Asymmetric Induction in Photocatalysis – Discovering a New Side to Light-Driven Chemistry

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Abstract

The state of asymmetric photocatalysis is exceptionally promising, as chemists from different fields and backgrounds have converged to solve a longstanding issue: stereocontrol in photochemistry. As a strategy that relies heavily on the elevated reactivity of radical intermediates, managing to suppress the background racemic reactions in favor of the stereoselective processes is a challenging endeavor many researchers have embarked on. In order to tackle this matter, conceptually diverse activation modes have been developed, obtaining valuable results across mechanistically-distinct types of reactions, all while setting the stage for future breakthroughs in the field.

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Photochemistry
Asymmetric catalysis
Lewis acid catalysis
Organocatalysis

1. Introduction

Photo-induced transformations have been at the forefront of chemical research for many years, yet lately they have received enormous interest.[1] The basis for modern photocatalytic methodologies is set on the transmission of photons to a specific molecule - a photosensitizer, which can be parlayed into the population of the molecule's excited state. This energy can then be transferred to other substrates via energy or electron transfer, wherein the pairing of excited-state energies and of redox potentials, respectively, of the sensitizer and the reactive substrate is crucial for a successful outcome in photochemical reactions.

Light absorption strategies are frequently employed across organic chemistry to construct bonds that are somewhat difficult to build through traditional two-electron pathways. Conventional formation of carbon-carbon bonds is fundamentally based on reagents that require a preactivation step. However, many photochemical procedures allow the researcher to work with substrates that are simple, diverse, and commercially available. The straightforwardness of these reactions is also latent in the mild conditions under which they usually take place, leading to immense potential in functional group tolerance. Furthermore, the photogeneration of open-shell intermediates is an exciting aspect as well, as they are ideal species to interact with highly-congested carbons in unusually complex molecules. Therefore, direct synthetic routes, which yield novel bond constructions in intricate environments, are discovered.

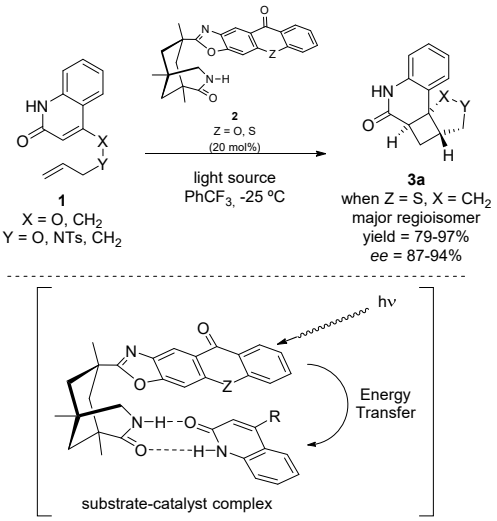
Photocatalytic approaches repeatedly depend on either an external photosensitizer or a photoactive species generated *in situ* by means of substrate-catalyst interactions. As shown in the increasing body of published work in photochemistry, new synthetic pathways can be opened through visible light irradiation, a benign energy source under which organic molecules tend to be inert. Consequently, the more powerful UV irradiation can be avoided.

Asymmetric induction in photochemical reactions is a formidable challenge that has recently been rediscovered by the scientific community.[2] The involvement of high-energy intermediates is translated into short lifetimes for these species and quick follow-up reactions featuring low energetic barriers. For this reason, the implementation of an asymmetric catalyst capable of controlling the sterics of the reaction while also suppressing the background racemic process is the quintessential issue. If the structural variety of these reaction intermediates is considered as well, the development of optimal chiral catalysts that should fit the geometrical prerequisite for each species can be labeled as arduous.

Nevertheless, organic chemists have recognized this challenge by developing a wide array of truly remarkable strategies based on different concepts and applied to several kinds of reactions and substrates. Herein, the most noteworthy contributions to the field of asymmetric photocatalysis are presented.

2. The advent of energy transfer processes. Photocycloadditions and other reactions

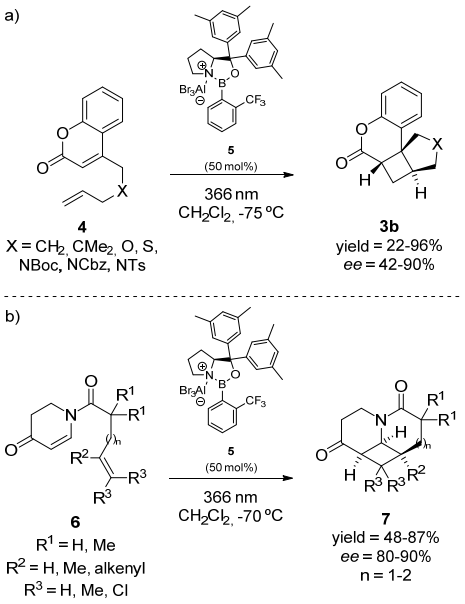
An initial report on enantioselective photocatalysis surfaced in 2005, wherein Bach's group displays initial studies on a photo-induced electron transfer (PET), employing a chiral organocatalyst equipped to fulfil two roles.[3] Firstly, it presents two hydrogen bonding sites to establish a chiral environment around the substrate. Secondly, a benzophenone-type unit can act as a photosensitizer under UV irradiation. This approach was further investigated, yielding excellent results for intramolecular [2+2] photocycloadditions (PCAs) completed with quinolones **1**, presumably catalyzed through an energy transfer process.[4] The substrate-catalyst complex shown in Scheme 1 enables the energy transfer from the light-harvesting xanthone sensitizer **2** to the substrate, which then undergoes the ensuing PCA in enantioselective fashion because of the control element inherent of the rigid oxazole structure. An interesting variant was introduced when the xanthone moiety was replaced by a thioxanthone group, allowing the reaction to proceed under visible light irradiation.[5]



Scheme 1. Bach's PCA strategy employing chiral photo-organocatalysts **2**. Z = O (366 nm), Z = S (400-700 nm).

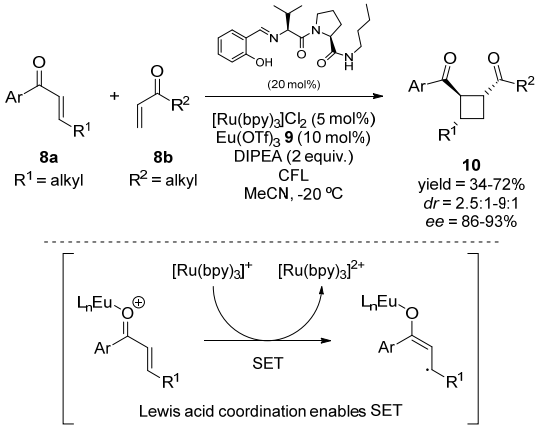
Additionally, Sibi and Sivaguru introduced a different form of H-bond organocatalysis in this field by developing atropoisomeric binaphthyl-derived thioureas to catalyze the intramolecular [2+2] PCA of 4-alkenyl-substituted coumarins.[6] The interaction between the organocatalyst and the substrate leads to a bathochromic shift of the mixture when compared to each component on its own. Irradiation at the appropriate wavelength delivers an enantioselective energy-transfer-driven transformation, while stifling the background racemic reaction.

Bach and co-workers had already disclosed an enantioselective intramolecular PCA of coumarins **4**, featuring in this case the unexplored use of chiral Lewis acids in photochemical reactions (equation a, Scheme 2).[7] Oxazaborolidines activated by $AlBr_3$ (**5**) display exceptional behavior, inducing a bathochromic shift upon coordination to the substrates. Application of these highly-stereoinducing Lewis acids to the intramolecular [2+2] PCA of synthetically useful enones, such as 5,6-dihydro-4-pyridones **6**, was later reported by Bach (equation b, Scheme 2).[8] The strong absorption of the enone-Lewis acid complex prevents any background reaction of uncomplexed enones **4** or **6**.



Scheme 2. Lewis acid-enabled PCAs reported by Bach's group.

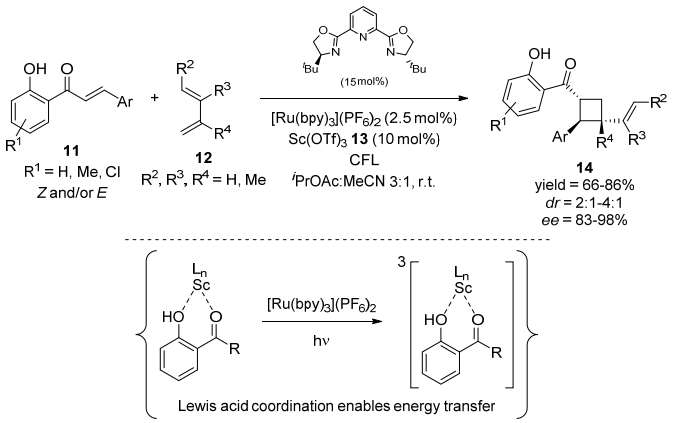
A broader synthetic approach towards cyclobutanes **10** was described in 2014 by Yoon's group (Scheme 3).[9] Lanthanide-based Lewis acids **9** proved to be effective cocatalysts for the promotion of intermolecular [2+2] PCAs, involving α,β-unsaturated ketones **8a** and **8b**. The independent photocatalyst $[Ru(bpy)_3]^{2+}$ used in this transformation gives way to a wider substrate scope since the reaction is no longer dependent on the spectral properties of the starting material.



Scheme 3. Yoon's [2+2] PCA featuring $[Ru(bpy)_3]^{2+}$. CFL: compact fluorescent lightbulb.

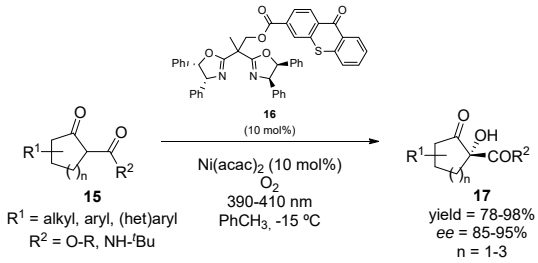
Lewis acid-coordination to the substrate to induce a bathochromic shift in the energy of its singlet excited state represented an alternative to stereoselective energy transfer PCAs (Bach's strategy).[7,8] Yoon expanded this concept, triggering a similar effect on the energy of the triplet excited state of the Lewis acid-substrate complex (Scheme 4).[10] Studies effected on 2'-hydroxychalcones **11** showed a major decrease in the energy of the triplet excited state upon coordination to an oxophilic Lewis acid **13**. Therefore, a suitable photocatalyst had to be selected to ensure the triplet energy transfer takes place solely between the Lewis acid-coordinated substrate and the excited photocatalyst. Once again, excellent scope to obtain cyclobutanes **14** can be achieved following this methodology, which provides a general strategy concerning excited-state photoreactions. Additionally, in a very recent work developed by Meggers, a similar strategy using a chiral rhodium complex enabled the

photocatalytic [2+2] cycloaddition with α,β-unsaturated 2-acyl imidazoles.[11]



Scheme 4. Yoon's energy transfer-driven intermolecular PCA.

Photo-induced energy transfer reactions are mainly linked to [2+2] PCAs. However, other transformations such as aerobic oxygenations have emerged. Xiao and co-workers have developed a photocatalyst **16** containing a thioxanthone component, acting as the energy transfer sensitizer attached to a chiral bisoxazoline-BOX-ligand, which establishes a complex with a suitable Lewis acid and the substrate, thus inducing the enantioselective process on β-keto esters **15** (Scheme 5).[12a] In addition, the ring-opening expansion of cyclopropanes by means of an energy transfer process has been reported with excellent degrees of enantioselectivity.[12c]



Scheme 5. BOX-thioxanthone as bifunctional photocatalyst.

3. Transition metal asymmetric photoredox transformatios

A unique approach tackling enantioselective electron transfer reactions was introduced in 2014 by Meggers: chiral-at-metal photocatalysts (**18**-**19**, Figure 1). These asymmetric species feature a metal center with the ability to act as a photoredox-, a catalytically active Lewis acid-, and a stereoinducing-center.

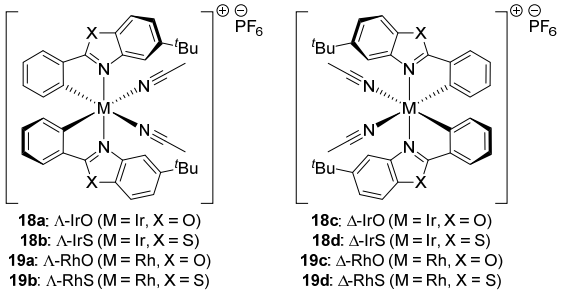
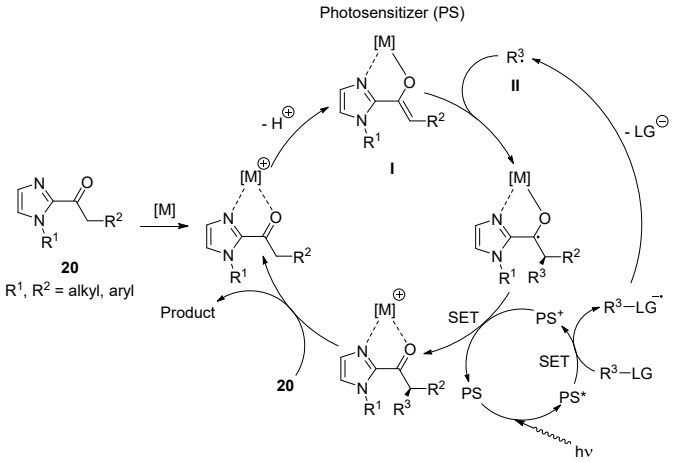


Figure 1. Chiral-at-metal complexes developed by Meggers.

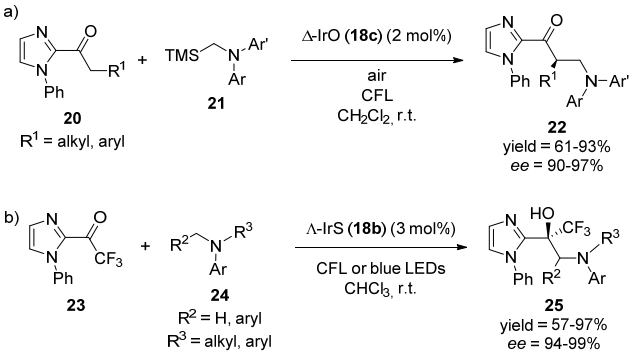
The versatility and generality of the family of catalysts, shown in Figure 1, has been established in diverse reactions. They have proven to be effective following clearly distinct photoredox pathways, while achieving a very generous scope regarding reactivity under their activation.

For instance, chiral iridium complex **18b** (Λ-IrS) successfully photocatalyzes the α-alkylation, α-trichloromethylation and α-perfluoroalkylation of acyl imidazoles **20**.[13] Meggers and co-workers suggest that an iridium-enolate complex intermediate **I** assembled *in situ* acts as the photosensitizer, reaching its excited state upon visible light irradiation and reducing the corresponding radical precursor (Scheme 6). The subsequent carbon-centered radical **II** reacts with enolate **I** to yield the desired α-alkylated product, following SET and release of the iridium complex. Chiral rhodium complex **19c** (Δ-RhO) is also capable of promoting the α-amination of acyl imidazoles **20**, obeying a similar oxidative quenching cycle.[14]



Scheme 6. Mechanism proposal based on the metal-enolate photosensitizing unit **I**. LG: leaving group.

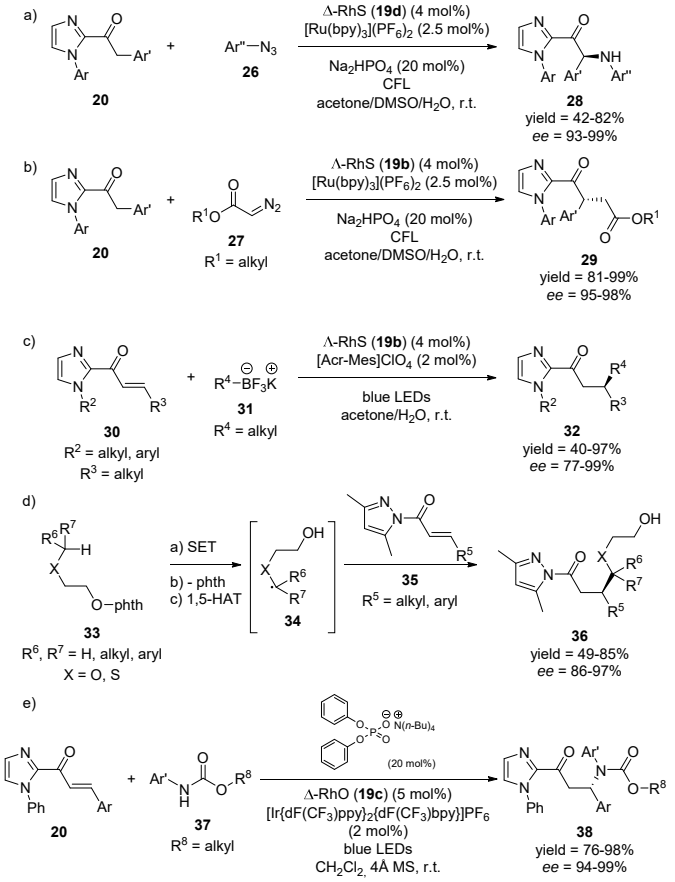
Moreover, impressive results were attained when the octahedral iridium complexes **18c** and **18b** (Δ-IrO and Λ-IrS, respectively) were employed in reductive quenching cycles focused on the single electron oxidation of α-silyl amines **21** in α-amino alkylation reactions. The ability of the iridium catalysts to act as photosensitizer, Lewis acid, and stereocontrol element is fully displayed; firstly, via a chiral enolate nucleophilic attack on an electron-deficient iminium ion (equation a, Scheme 7),[15] and then, through the coupling of an α-aminoalkyl radical and a ketyl radical (equation b, Scheme 7).[16] Furthermore, both publications present partially different mechanisms. The former reaction features a two-electron oxidation of α-silyl amines performed through the combined efforts of the acting photosensitizer (complex **20**-**18c**) and a terminal oxidant (oxygen) to yield the electrophilic iminium species. The latter example, on the other hand, showcases the effect iridium coordination can inflict upon trifluoroacetyl imidazole **23** to facilitate their single electron reduction, and subsequent stabilization of the resultant ketyl radical.



Scheme 7. Alkylations via reductive quenching cycle employing multifunctional chiral-at-metal catalysts. LED: light-emitting diodes.

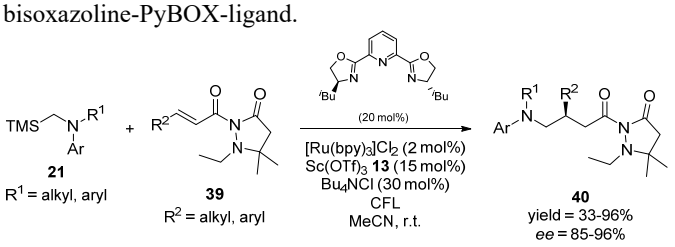
Despite the unequivocal appeal these chiral complexes hold as trifunctional moieties, rhodium-based compound **19b** (Λ-RhS) can function as a chiral Lewis acid catalyst in the presence of an external photocatalyst as well. The scope of the radical-radical cross-coupling, shown in Scheme 7b, was largely increased due to the introduction of a photosensitizing ruthenium polypyridyl complex, enabling the reaction to proceed adequately with any aromatic or aliphatic substituent at the acyl group.[17]

Similarly, the Meggers group has developed a diverse collection of useful transformations following this idea. Novel radical precursors aryl azides **26** and α-diazo carboxylic esters **27** were implemented for the α-amination and α-alkylation, respectively, of 2-acyl imidazoles **20** (equations a and b, Scheme 8).[18] This is an attractive process due to the lack of byproducts (only N_2 is produced) and excellent functional group tolerance displayed by the reaction. Stereocontrolled additions to alkenes **30** and **35** galore in the compilation of methods developed by Meggers' lab (equation c, Scheme 8),[19] some of which interestingly rely on a radical translocation from a heteroatom-centered radical to a carbon-centered radical **34** (equation d, Scheme 8).[20] Lastly, an intriguing β-amination of α,β-unsaturated 2-acyl imidazoles has been recently reported (equation e, Scheme 8).[21] Based on a proton-coupled electron transfer (PCET), highly reactive *N*-centered radicals (generated from *N*-aryl carbamates **37**) undergo a stereoselective radical-radical coupling.



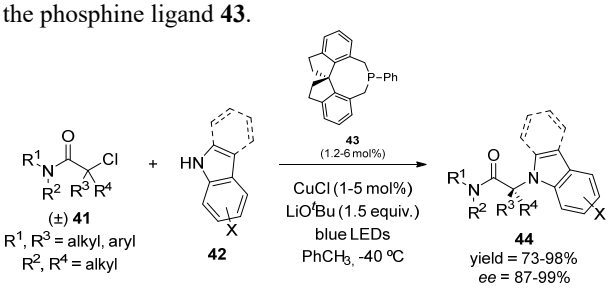
Scheme 8. a-b) α-Functionalization of 2-acyl imidazoles in the presence of a Ru-based external photocatalyst. c-d) Conjugate addition to α,β-unsaturated ketones; phth: *N*-phthalimide, HAT: hydrogen atom transfer. e) β-Amination of α,β-unsaturated ketones governed by a PCET.

Yoon's lab has also contributed towards the involvement of Lewis acids in electron transfer reactions.[22] Through oxidation of α-silyl amines **21** mediated by a Ru-based photocatalyst, the conjugate addition of the corresponding α-amino radicals to Michael acceptors **39** was accomplished (Scheme 9). The scandium Lewis acid **13** plays a significant role by increasing the rate of the reaction and providing a chiral environment around the Michael acceptor through coordination with a chiral pyridine bisoxazoline-PyBOX-ligand.



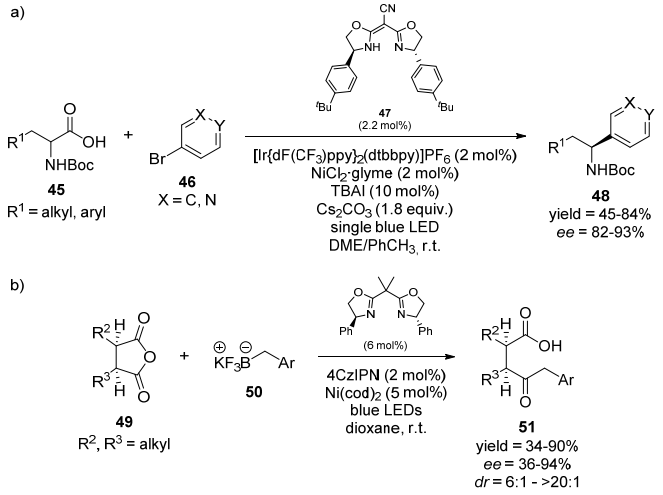
Scheme 9. Yoon's electron transfer-driven conjugate addition.

Copper asymmetric catalysis has been studied for many years, yet its potential to operate as a photocatalyst has been markedly unexplored. However, Fu's group reported an exciting C-N coupling reaction catalyzed by copper in the presence of a chiral phosphine ligand **43** and visible light (Scheme 10).[23] It stands as a rare example, in which tertiary electrophiles **41** are stereoselectively cross-coupled with a nucleophilic partner (a carbazole **42**). The reaction is believed to proceed initially through ligand substitution on the initial copper complex (**43**+CuCl) by the nucleophilic carbazole, leading to a photoactive species capable of absorbing visible light to access an excited state adduct. Following electron transfer to the tertiary alkyl halide **41**, which generates the corresponding radical, the cross-coupling product is obtained after C-N bond formation in an enantioselective manner due to the steric hindrance enforced by the phosphine ligand **43**.



Scheme 10. Visible light-induced C-N cross-coupling reaction catalyzed by Cu.

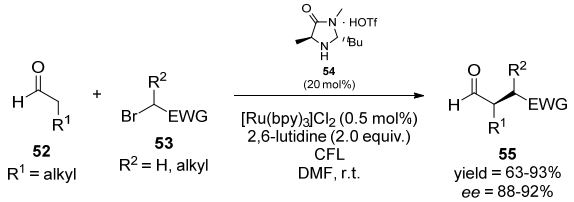
Additionally, Fu's and MacMillan's groups successfully merged photoredox and nickel catalysis to achieve a valuable enantioselective route to benzylic amines **48** from inexpensive materials such as α-amino acids **45** and aryl halides **46** (equation a, Scheme 11).[24] The process follows a photocatalyst-mediated oxidation and decarboxylation of an α-amino acid **45**, generating an α-amino radical, which is trapped by the Ni(II)-aryl complex. Ensuing reductive elimination produces the cross-coupling adduct **48**. Ligand **47** induces the optimal enantioselectivity under the present conditions. Later, Rovis' and Doyle's groups published a similar metallophotoredox procedure (equation b, Scheme 11).[25] A nickel-organophotocatalyst tandem allowed the desymmetrization of cyclic *meso*-anhydrides **49** using benzyl trifluoroborates **50** as radical precursors.



Scheme 11. Metallophotoredox strategies.

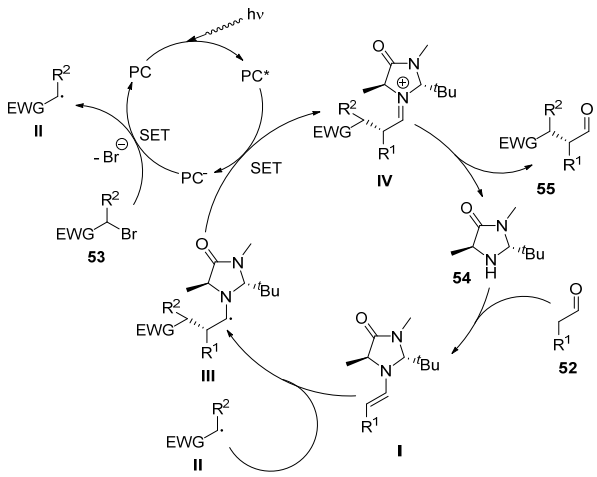
4. Organocatalytic asymmetric photoredox transformations

Nonetheless, MacMillan's seminal work in this area has been linked to his initial report on the merger of photoredox catalysis and organocatalysis in 2008.[26] Founded on the concept of singly occupied molecular orbital (SOMO) catalysis developed by his group, a longstanding challenge in organic chemistry such as the enantioselective α-alkylation of aldehydes **52** was resolved by blending both catalytic approaches into one impressively efficient method (Scheme 12).[27] The α-functionalization process has since been expanded, yielding a great assortment of methodologies including the α-trifluoromethylation,[28] α-benzylation,[29] and α-amination of aldehydes.[30] Moreover, the α-alkylation protocol has been further developed to give access to β-cyanoaldehydes.[31] Additional reports on the α-alkylation and α-alkynylation of β-ketocarbonyls have been published by Luo and co-workers, highlighting the possibility to access full-carbon quaternary centers employing primary amine catalysts.[32]



Scheme 12. MacMillan's initial report on the merger of photoredox catalysis and organocatalysis.

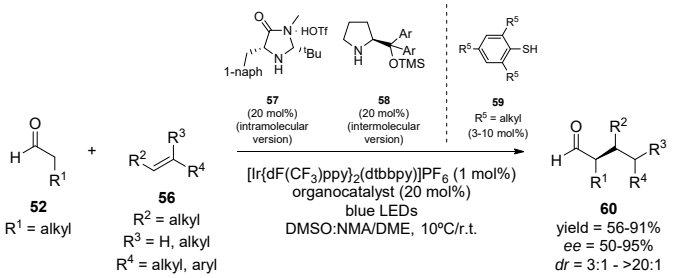
The prototypical mechanism for these transformations is centered on the combination of organocatalytic and photoredox cycles (Scheme 13). From the photocatalyst (PC) standpoint, the initial photoexcitation leads to SET oxidation of a sacrificial amount of enamine **I**. Electron-rich PC$^-$ then reduces the corresponding radical precursor to return to its ground-state while affording electron-deficient radical **II**. On the other hand, the organocatalytic cycle begins with the well-known condensation of a chiral secondary amine (imidazolidinone catalyst **54**) and the aldehyde **52**. The ensuing enamine **I** takes part in the enantioselective C-C bond forming event with the photo-generated radical **II**. Lastly, the SET oxidation of the α-amino radical **III** would generate the iminium ion **IV,** which undergoes fast hydrolysis to afford the final α-alkylated product **55**.



Scheme 13. Mechanism for the α-alkylation of aldehydes.

In-depth analysis provided by Yoon and Melchiorre several years later has otherwise shown that the α-alkylation of aldehydes is mainly governed by a radical chain process in which the photocatalyst only intervenes in an initiation step, while intermediate **III** reduces electron-poor halide **53**.[33]

Recently, a conceptually different α-alkylation of aldehydes **52** has been disclosed by MacMillan's lab, reliant on a multicatalytic system comprised of an organocatalyst (**57** or **58**), an iridium photoredox catalyst and a hydrogen atom transfer (HAT) catalyst **59** (Scheme 14).[34] Photooxidation of the enamine enables the trapping of the generated 3πe$^-$ enaminyl radical by an olefin coupling partner **56**, producing an intermediate, which undergoes HAT to give the final product **60**. Remarkably, the reaction can take place in intra- and intermolecular fashion with perfect atom economy only requiring photons to be propelled.



Scheme 14. Multicatalytic α-alkylation of aldehydes with simple olefins.

Alternatively, Melchiorre and co-workers have established metal-free approaches for the enantioselective α-alkylation of aldehydes (Figure 2, Scheme 15).[35] The chiral organocatalyst is tasked with stereocontrol exertion as well as substrate photoactivation. This process takes place through the formation of colored electron donor-acceptor (EDA) complexes capable of absorbing visible light, which then engage in an SET between the two complexed reacting partners: donor (enamine) and acceptor (alkyl bromide) (Figure 2). Further expansion of this strategy has led to the α-alkylation of unmodified cyclic ketones.[36] Additionally, γ-functionalization of enals via dienamine chemistry was also accomplished, albeit with diminished enantioselectivity.

Although EDA complex formation between chiral enamines and alkyl bromides has unveiled captivating information lying within these transformations, Melchiorre uncovered the hidden photochemical activity of enamines shortly afterwards (Scheme 15).[37] Consequently, the enantioselective α-alkylation of aldehydes **52** and γ-alkylation of enals **61** were completed with bromomalonates **53**, wherein the brominated reagents no longer

require an electron deficient aryl group in their structure since the photoactive species is the enamine instead of the EDA complex. Another application of the direct photoexcitation of enamines can be found in a recent publication disclosed by Melchiorre's lab, yielding a formal α-methylation and α-benzylation of aldehydes.[38]

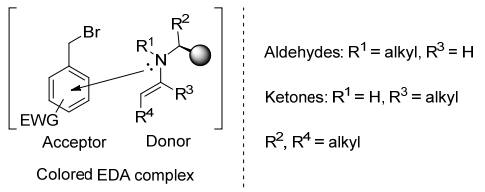
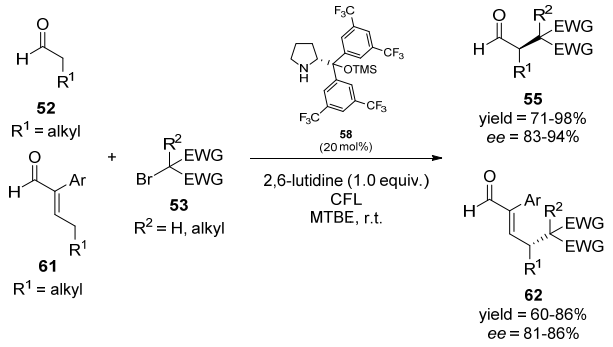


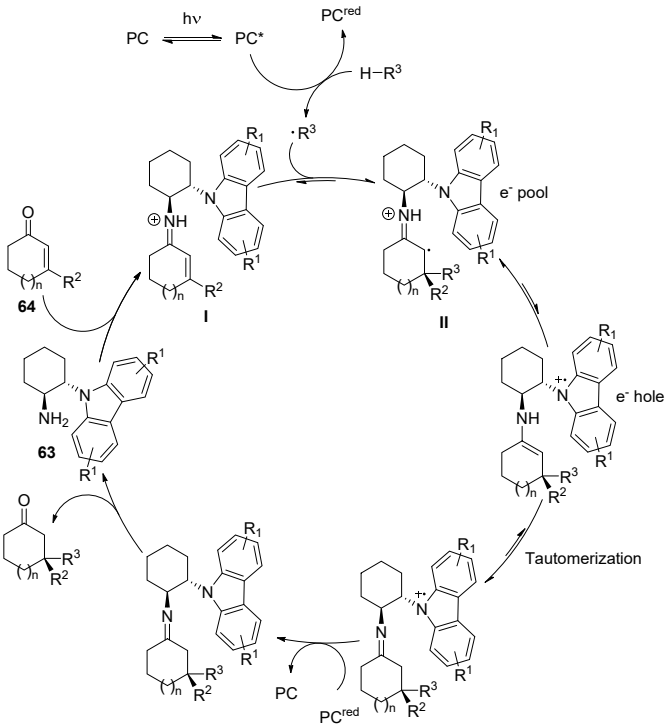
Figure 2. Colored EDA complex strategy exploited by Melchiorre.



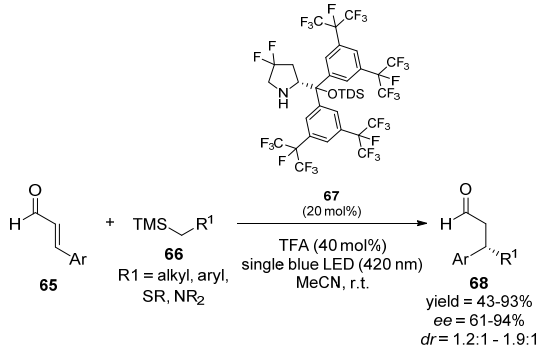
Scheme 15. Alkylation of aldehydes via direct photoexcitation of enamines.

Despite the prominence of enamine chemistry in asymmetric photocatalysis, there has been a striking lack of reports on chiral iminium-mediated photochemical procedures. This is largely due to the short-lived α-iminyl radical cation **II** shown in Scheme 16 formed upon radical conjugate addition (RCA) to an iminium cation **I**. Melchiorre's initial answer to this challenge was to locate a redox-active moiety in the organocatalyst **63**, therefore stabilizing the radical cation **II** long enough for the electron-relay strategy to come to fruition and avoiding the back electron transfer from **II** to **I**.[39] Therefore, a carbazole unit proved to be an ideal scaffold serving as an e^- pool and e^- hole entity throughout the process, and it was consequently added to the cyclohexylamine organocatalyst framework to fulfil the β-functionalization of β,β-disubstituted cyclic enones **64**. Unlike the majority of Melchiorre's work, external photocatalysts are required to power the photochemical reaction, whether through an HAT mechanism (TBADT) or an SET mechanism (iridium complex).

In an attempt to increase the applicability of chiral iminium ions in photochemistry and complement the variety of methods regarding photofunctionalization of enamines already in place, the latest groundbreaking work by Melchiorre's group focuses on the enantioselective β-alkylation of enals **65** (Scheme 17).[40] In this report, a similar approach to the one followed in the direct excitation of enamines is taken, bypassing the issues RCAs present in iminium chemistry. They envisioned that an electronically excited iminium ion could perform as a strong oxidant in the SET reduction of a given radical precursor. Indeed, after proper design and tailoring of the electronic properties of the employed organocatalyst **67**, the radical-radical coupling is completed with solid levels of both reactivity and enantiocontrol.



Scheme 16. Electron-relay mechanism for the β-functionalization of β,β-disubstituted cyclic enones. n = 0-3; R^1, R^2, R^3 = alkyl. PC = tetrabutylammonium decatungstate (TBADT) or $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$.



Scheme 17. Enantioselective β-alkylation of enals via direct photoexcitation of iminium ions.

Lastly, several types of organocatalytic-based activations found across pre-established methods in organocatalysis have also been utilized in distinct photocatalytic procedures, i.e. *N*-heterocyclic carbenes (NHCs),[41] phosphoric acids,[42] thioureas,[43] and aminophosphonium ion-pairing.[44] A noticeable common thread in these final dual catalytic procedures is the presence of an external photocatalyst thrust into the reaction mixture with one specific goal: the generation of the highly reactive radical species. On the other hand, the organocatalyst establishes its featured interaction with the other reagent partner, enforcing the stereocontrol upon the reaction and affording an enantioselective process.

5. Conclusions

The recent renaissance in photocatalysis has driven researchers to solve persistent shortcomings in this field which have prevented its growth and development. As proof of concepts, racemic transformations can be incredibly useful for the scientific community. However, the asymmetric versions of racemic methodologies give access to purposefully relevant product syntheses in drug discovery and development.

Therefore, asymmetric photocatalysis has received heightened levels of attention over the past decade. Several strategies have been outlined over that time frame attempting to cover the different classes of reactivities frequently found across photochemistry. Noteworthy activation pathways summarized in this review, such as chiral Lewis acid catalysis and organocatalysis, have been brilliantly used in photochemical processes to ensure stereoselectivity.

Notwithstanding the large amount of work published in asymmetric photocatalysis, we believe chemical researchers will continue to tackle the remaining weaknesses in the field as it flourishes and matures into one of the most relevant topics in organic chemistry.

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