the alkylation to take place. Anyway, interesting compounds **5** could be obtained using this methodology (Figure 8) [37].





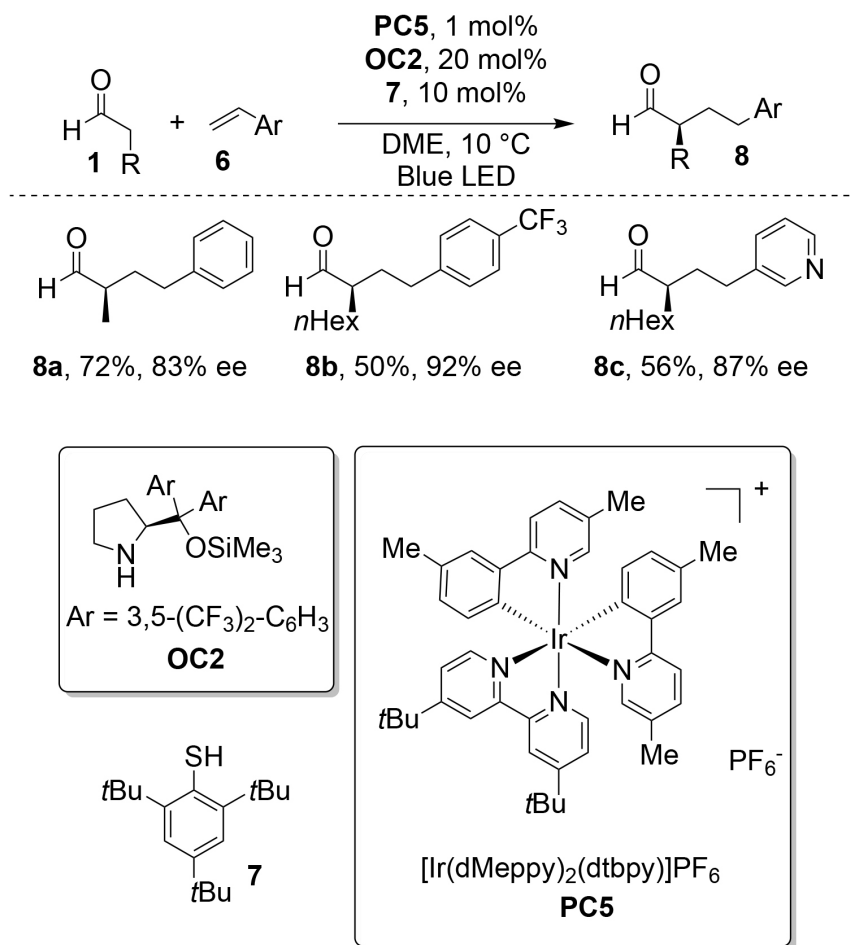
**Figure 8:** Photocatalytic stereoselective alkylation of aldehydes with benzylic bromides promoted by an iridium (III) catalyst.

Stern–Volmer experiments were performed to provide insight into the mechanistic details of the reaction. While *fac*-\*Ir(ppy)<sub>3</sub> oxidation of the enamine (Figure 8) is not observed, aryl and heteroaryl methylene bromides **4** were able to display efficient quenching of the PC, suggesting that the electron transfer event occurs between the PC and organic halides, as shown in the illustrated cycle. The organocatalytic  $\alpha$ -trifluoromethylation and  $\alpha$ -perfluoroalkylation of aldehydes were reported by MacMillan, by using the imidazolidinone catalyst and an iridium (III) complex [38].

Although Ir(ppy)<sub>3</sub> was able to catalyze the reaction, the authors found that another Ir(III) complex, Ir(ppy)<sub>2</sub>(dtbbpy)<sup>+</sup> (dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine), that has a reduction potential in its reduced Ir(II) state of  $-1.51$  V (vs. SCE in CH<sub>3</sub>CN), was more effective. In fact, a SET with trifluoromethyl iodide ( $-1.22$  V vs. SCE in DMF) is favored if the reduction potential of the species is more negative. The asymmetric trifluoromethylation was compatible with a wide range of functional groups including ethers, esters, amines, carbamates, and aromatic rings (61–86 % yield, 93–98 % ee), and the use of hindered aldehydes was also possible. The catalytic cycle started with reduction of the \*Ir(III) complex from the enamine generating the strong reductant Ir(II) species able to produce the CF<sub>3</sub> radical from CF<sub>3</sub>I. After the addition of the radical to the enamine, the  $\alpha$ -aminyl radical obtained is the reductant for Ir(III) in its excited state, restoring and maintaining the catalytic cycle. As pointed out, the catalyst behaves like [Ru(bpy)<sub>3</sub>]<sup>2+</sup> in the photocatalytic alkylation of aldehydes (Figure 5). The ruthenium PC could not be employed in this photoredox reaction due to an inferior ( $-1.33$  vs.  $-1.55$ , vs SCE) reduction potential.

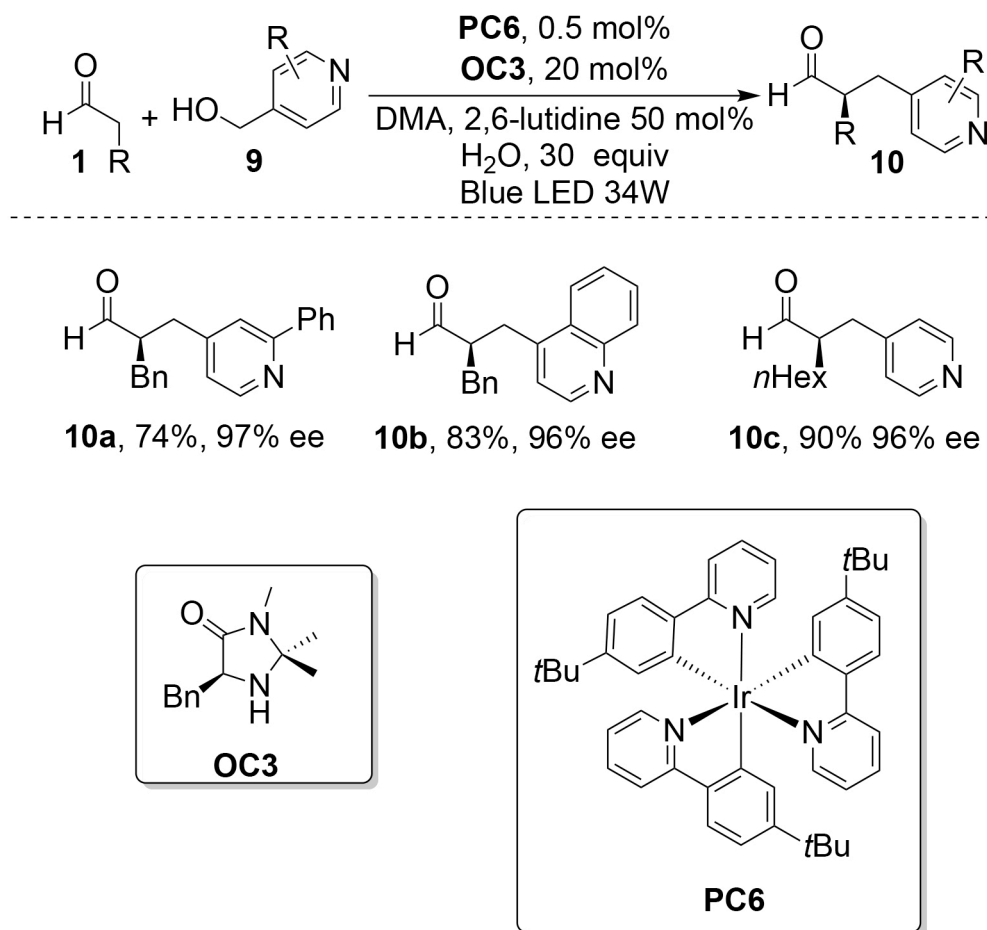
### 3.5 Stereoselective photoredox catalysis and HAT

The synergistic merger of three different catalytic processes (photoredox, enamine and hydrogen-atom transfer) was shown by MacMillan being quite effective and allows the direct alkylation of aldehydes with aryl alkenes **6** (Figure 9) [39].



**Figure 9:** Photocatalytic stereoselective alkylation of aldehydes with alkene by hydrogen-atom transfer (HAT) catalysis.

The reaction uses a chiral imidazolidinones or prolinols as the organocatalysts, in combination with a hindered thiophenol **7** and the iridium photoredox catalyst **PC5**. The process needs visible light, through a complex series of independent events connected by three catalytic cycles. The iridium PC used in the process is Ir(III)(Fmppy)<sub>2</sub>(dtbpy)PF<sub>6</sub> [Fmppy = 2-(4-fluorophenyl)-4-(methylpyridine), dtbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine] (**PC5**), able to absorb visible light, with a long-lived triplet ( $\tau = 1.2 \mu\text{s}$ ) excited-state. The PC is assumed to behave as an oxidant, ( $E_{1/2}[*\text{Ir(III)}/\text{Ir(II)}] = +0.77 \text{ V vs. SCE}$ ), capable of oxidizing the enamine. This electron transfer reaction produces the Ir(II) complex and the enaminy radical species. The enamine radical species is an electrophilic radical, capable of intercepting in a stereoselective manner the alkene present in solution. This C–C bond forming reaction generates another nucleophilic radical species. This species is therefore able to react in a radical manner with the electrophilic species. The hindered thiol added to the reaction mixture is this specie, and the S–H bond now reacts by a HAT (hydrogen atom transfer) mechanism forming a thiol radical. The sterical hindrance of the thiol is crucial to stabilize the thiyl radical and allows an electron transfer from Ir(II). This electron transfer is highly favorable ( $E_{1/2}[\text{PhS}\cdot/\text{PhS}^-] = +0.02 \text{ V vs. SCE, DMSO}$ ) and regenerates both the ground state Ir(III) **PC5** as well as the HAT thiol catalyst, after thiolate protonation. Another remarkable process in which a proton and a spin transfer are operative is the alkylation of aldehydes, in the presence of organocatalyst with benzylic alcohols **9** derived from pyridine and quinolines (Figure 10) [40].

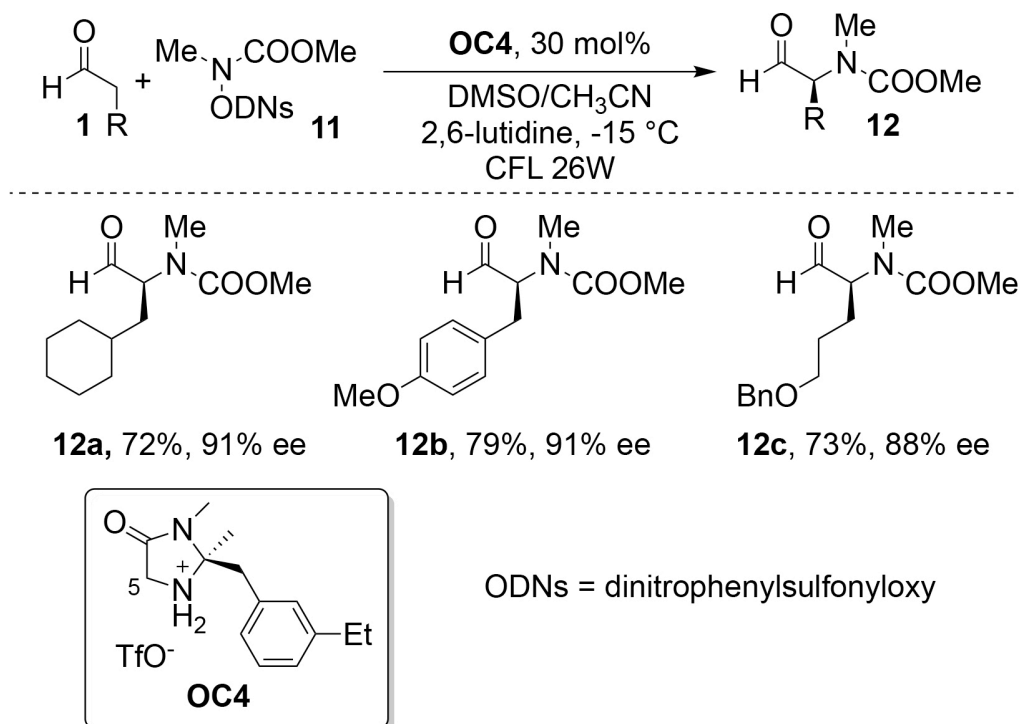


**Figure 10:** Photocatalytic stereoselective alkylation of aldehydes with methanol azines.

The single-electron reduction of a pyridinemethanol can be obtained by a photoredox catalyst, as pyridine is an electron withdrawing group. The HAT process and the spin rearrangement of the obtained species give a benzylic C–O bond cleavage, facilitated by the protonation of the alcohol intermediate. The electron poor radical, produced by the rearrangement, is able to react with electron rich enamines in a stereoselective manner. The strong reducing PC in its excited state Ir(III)(ppy)<sub>3</sub> was employed in the reaction. The formed Ir(IV) intermediate **PC6** ( $E_{1/2}[\text{Ir(IV)/(III)}] = +0.77$  V vs. SCE in CH<sub>3</sub>CN) is capable of oxidizing the resulting  $\alpha$ -amino radical (Figure 5)  $E_{1/2} = -1.12$  to  $-0.92$  V vs. SCE in CH<sub>3</sub>CN), restoring the PC to the ground state.

### 3.6 Stereoselective formation of C–N bonds with photoredox enamine catalysis

The enantioselective construction of C–N bonds for the synthesis of key intermediates or natural products is an important goal in modern stereoselective catalysis. Photoredox stereoselective catalysis can also be applied to form C–N bonds. In particular, as  $\alpha$ -amino aldehydes are quite useful starting materials, the approach to asymmetric  $\alpha$ -amination of aldehydes by photoredox enamine catalysis, can solve some problematic issues related to the introduction of nitrogen on acidic substrates. In this perspective, MacMillan has reported the formation of N-centered radicals that undergo enantioselective  $\alpha$ -addition to chiral enamines (Figure 11) [41].

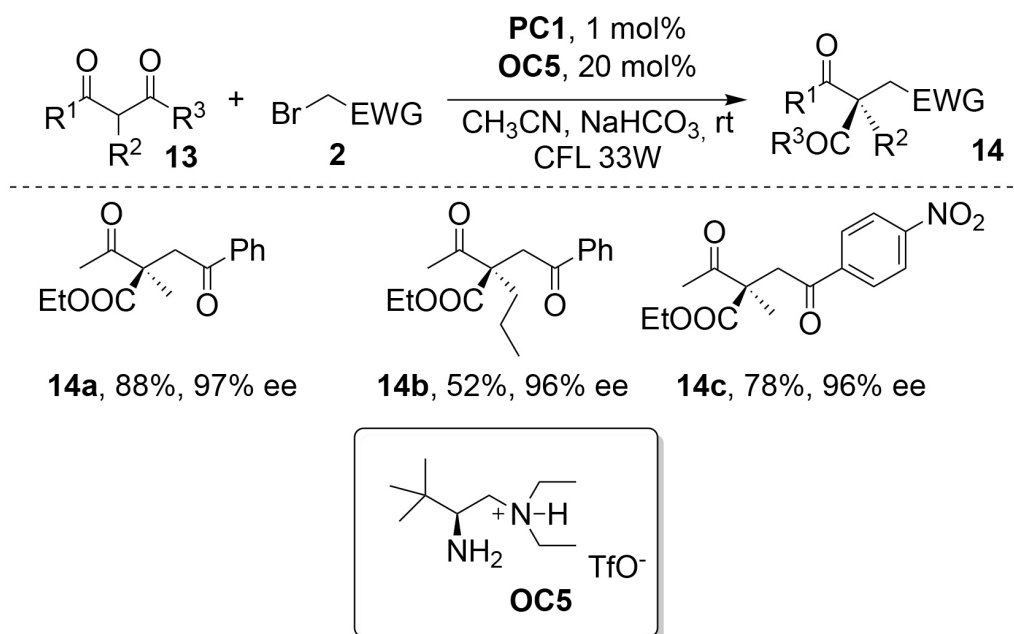


**Figure 11:** Photocatalytic stereoselective amination of aldehydes with a tailored organocatalyst.

By absorption of light from amine **11**, it is possible to generate a N-based radical under mild conditions. The cycle starts with the generation of an aminyl radical, induced by UV light. The light source for the reaction is a CFL (Compact Fluorescent Lamp), and although the lamp has normally a broad emission (white light) some UV components are also emitted. The aminyl radical formed reacts with the enamine giving rise to the formation of a  $\alpha$ -amino radical species. This species is oxidized by a SET process that involves the amino reagent **11** in its excited state. The scope of the reaction is broad, and many functional groups present on the aldehydes (ethers, amines, alkenes, and aromatic rings) are tolerated, with products isolated in 71–79% yields, and 88–91% ees. It is also quite important to mention that a new type of imidazolidinone catalyst (**OC4**) was introduced for the transformation. A chiral imidazolidinone catalyst less hindered in position 5 was considered important. Careful analysis of the remaining catalyst clarified that the imidazolidinone was not very stable under the reaction conditions as it underwent H radical abstraction at the aminal C2 position. Therefore, the need to reduce sterical hindrance and eliminate the undesired decomposition pathway led to the design of a novel organocatalyst with a fully substituted carbon stereocenter at the aminal positions. The trial and error design was justified by density functional theory (DFT) of the corresponding enamine intermediate, with the position of the electron-rich enamine away from the fully substituted carbon center on the imidazolidinone framework. The presence of a *meta* substituent and the orientation of the arene group are important to effectively cover the enamine stereoface.

### 3.7 Other stereoselective processes with enamine catalysis

The photocatalytic stereoselective  $\alpha$ -alkylation of  $\beta$ -ketocarboxyls **13** by synergistic photoredox catalysis with enamine catalysis was described (Figure 12) [42].

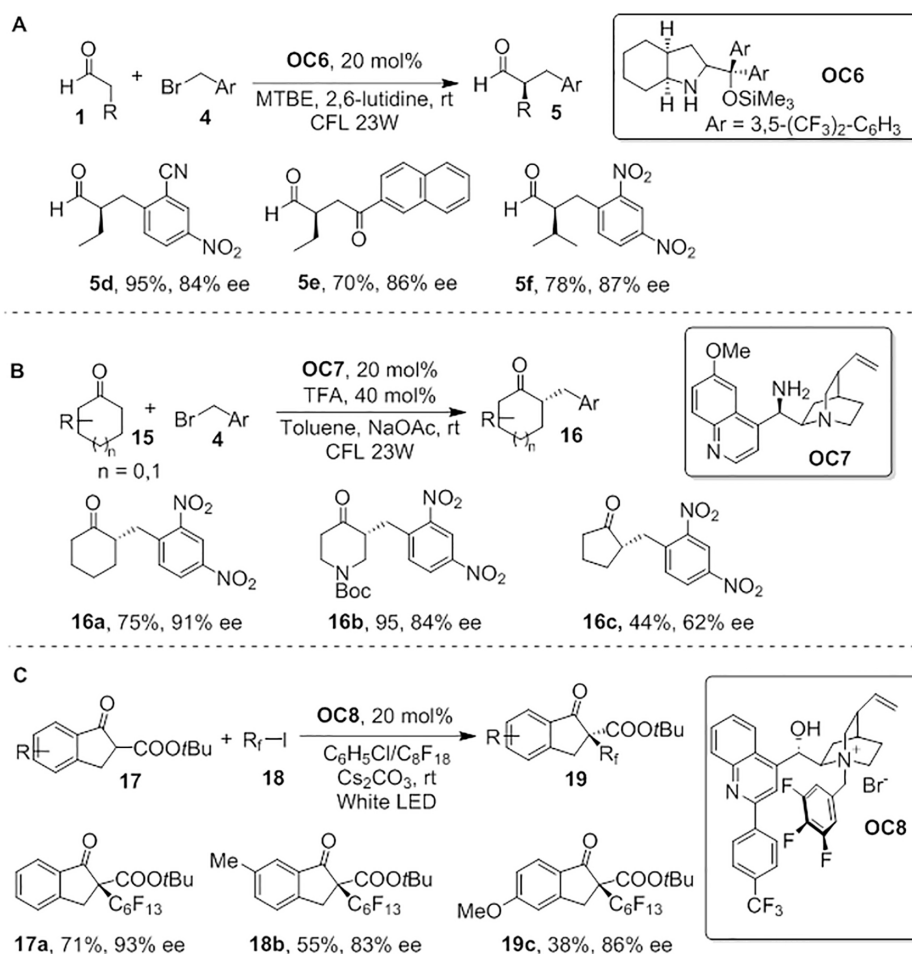


**Figure 12:** Photocatalytic stereoselective alkylation of ketoesters with a chiral primary amine organocatalyst.

In this example all-carbon quaternary stereocenter with high enantioselectivity was prepared from acyclic and cyclic ketoesters. Acyclic acetoacetates bearing either steric bulky *tert*-butyl or benzyl ester groups are useful substrates giving products in high yields and excellent enantioselectivities. In addition, the described catalysis is quite successful with cyclic  $\beta$ -ketoesters. Photophysical studies were not reported, as the reaction employed  $[\text{Ru}(\text{bpy})_3]^{2+}$  as the PC and the reaction mechanism is quite similar to the previously discussed proposal by MacMillan. The organocatalyst **OC5** needs a brief comment. As the formation of ketone enamine is involved, the catalysis by primary amine is quite crucial [43], in order to reach a sufficient concentration of enamine able to quench the excited state and interact with the formed radical.

#### 4 Stereoselective alkylation of enamines through EDA

One of the main issues related to stereoselective photoredox processes, discussed in the previous sections, was the demand of a PC (either a metal complex, semiconductor, or organic molecule) able to intercept light, reaching the excited state suitable for the electron transfer event. As chiral enamines are strong donors and enamines are the key catalyst for the stereoselective formation of C–C bonds, it would be possible to induce photon-absorption by chiral electron donor – acceptor (EDA) complexes. The energy necessary to favor the electron transfer between the two partners is then furnished by the absorbed light. The strong radical couple formed could then collapse through radical-radical coupling, forming a new bond in a stereoselective manner. EDA complexes are well known and reported in literature [43]. Also the ability of tertiary amines to form EDA complexes with electron-accepting molecules of high electron affinity is well established [44]. In enamines, the nitrogen lone pair is suitable to form EDA complexes with an acceptor compound or an electron poor compound. This behavior can easily be confirmed, as EDA complexes are characterized by the appearance of a weak absorption band, called the charge-transfer band, associated with an ET transition from donor to acceptor [45]. In many cases, the absorption is visible to the naked eye, with the appearance of a colored solution. This means that the energy associated with this absorption is within the visible wavelength range. If it would be possible to produce an EDA complex using a chiral enamine, the ET event can drive the stereoselective  $\alpha$ -alkylation of aldehydes. This possibility and the processes associated with a rational design of EDA complexes in enamine catalysis were introduced in literature by Melchiorre (Figure 13(a)) [46].

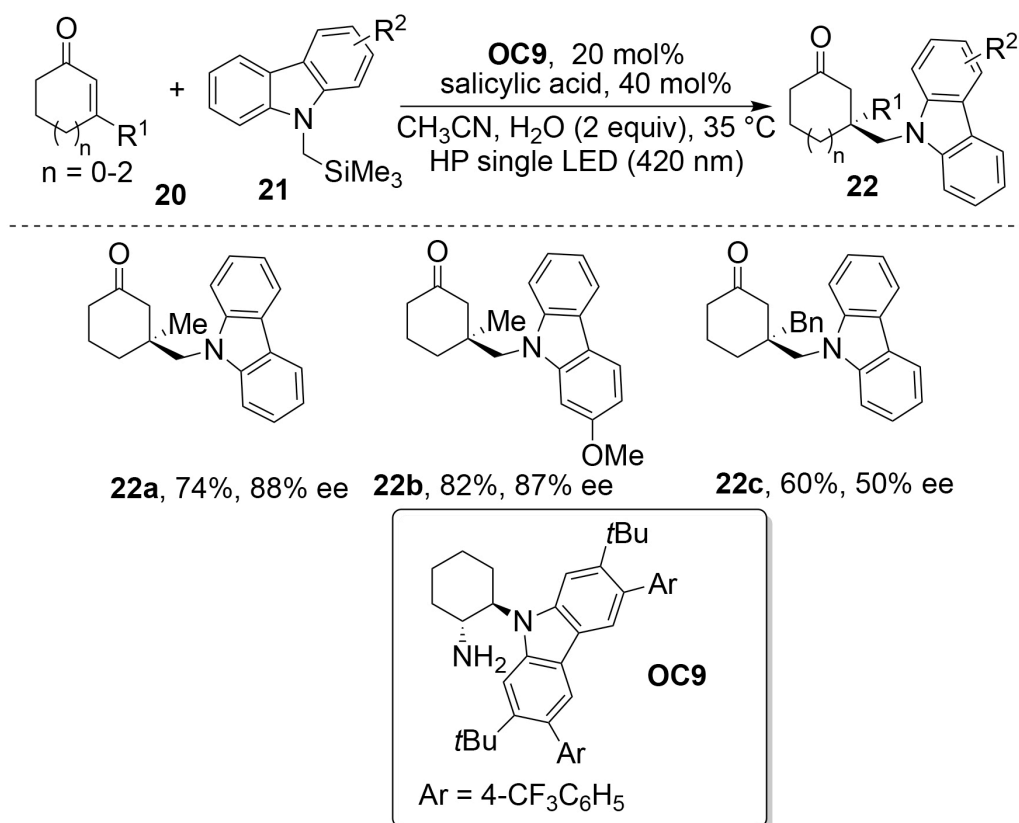


**Figure 13:** Examples of EDA mediated organocatalytic stereoselective alkylation.

The alkylation was realized using suitable alkyl halides **4**, such as benzyl bromides carrying a nitro group on the aromatic ring. They have a low reduction potential and they are capable of forming EDA complexes with enamines, by a  $n-\pi^*$  type interaction [47]. Interestingly, the commercially available diarylprolinol silylether catalyst **OC6** was selected. This selection agreed with the better nucleophilic properties of the enamines derived from Hayashi–Jørgensen catalyst **OC2**. In addition, the pyramidalization of the nitrogen atom in the MacMillan catalysts [21] can reduce the availability of the nitrogen lone pair.

For the stereoselective reaction, a more hindered Hayashi–Jørgensen type of catalyst was prepared, and with this catalyst, good yields, broad scope and high stereoselectivities were observed. Not only benzyl bromides bearing electron-withdrawing groups were useful substrates, but also aromatic and heteroaromatic  $\alpha$ -bromo ketones. The reaction also proceeded using branched aldehydes and ketones [48] in case primary amine obtained from the cinchona alkaloid **OC7** was used as organocatalyst (Figure 13(b)). The photochemical enantioselective perfluoroalkylation of  $\beta$ -ketoesters was developed using a similar concept (Figure 13(c)) [49]. An EDA complex arises from the association of a perfluoroalkyl iodide **18** and the chiral enolate of the ketoester. The latter was generated by phase transfer catalysis (PTC) [50], where the phase transfer catalyst is a chiral quaternary ammonium salt **OC8**, commercially available or obtained in a straightforward manner from a cinchona alkaloid. The reaction proceeded in the presence of  $\text{Cs}_2\text{CO}_3$  (2 equiv) and under irradiation with white LEDs at room temperature for 16 h in good yields and high enantiomeric excesses. Due to the scarce solubility of perfluorinated compound in organic solvents, a mixture chlorobenzene/perfluorooctane (2:1 ratio) was used as the reaction solvent to allow the reaction to proceed. Investigation on a model capable of explaining the stereochemical outcome of the reaction, by DFT calculations, was reported by Li [51]. The calculations showed that stereoselection was not determined by  $\pi-\pi$  stacking interaction between the cinchona catalyst and the ketoester, but rather multiple hydrogen-bonding interactions play a decisive role.

An interesting formation of quaternary stereogenic centers by EDA process, in a photoinduced Michael type reaction, was reported quite recently by Melchiorre (Figure 14) [52] illustrating the concepts of careful design of a photoactive organocatalyst [53].

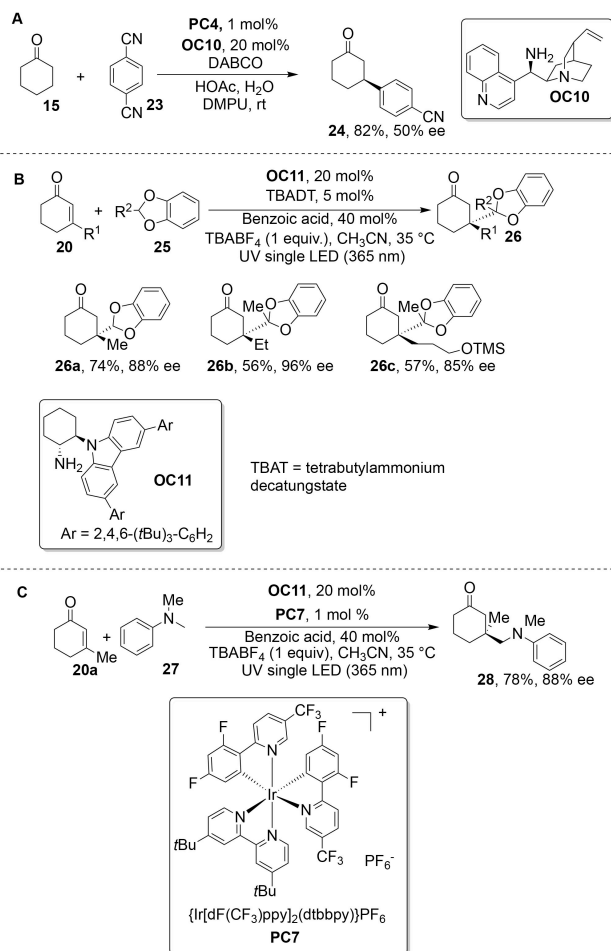


**Figure 14:** Formation of quaternary stereogenic centers by photoinduced type Michael EDA.

The strategy is based on the formation of an intramolecular EDA complex, capable of triggering a photochemical catalytic enantioselective radical process. A radical conjugate addition to  $\beta$ -substituted cyclic enones, challenging substrates for Michael reactions, was described. Although the scope is limited to certain substrates, the chiral iminium ion formed in these reactions testify to the possibility to expand the repertoire of photocatalytic processes using both iminium and enamine catalysis. As a result of conjugation and the presence of a carbazole moiety in the design of the organocatalyst **OC9**, the chiral iminium ions formed show a broad absorption band in the visible region. This absorption band originates from an intramolecular charge transfer  $\pi$ - $\pi$  interaction between the electron-rich carbazole and the electron-deficient iminium double bond. The catalyst is able to transfer an electron to the double bond, by irradiation, forming a radical couple. Crucial to the design of the catalyst is the carbazole moiety, as the long-lived carbazole radical cation formed by electron transfer is a persistent species and can behave as an oxidant. After formation of the radical couple, the carbazole radical cation can oxidize suitable species forming the corresponding radical that undergoes the coupling with the enaminyll radical intermediate.

## 5 Stereoselective alkylation through iminium intermediate and a PC

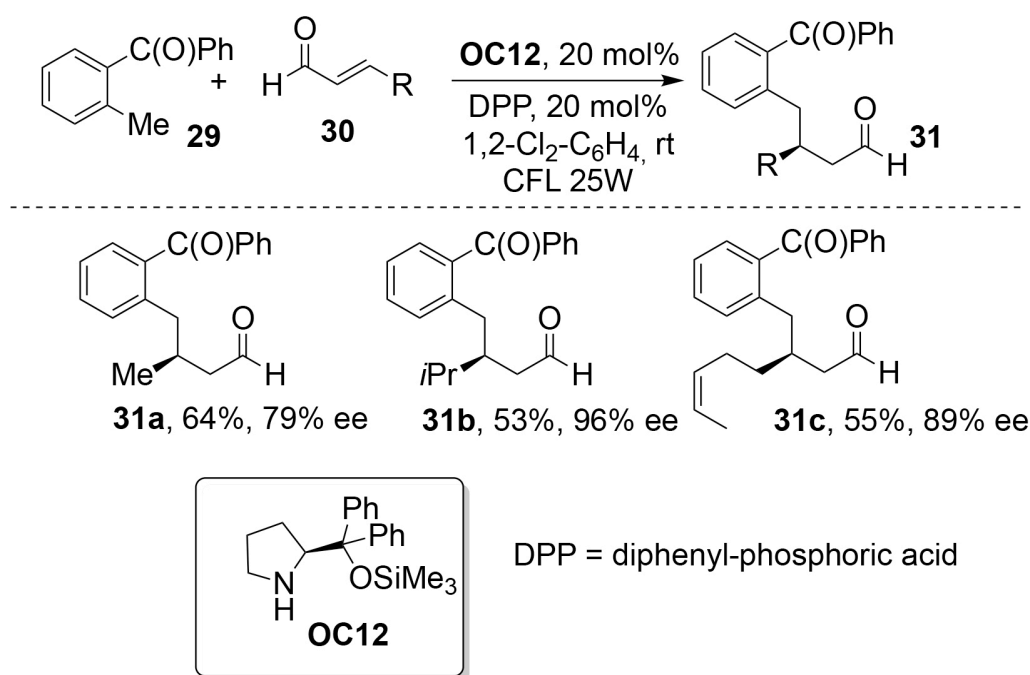
The stereoselective Michael-type conjugate addition to unsaturated carbonyl substrates is a powerful methodology to access interesting molecules and introduce a variety of moieties. Remarkably, stereoselective radical additions were also investigated using chiral auxiliaries or ligands, to provide a good level of stereoselection [54]. As photoredox catalysis can be used to access radicals and iminium catalysis is a well-established activation mode in organocatalytic methodologies [55], it could beg the question if the effective combination of photocatalytic production of radicals with the effective iminium activation mode, can give powerful and selective methodologies. MacMillan in 2013 reported an elegant strategy for the  $\beta$ -arylation of carbonyl compounds by combining photoredox and organocatalysis using a chiral amine derived from cinchona alkaloid **OC10** and cyclohexanone (Figure 15(a)) [56].



**Figure 15:** Michael and arylation in  $\beta$ -position of a carbonyls by organo-photoredox catalysis.

However, the enantioselectivity was only moderate (50% ee), and no substrate scope was reported. This limitation is due to the fast ET that occurs by the generated short-lived, highly reactive  $\alpha$ -iminyl radical cation, which has a high tendency to undergo radical elimination ( $\beta$ -scission) to re-form the more stable iminium ion. Probably, for this reason, the stereoselective photoredox iminium-type reactions were underdeveloped. However, moving towards the formation of quaternary centers and providing a better stabilization/protection of the radical, Melchiorre [57] (Figure 15(b)) reported a remarkable Michael type addition of benzodioxole **25** to  $\beta$ -alkylated cyclohexenones **20**. In order to allow the reaction to proceed, different design elements were considered. Due to the high reactivity of the  $\alpha$ -iminyl radical cation, a very rapid SET reduction is necessary to stabilize the adduct as an enamine adduct before  $\beta$ -scission occurs to re-form the more stable iminium ion. An electron rich carbazole moiety, capable of ET, was inserted in the chiral primary amine used as the catalyst, to favor iminium formation. Finally, in order to generate the benzodioxole radical, a PC capable of abstracting a hydrogen atom, tetrabutylammonium decatungstate (TBADT, 5 mol%) was employed. However, this catalyst needs a (UV)-light emitting diode (UV LED,  $\lambda_{\max} = 365$  nm) to be excited. Five, six and seven membered ketones, with different alkyl substituent in the  $\beta$  positions gave the observed products, in good yields and moderate to good selectivity. The photoredox reactions can also be promoted by **PC7** Ir[dF(CF<sub>3</sub>)ppy]<sub>2</sub>(dtbbpy)PF<sub>6</sub>, that was used (Figure 15(c)) to generate  $\alpha$ -amino radicals directly from tertiary amines. For these reactions, due to the more favorable photophysical properties of Ir(III) catalyst, a blue LED was employed. The combination of electrochemical, spectroscopic, computational, and kinetic studies was also employed to investigate the reaction mechanism of the reaction [58]. Another interesting process that coupled stereoselective iminium catalysis with a photoredox event is the photoenolization/Diels – Alder sequence, to produce benzannulated carbocyclic molecule (Figure 16) [59].



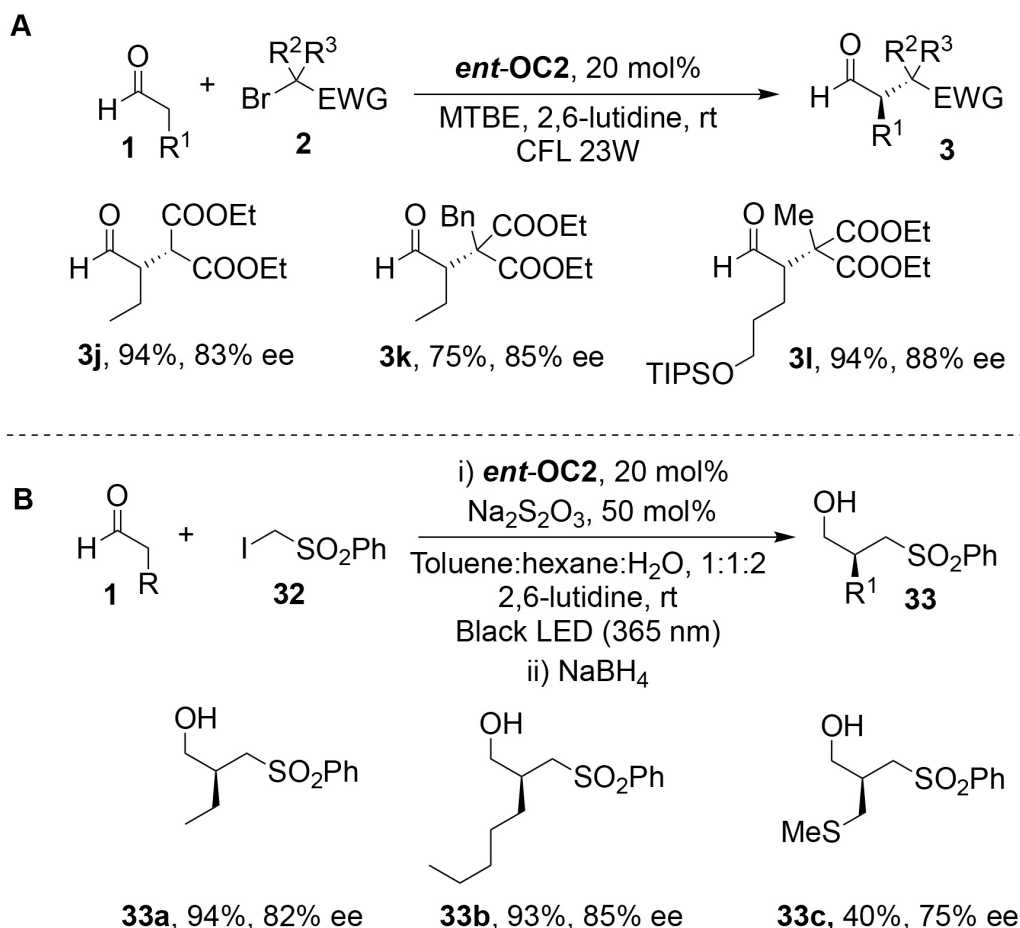


**Figure 16:** Photoenolization/Diels–Alder sequence for the synthesis of benzannulated carbocyclic molecules.

This approach exploits the light-triggered enolization of 2-alkyl-benzophenones **29** forming in situ the transient hydroxy-*o*-quinodimethanes, highly reactive intermediates that can behave as a Michael donor towards electron-poor alkenes. If the electron poor alkene is a chiral iminium, a conjugate stereoselective addition is observed. This chemistry provides a straightforward method for the direct  $\beta$ -benzylation of enals. Using the optimized reaction conditions, a variety of diversely substituted enals can be used for the reaction and sterically hindered groups are also tolerated. In order to perform the reaction, and allow the formation of the key intermediate, a BLB (black light bulb  $\lambda_{\text{max}} = 365 \text{ nm}$ ) was employed. Beside enals, also 3-substituted-2-cyclohexenones can be employed [60]. Since ketones were used in the reaction, chiral primary amines derived from amino acids were employed as organocatalysts, to promote the formation of the chiral iminium ion.

## 6 Stereoselective alkylation through enamine as the PC

An interesting feature of the enamines is their ability to reach an electronically excited state upon light absorption. As the other organic species present in the reaction mixture are not capable to absorb light at wavelength where enamines are absorbing, the formation of catalytic amount of enamine can possibly provide the in situ PC preparation, without the need of adding other organic molecules or metals that behave as PC. In addition, reactive radicals formed by the photocatalytic event could be intercepted in a stereoselective fashion by the chiral enamine. This general activation mode, that can be added to the list of enamine catalysis, was first reported by Melchiorre (Figure 17(a)) [61].

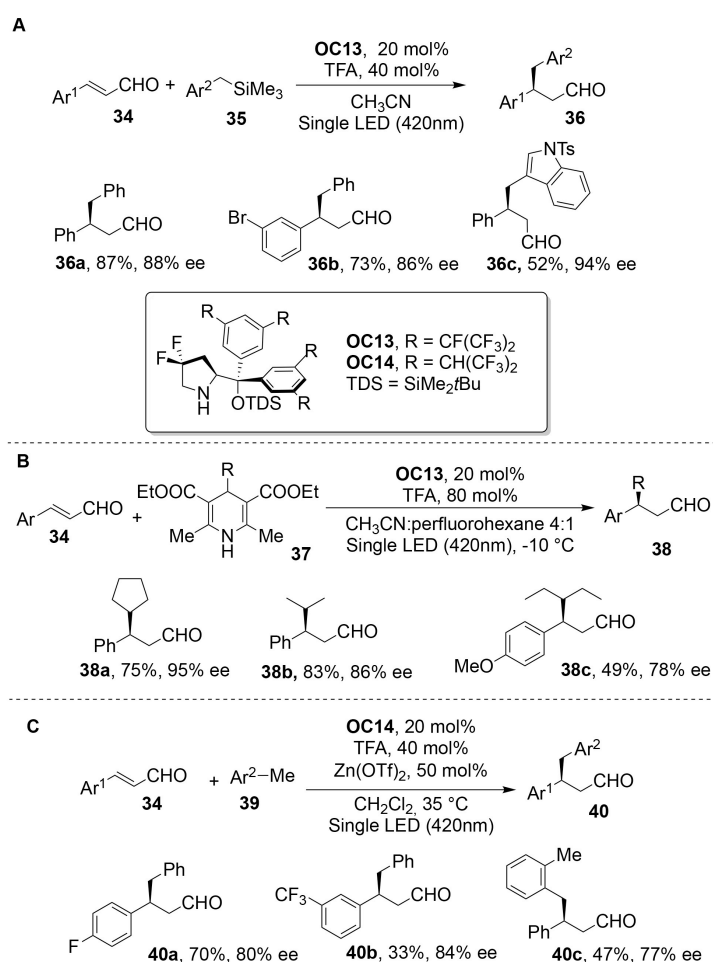


**Figure 17:** Stereoselective alkylation through enamine as the photocatalyst.

Quite remarkably, the enamine used for the direct photocatalytic alkylation is based on the Hayashi–Jørgensen catalysts *ent*-OC2 probably because of their nucleophilicity. The absorption and emission of light by the enamine prepared from condensation of the chiral Hayashi–Jørgensen catalyst with 2-phenylacetaldehyde was demonstrated [61]. Furthermore, the Stern–Volmer experiment performed between chiral enamine and bromomalonate indicated the electron transfer between the two. Based on this finding, a radical chain mechanism was proposed, in which starting radicals are formed by the enamine PC. Remarkably, the calculated redox potential of the enamine in its excited state was estimated to be  $-2.50$  V (vs Ag/AgCl, NaCl sat.) based on electrochemical and spectroscopic measurements. Differently substituted bromomalonates can be used for the enantioselective alkylation and a variety of aldehydes bearing diverse functional groups are compatible. A substantial difference is observed in the reaction conditions employed. Normally, photocatalytic alkylation of aldehydes using the MacMillan catalyst in the presence of ruthenium or iridium are conducted in DMF, while in the current case, *tert*-butyl methyl ether (MTBE) is employed. Contrary to the reactions catalyzed by ruthenium and iridium complexes, the use of a CFL is necessary due to the absorption of enamines in the near UV region. It is also possible to apply this chemistry to dienamine catalysis [62] by introducing stereocenters in remote  $\gamma$ -position. What is also important to mention, is that a comprehensive and authoritative mechanistic analysis of the process, including kinetic studies and full photochemical investigations, was published [63]. The high reduction potential of enamines in their excited states can be exploited to provide a general stereocontrolled  $\alpha$ -alkylation of carbonyl compounds. Alkyl halides could not be employed as electrophiles in enamine catalysis, apart from rare examples of  $S_N2$ -type alkylation [64]. Only one effective procedure was published by List, limited to branched aldehydes with benzyl bromide derivatives [65]. More successful methodologies for the alkylation of aldehydes are based on  $S_N1$ -type reactions [66]. An organo-photocatalytic methodology to install either a methyl or a benzyl moiety onto simple aldehydes with high stereoselectivity was reported by Melchiorre (Figure 17(b)) [67]. Because of the ability of chiral enamines to be strong reductant in their excited states, SET reduction of the (phenylsulfonyl)alkyl iodides **32** gave (phenylsulfonyl)alkylated intermediates that can easily be desulfonated. As the reduction potential of iodosulfones is  $-1.49$  V ( $E_{1/2}$  vs. Ag/Ag + in  $\text{CH}_3\text{CN}$ ), the reaction is thermodynamically favored. The desulfonation is performed by activated magnesium in anhydrous MeOH.

## 7 Stereoselective reactions of iminium ions as the PC

As enamines can directly absorb light and become stronger reductants, conversely, iminium ions in their excited states can behave as strong oxidants. Starting from suitable precursors, iminium ions could be used in effective stereoselective Michael reactions. This process is also observed in nature where iminium ions are involved in visual processing invertebrates responsible for light excitation of the formed iminium ion from condensation of 11-*cis*-retinal with the  $\epsilon$ -amino group of a lysine residue occurs within opsins [68]. This strategy was implemented by Melchiorre, (Figure 18) detailing the stereoselective addition of benzylic substrates **35** to cinnamyl aldehydes **34** [69].

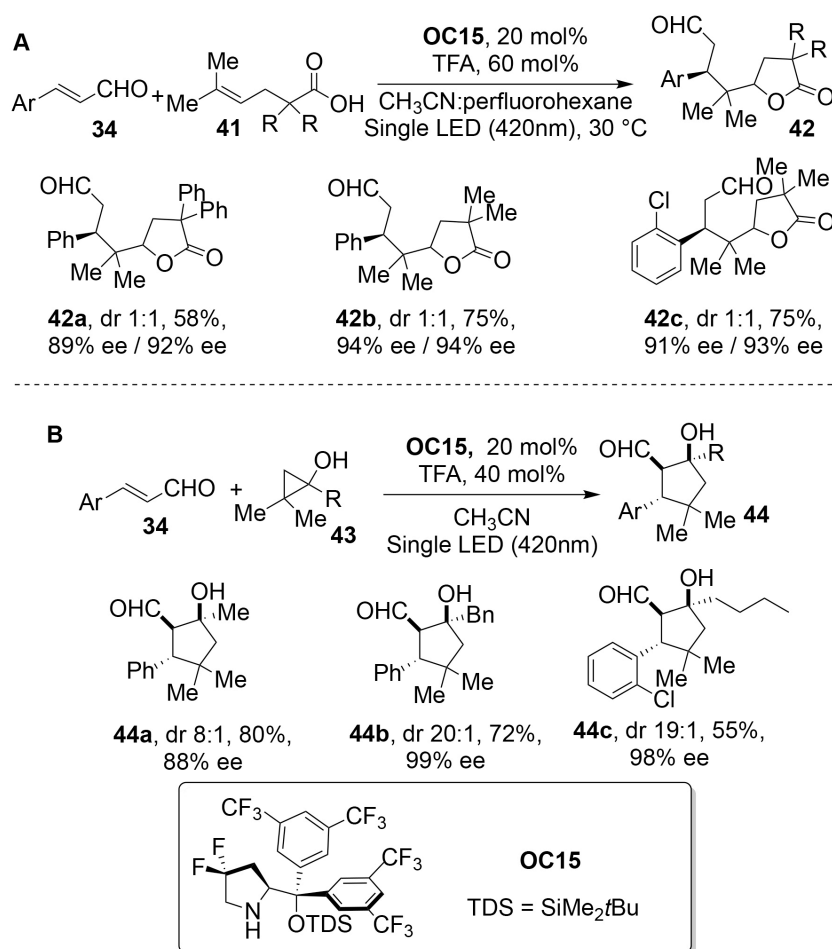


**Figure 18:** Stereoselective addition of benzylic substrates to cinnamyl aldehydes.

The potential of the excited iminium ion ( $E_{1/2} [^*Ia/Ia^-]$ ), was estimated to be +2.3 V [vs. Ag/Ag<sup>+</sup>] and therefore the oxidation of benzylic trimethylsilane derivative **35** ( $E_{1/2} = +1.74$  vs. Ag/Ag<sup>+</sup> for benzyl trimethylsilane) is a thermodynamically favored process. As iminium ions are capable of absorbing visible light, the excitation was performed using blue LEDs ( $\lambda_{\text{max}} = 420$  nm). Stern–Volmer experiments were able to demonstrate that benzylic silane effectively quenched the excited state of the iminium ion. The reaction scope was investigated with different cinnamyl derivatives as well as benzylic silanes. Unsaturated aliphatic aldehydes did not undergo any reaction, probably due to the low molar extinction coefficient of the corresponding iminium ions. Importantly the iminium ion in its excited state reaches a very high oxidation potential. This strong oxidant is also capable of decomposing the catalyst in solution. A modified diarylprolinol catalyst in which fluorine atoms were introduced to guarantee stability towards oxidations was prepared and evaluated. The *gem*-difluorinated catalyst retains strong oxidation properties in its excited state, ( $E_{1/2} [I^+ \cdot / ^*I] = +2.20$  V vs. Ag/Ag<sup>+</sup> in CH<sub>3</sub>CN) and proved to be a productive catalyst. Several  $\beta$ -benzylated aldehydes were obtained in high yields and stereoselectivities through this methodology. In order to introduce alkyl groups in cinnamyl aldehydes, other suitable radical precursors were investigated, identifying the alternative precursors **37**. By using the *gem*-difluorinated diarylprolinol silyl ether catalyst **OC13** in the formation of chiral iminium ions, the reaction was effective in the presence of potassium alkyl tetrafluoroborates and substituted dihydropyridine **37**. Due to the higher solubility and easy preparation of substituted dihydropyridine, the reaction was described with these substrates

(Figure 18(b)) [70]. In order to improve the stereoselectivity of the reaction, a new chiral amine bearing bulkier perfluoro-isopropyl groups on the arene scaffold was prepared. The new alkylation methodology was general and was investigated with different 4-alkyl-1,4-dihydropyridines, both substituted with linear or cyclic fragments. The enantiomeric excesses obtained for the reaction were all under 90% with yields from moderate to good. More interesting is the possibility to directly form radicals by oxidation of cheap commercially available substrates. Because of the strong oxidation power of the iminium ion in its excited state, an organocatalytic direct C–H functionalization of toluene with Michael acceptors was developed (Figure 18(c)) [71]. The iminium ion in its excited state can trigger the formation of radicals through SET oxidation of inactivated benzyl substrates **39**. In fact, as redox properties of toluene can be evaluated ( $E_{1/2} = +2.26$  V vs. SCE), an oxidation of toluene mediated by the iminium acting as  $^*PC$  seems feasible. The radical cation obtained by oxidations of benzylic C(sp<sup>3</sup>)–H with an enhanced acidity ( $pK_a$  of the radical cation is estimated as  $-13$  in CH<sub>3</sub>CN) and the presence of a weak basic anion could generate the corresponding benzylic radical allowing the photochemical alkylation to take place. The authors, in order to facilitate the formation of iminium, and, at the same time, introduce a non-coordinating weak anion, used zinc triflates in sub-stoichiometric amount. With the optimized conditions, the reaction was shown to be general and suitable to introduce several benzylic derivatives directly when 10 equivalents of the toluene derivative are employed. The reaction was again limited to the employment of cinnamyl aldehydes, and the enantiomeric excesses obtained were in all cases below 84%. However, the reaction tolerates the presence of functional groups in the benzylic position.

Iminium-enamine catalysis can be a suitably coupled for cascade reactions [72]. Radical cascade processes can easily be realized exploiting the capabilities of iminium ions in their excited states. Melchiorre described a two sequential radical-based bond-forming events, using inactivated olefins and  $\alpha,\beta$ -unsaturated aldehydes to provide chiral products in a single step (Figure 19(a)) [73].



**Figure 19:** Photocatalytic annulations based on sequential radical bond-forming events.

Again, the chemistry works due to the powerful oxidizing properties of the iminium ion in its excited state and its ability to oxidize an alkene substrate bearing a carboxylate group in  $\gamma$  position. Upon oxidation driven by the iminium, the alkene was forming a radical cation that was intercepted by the carboxylate oxygen forming a five membered intermediate. This intermediate, by a quite rapid loss of a proton was forming an alkyl radical. The formed alkyl radical can then react with the iminium radical resulting from the electron transfer

event. This radical recombination is followed by hydrolysis of the intermediate enamine. Differently substituted olefins were suitable substrates, affording the products in good yields and stereoselectivities. Not only carboxylic acids but also alcohols can be used to trigger the formation of the radical adduct. Again, only cinnamyl aldehydes can be used, but many substitutions are tolerated on the aromatic moiety. As a last example of this chemistry, another photochemical cascade process that combines the excited-state and ground-state reactivity of chiral organocatalytic intermediates was described by Melchiorre (Figure 19(b)) [74]. The methodology used racemic cyclopropanols as starting material that, by oxidation, can be converted to the  $\beta$ -alkyl radical ketones. As racemic cyclopropanols have oxidation potentials around 1.60 V versus Ag/Ag<sup>+</sup> in CH<sub>3</sub>CN, oxidation of these substrates by the excited state of the enamine is thermodynamically possible. As the intermediate of the radical coupling between the ketone radical and the enamyl radical is an enamine, the carbonyl obtained by fragmentation engages in a stereoselective reaction with the enamine to give quite interesting cyclopentanols. The reaction is quite tolerant toward structural and electronic variations of the coupled substrates, and many complex cyclopentanols, in high yields and ees were obtained. Interestingly also spirocyclic compounds could be prepared.

## 8 Outlook and perspectives

Enamine and iminium activation modes can be effectively combined with PC, enhancing the possibility offered by organocatalysis to control the stereochemistry in product formation. As photoredox catalysis is a clean way to produce active radicals, many new radical reactions will be introduced in the future. In addition, cascade and domino reactions are available combining Michael radical reactions with enamines. As photoredox catalysis will be also possible in the presence of transition metals, the combination of enamine or iminium catalysis with transition metal catalysis triggered by photoredox event, will be certainly investigated. Finally, all investigated processes, involving iminium ions or enamines (with or without PC), were conducted in non-aqueous conditions. Merging water compatible photocatalysis with the chemistry already developed for enamine or iminium catalysis in water, or in the presence of surfactants, will be surely investigated, providing novel clean and green stereoselective processes.

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