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Bifunctional photoredox catalysts in asymmetric synthesis.

Catalitzadors bifuncionals fotoredox en síntesi asimètrica.

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Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less.

Marie Curie

Per començar, agrair al meu tutor, el Dr. Alberto Moyano, per la seva dedicació i per haver-me guiat quan ho he necessitat durant el transcurs del treball.

També agrair als amics i companys, que han contribuït amb tants bons moments i sempre hi han sigut per alleujar els més difícils.

Finalment, a la meva família pel seu suport incondicional i per què sempre m'han animat a continuar endavant.

REPORT

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1. SUMMARY

The demand for chiral compounds, often as single enantiomers, has escalated sharply in recent years, driven particularly by the demands of the pharmaceutical industry, but also by other applications, including agricultural chemicals, flavours, fragrances, and materials. This widespread demand for chiral compounds has stimulated intensive research in asymmetric or enantioselective synthesis, a key process in modern chemistry. On the other hand, photocatalysis, an environmentally friendly and sustainable form of energy for triggering chemical transformations, has emerged as one of the best strategies for the synthesis of organic compounds.

When enantiopure products are desired, it is difficult to control product formation since excited states have short lifetimes and it makes challenging to control electron transfer process which leads the catalyst to not dictate the stereochemistry of the products so that the transformations taken into account provide achiral or racemic compounds. Additionally, merging the photoredox catalyst with a chiral catalyst is difficult because of the high reactivity and low activation barriers of radical intermediates. In spite of this awkwardness, asymmetric photocatalytic transformations nowadays have been successfully accomplished by using a dual-catalyst approach using a combination of a photocatalyst and a chiral organocatalyst and also with only one catalyst, named a bifunctional catalyst, where the same molecule has a cromophore unit and a catalytic unit so that it combines chirality and photoredox properties. In such transformations, visible-light redox sensitizers are combined with asymmetric catalysts (either in a single molecule or in a dual catalysis system), such as chiral secondary amines, chiral N-heterocyclic carbenes, chiral Brønsted acids, chiral Lewis acids, or chiral thiourea under mild reaction conditions.

Overall, in asymmetric photoredox catalysis the photoactivated sensitizers (or the bifunctional catalyst with photoexcitation) initiate a SET from or to a closed-shell organic or metallic molecule to produce radical cations or radical anions whose reactivities are then exploited to synthetize the desired enantiopure product. To sum up, these advances allow it to forge a green, sustainable and economical chemistry without forgetting enantioselective properties.

Keywords: aminocatalysis, Lewis acid catalysis, metal catalysis, organocatalysis, enamine catalysis, hydrogen bond catalysis, photoredox catalysis, asymmetric catalysis, bifunctional catalyst, enantioselective catalysis, sustainable chemistry, green chemistry.

2. RESUM

La demanda de compostos quirals, sovint com a enantiòmers simples, ha augmentat considerablement en els darrers anys, sobretot per les demandes de la indústria farmacèutica, però també per altres aplicacions, incloent productes químics agrícoles, sabors, fragàncies i materials. Aquesta demanda generalitzada de compostos quirals ha estimulat la investigació intensiva en síntesi asimètrica o enantioselectiva, un procés clau en la química moderna. D'altra banda, la fotocatàlisi, una forma d'energia sostenible i respectuosa amb el medi ambient per desencadenar transformacions químiques, ha sorgit com una de les millors estratègies per a la síntesi de compostos orgànics.

Quan es desitgen els productes enantiomèrics, és difícil controlar la formació del producte ja que els estats excitats tenen un temps de vida curta i és difícil controlar el procés de transferència d'electrons que provoca que el catalitzador no pugui controlar la estereoquímica dels productes, de manera que les transformacions proporcionen compostos aquirals o racèmics. A més, la fusió del catalitzador fotoredox amb un catalitzador quiral és desafiant a causa de l'elevada reactivitat i les baixes barreres d'activació dels intermediaris radicalaris. Malgrat aquesta complicació, avui en dia les transformacions fotocatalítiques asimètriques s'han aconseguit amb èxit combinant un fotocatalitzador i un organocatalitzador quiral o bé amb un catalitzador bifuncional, on la mateixa molècula té un cromòfor i una unitat catalítica, de manera que combina quiralitat i propietats fotoredox. En aquestes transformacions, els sensibilitzadors redox de llum visible es combinen amb catalitzadors asimètrics (ja sigui en una sola molècula o en un sistema de catàlisi dual), com ara amines secundàries quirals, carbens N-heterocíclics quirals, àcids quirals de Brønsted, àcids quirals de Lewis o tiourea quiral en condicions de reacció suaus.

En general, en la catàlisi fotoredox asimètrica, els sensibilitzadors fotoactivats (o el catalitzador bifuncional amb fotoexcitació) inicien la transferència d'un electró a partir d'una molècula orgànica o metàl·lica per tal de produir cations radicalaris o anions radicalaris, que després s'utilitzen per sintetitzar el producte enantiomèricament desitjat. En resum, aquests avenços permeten forjar una química verda, sostenible i econòmica sense oblidar l'enantioselectivitat.

Paraules clau: aminocatàlisi, catàlisi per àcid de Lewis, catàlisi metàl·lica, organocatàlisi, catàlisi per enamina, catàlisi per enllaç d'hidrogen, catàlisi fotoredox, catàlisi asimètrica, catalitzador bifuncional, catàlisi enantioselectiva, química sostenible, química verda.

3. INTRODUCTION

The demand for chiral compounds, often as single enantiomers, has escalated sharply in recent years, driven particularly by the demands of the pharmaceutical industry, but also by other applications, including agricultural chemicals, flavors, fragrances, and materials. Although the most obvious applications are bio-related, materials science also relies on the properties imparted by chirality, notably in chiral polymers and liquid crystals[1]. This widespread demand for chiral compounds has stimulated intensive research in asymmetric or enantioselective synthesis, a key process in modern chemistry. Asymmetric synthesis is defined by the IUPAC as *a chemical reaction (or reaction sequence) in which one or more new elements of chirality are formed in a substrate molecule and which produces the stereoisomeric (enantiomeric or diastereoisomeric) products in unequal amounts*[2], so that asymmetric catalysis consists in the use of one pure enantiomeric chiral catalyst in order to carry out the synthesis of the desired enantiomer with chiral reagents.

On the other hand, photocatalysis has emerged as one of the best strategies for the synthesis of organic compounds. It consists in a change in the rate of a chemical reaction or its initiation under the action of ultraviolet, visible or infrared radiation in the presence of a substance, the photocatalyst, that absorbs light and is involved in the chemical transformation of the reaction partners[3].

Nevertheless, most of the transformations taken into account provide achiral or racemic compounds using both metallic complexes and organic molecules as the photocatalysts. These results are obtained because the photocatalyst cannot induce a stereochemical control and merging it with a chiral catalyst is difficult because of the high reactivity and low activation barriers of radical intermediates. In spite of this awkwardness, asymmetric photocatalytic transformations have been studied and nowadays have been successfully accomplished by the use of a dual-catalyst approach using a combination of a photocatalyst and a chiral organocatalyst and also with only one catalyst[4], named a bifunctional catalyst, that combines chirality and photoredox properties.

Lots of strategies have been developed in which efficient catalytic photochemical processes that work under stereochemical control and provide chiral molecules in an asymmetric fashion can be carried out by two catalysts in tandem for a single chemical transformation. In such dual-catalyst reactions, visible-light redox sensitizers are combined with asymmetric co-catalysts, such as chiral secondary amines, chiral N-heterocyclic carbenes, chiral Brønsted acids, chiral Lewis acids, or chiral thiourea. With respect to single catalysts, ultraviolet light in combination with hydrogen bonding or Lewis acid interaction has been used in triggering enantioselective catalysis. In addition, photoactivated enamine catalysis, in which a transient electron donor–acceptor complex is capable of absorbing visible light and triggering a charge transfer, is another pathway in bifunctional photoredox asymmetric catalysts.

3.1. PHOTOREDOX CATALYSIS

Owing to its natural abundance, ease of use, and fascinating potential of applications, visible-light photoredox catalysis has been developed into a powerful tool to construct carbon−carbon or carbon−heteroatom bonds in organic synthesis. Through high-energy intermediates such as radicals and radical ions, unique reactions that are unavailable under thermal conditions can be accessed. Significant advances have been achieved in this field by employing ruthenium(II), iridium(III) complexes, or organic dyes as photoredox catalysts[5,6].

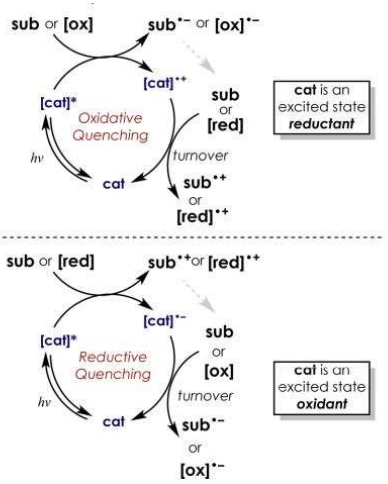

Figure 1: Oxidative and Reductive Quenching Cycles of a Photoredox Catalyst[7]

Photoredox catalysis is a branch of catalysis that harnesses the energy of light to accelerate a chemical reaction via single-electron transfer events. In particular, it employs small quantities of a light-sensitive compound that, when it is excited by light, can mediate the transfer of electrons between chemical compounds that would usually not react at all. Most photoredox catalytic reactions follow one of the two mechanistic schemes depicted in figure 1.

In a catalytic photochemical reaction, the catalyst acts as an antenna collecting the light and transferring it to the substrate via sensitization. Sensitization can occur by energy or electron transfer. The most successful enantioselective sensitizers rely on chirality transfer in a conformationally restricted exciplex[8]. Photosensitization provides the opportunity to induce single electron-transfer (SET) processes under very mild conditions, thereby producing intermediate radical ions and radicals with useful reactivities[9]. A direct photoinduced electron exchange between two involved substrates, one electron acceptor and one electron donor, creates two odd-electron species, which then generate a new bond upon radical–radical recombination[10].

In photochemical reactions applied to synthesis, light plays the role of a reagent that induces a transformation of a chemical compound as it is more commonly done by chemical reagents. In this context, the photon is considered as a traceless reagent. This effect is explained by the fact that electronic excitation by light absorption causes a particular reactivity that is often complementary to that of the ground state. In this regard, combination of catalysis with photochemical reactions should generate synergistic effects for sustainable transformation of matter[11].

Different labels can be used to describe molecules which participate in light driven chemical processes without being consumed, like photocatalyst, photosensitizer (or simply sensitizer), and PET sensitizer. Maybe the term photoredox catalyst provides a more precise definition because the implication of the catalytic involvement of photons, which is relevant in transformations which proceed by chain mechanisms but is misleading for those that do not, and also sensitizer is a term traditionally used to describe a molecule which participates in energy transfer processes, particularly where dioxygen (O_2) is involved[7]. To sum up, the term photoredox includes the fact that after the excitation of the catalyst by light (what would be photocatalysis succinctly) a SET event occurs.

These catalysts are generally drawn from three classes of materials: transition-metal complexes (which lead to reductive reactions), organic dyes (like arenes and amines, which

perform oxidative reactions), and semiconductors. Photoredox reactions tend to be reductive or oxidative reactions as well as neutral redox reactions. In reductive reactions an electron donor is required to serve as the stoichiometric reductant likewise species that can function as a stoichiometric electron acceptor it may lead to oxidative reactions. Finally, in neutral reactions the substrate or substrates undergo both a single-electron oxidation and a single-electron reduction at disparate points in the reaction mechanism. As a result, there is no net oxidation state change between starting materials and products, and no stoichiometric external components are required to turn over the photocatalytic cycle[12].

A photoinduced electron transfer (PET) is an excited state electron transfer process by which an excited electron is transferred from donor to acceptor. When a photon excites a molecule, an electron in a ground state orbital can be excited to a higher energy orbital. This excited state leaves a vacancy in a ground state orbital that can be filled by an electron donor. It produces an electron in a high energy orbital which can be donated to an electron acceptor. In these respects, a photoexcited molecule can act as a good oxidizing agent or a good reducing agent.

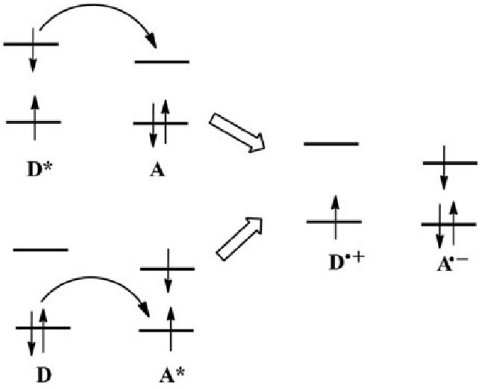

Figure 2: Schematic representation of PET (D is electron donor, A is electron acceptor, and * denotes an excited state)[13]

3.2. ASYMMETRIC CATALYSIS

Structural and stereochemical complexity is often associated with superior biological properties regarding target affinity and binding selectivity and has therefore become an important concept for drug development[14]. The good selectivity achieved when using also complexes and organic molecules in asymmetric catalysis has been demonstrated in asymmetric transformations through various mechanisms, including hydrogen bond donor–acceptor, secondary amine or

Brønsted base hydrogen-bond donor bifunctional catalysis, Lewis acid and photoredox catalysis under mild reaction conditions[15]. In the following sections the main types of asymmetric catalysis are going to be discussed.

3.2.1. Lewis Acid Catalysis

In Lewis acid catalysis of organic reactions, a metal-based Lewis acid acts as an electron pair acceptor to increase the reactivity of a substrate. The metal atom forms an adduct with a lone-pair bearing electronegative atom in the substrate, such as oxygen, nitrogen, sulfur, and halogens. The complexation has partial charge-transfer character and makes the lone-pair donor effectively more electronegative, activating the substrate. Asymmetric catalysis by Lewis acids rely on catalysts with chiral ligands coordinated to the metal center. Over the years, a small number of chiral ligand scaffolds have stood out as having privileged catalytic properties suitable for a wide range of applications, often of unrelated mechanisms. Current research efforts in asymmetric Lewis acid catalysis mostly utilize or modify those ligands rather than create new scaffolds. These scaffolds share a few common features, including chemical stability and relative ease of elaboration. The majority of the scaffolds are multidentate. Most of them also have high scaffold rigidity within the ligand; the catalysts are almost invariably rendered chiral by using chiral ligands (it is also possible to generate chiral-at-metal complexes using simpler achiral ligands).

Lewis acids are capable of activating a large variety of carbon-heteroatom and carbon–carbon bond forming reactions and chiral Lewis acids have therefore become indispensable tools for asymmetric catalysis. Their canonical design consists of a central metal ion coordinated to chiral organic ligands so that one-point or two-point binding of a substrate to the Lewis acidic metal ion activates the substrate towards nucleophilic or electrophilic attack by a co-substrate or reagent and at the same time provides the mode of asymmetric induction by transferring chirality from the organic ligands to the product, typically through shielding one face of a prochiral center[16].

3.2.2. Enamine Catalysis

The catalysis by primary and secondary amines of electrophilic substitution reactions in the α-position of carbonyl compounds and related reactions via enamine intermediates are called enamine catalysis. Enamine catalysis is a general activation mode in which the formation of an enamine from a secondary amine and a carbonyl compound activates the α- position of the carbonyl toward a range of electrophilic functionalization reactions.

One strategy in this subfield is the use of chiral secondary amines to activate carbonyl compounds. In this case, amine condensation with the carbonyl compound generates a nucleophilic enamine[17]. The chiral amine is designed so that one face of the enamine is sterically shielded and so that only the unshielded face is free to react.

3.2.3. Hydrogen bond Catalysis

Hydrogen-bond catalysis is a type of organocatalysis (form of catalysis whereby the catalyst is an organic molecule consisting of carbon, hydrogen, sulfur and other non metal elements) that relies on use of hydrogen bonding interactions to accelerate and control organic reactions. Catalytic amounts of hydrogen-bond donors can promote reactions through a variety of different mechanisms. During the course of a reaction, hydrogen bonding can be used to stabilize anionic intermediates and transition states. Alternatively, some catalysts can bind small anions, enabling the formation of reactive electrophilic cations. More acidic donors can act as general or specific acids, which activate electrophiles by protonation. A powerful approach is the simultaneous activation of both partners in a reaction, for example nucleophile and electrophile. In all cases, the close association of the catalyst molecule to substrate also makes hydrogen-bond catalysis a powerful method of inducing enantioselectivity.

Nevertheless, Lewis acid catalysis has been more developed than hydrogen bond catalysis because current known reactions are very substrate specific and generally exhibit low rate acceleration and turnover, thus requiring high catalyst loading[18, 19].

4. OBJECTIVES

The aim of this project is to critically review asymmetric photocatalytic transformations and the catalysts that are used in that.

Until a past few years, these transformations were accomplished by means of a dual-catalyst system, composed by the combination of a photocatalyst and a chiral organocatalyst. Now, some scientists have developed chiral bifunctional catalysts, where the same molecule has a chromophore unit and a catalytic unit (Lewis acid, Lewis base, hydrogen-bond donor, transition metal…). Therefore, this project is primarily focused on these new researches, even so a brief review about the pioneer dual systems is going to be done.

Additionally, the understanding and summarisation of the chemical processes that take place in these transformations and the exploration of the topic in different databases have been set as objectives.

5. METHODS

The bibliographic research has been done using scientific data bases as SciFinder, Reaxys, ResearchGate and Google Scholar.

In order to contextualize; the project has been started with the exploration of one article about the topic; *A Bifunctional Photoaminocatalyst for the Alkylation of Aldehydes: Design, Analysis, and Mechanistic* from J. Alemán and co-workers. Due to this read, an example of the processes and transformations that are going to be studied has been probed.

SciFinder has been of great help, thematic searches with "bifunctional photoredox catalyst" or "catalysis" and "in enantioselective synthesis" or "in asymmetric synthesis" have conducted to get pleasant results. After the exploration of the twelve references found, six articles have been selected to be reviewed. The starter reference has also been found in this search.

Reaxys has not been so useful; nine references have appeared and seven of these concur with the results of SciFinder. The different two articles found have been discarded because the catalyst used in the related transformations is not bifunctional.

Moreover, a search in Google Scholar, using the title of the project as keyword, has been done with no favourable results; more than two thousand results were found. Research Gate has been also useful; although there were not as many published papers as in other data bases, but it has served to look for short and concise definitions.

Once the literature found on the databases was revised, the references cited on these articles were examined carefully in order to locate more chemical processes with this type of catalysts involved. Through this revision nineteen new articles have been incorporated to the literature with which the review is going to be done.

To follow up, the results were analysed visually one by one to ascertain whether the chemical transformations gathered the desired characteristics. Because the search was made using different databases and strategies, some results were duplicated, and it was necessary to reject those. Finally, a table was generated to organize the selected data, which is collected in appendix 1.

6. RESULTS AND DISCUSSION

As it has been described before, PET is frequently used to synthetize complex molecules from simple precursors. These reactions start with the generation of molecules in excited electronic states, because of the light absorption, that are capable of accepting or donating electrons. If enantiopure products are desired, it is difficult to control product formation since excited states have short lifetimes and it makes challenging to control electron transfer process which leads the catalyst to not dictate the stereochemistry of the products[20]. This is the reason why lately it has been examined dual-catalyst or bifunctional catalyst systems, so that the catalyst not only takes part in photoredox process but also acts as an asymmetric catalyst.

In most reported examples, this task is shared by two catalysts, a photoredox sensitizer for triggering light-induced redox chemistry, in combination with an asymmetric catalyst to provide the activation of one substrate and the required stereodifferentiation[21]. In recent years good few examples of bifunctional catalysts have been applied to different organic transformations in which enantioselectivity is a very important thing. In the ensuing pages it is going to be related the advances that have occurred in terms of bifunctional photoredox and asymmetric catalysis with a single molecule as a catalyst in the last decade. The results are classified as concerns the mode in which asymmetric catalysis is undergoing.

6.1. HYDROGEN BOND CATALYSIS

The first works in this area are from Bach, who described a catalytic photoinduced electron transfer reaction with high enantioselectivity using an electron accepting chiral organocatalyst acting as hydrogen bond catalysis. The reaction devised for this study, shown in figure 4 was based on PET catalysed conjugate additions of α-amino alkyl radicals to enones that had been performed previously with non-enantioselectivity. In the mentioned reaction, the catalyst used, displayed in figure 3, served only as a PET catalyst, thus enantioselectivity was not achieved.

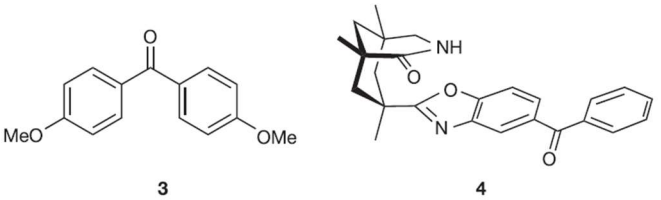

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Figure 3: Structures of the achiral PET catalyst (3) and the chiral enantiomeric PET catalyst (4)[8].

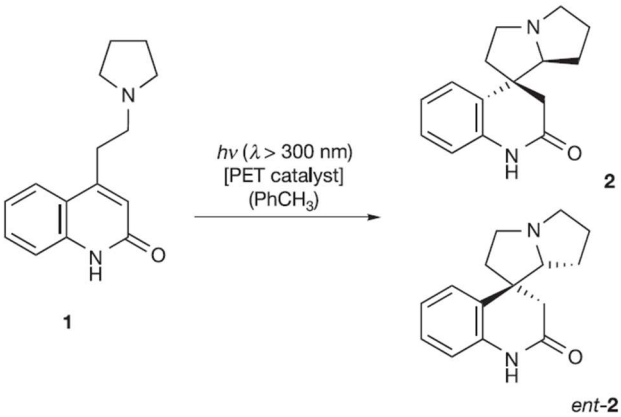

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Figure 4: PET-catalysed cyclization of the prochiral substrate (1) to the chiral pyrrolizidine (2) and its enantiòmer (ent-2)[8].

With the presence of the catalyst with enantioselective control, exhibited on figure 3 also at the right, ultraviolet irradiation induces a PET from the amine to the photoexcited catalyst and the subsequent proton loss from the intermediate cation radical presumably leads to an α-aminoalkyl radical which adds intramolecularly to the quinolone. Finally, after the radical addition, back electron transfer from the catalyst generates an enolate, which is protonated to yield the products. The catalyst used for this reaction, serves not only as a PET catalyst, but also as a stereo controlling device inducing the desired enantioselectivity. The mechanistic details of this reaction were not elucidated by the authors, but it is known that the chirality multiplication was due to hydrogen-bond catalysis[8].

6.2. ENAMINE CATALYSIS

In 2013, Melchiorre and his companions reported chiral amines as organic catalysts, with well-known utility in thermal asymmetric processes, that conferred a high level of stereocontrol in synthetically relevant intermolecular carbon-carbon bond forming reactions driven by visible light without any photosensitive unit. It was well-established that chiral secondary amines guided the transient formation of photon-absorbing chiral electron donor-acceptor (EDA) complexes and an in-cage radical combination as the stereodefining step was involved. The reaction studied, consisting in α-alkylation of aldehydes with alkyl halides, starts with the formation of a photon-absorbing enamine-derived EDA complex, which is necessary to initiate the photochemical process. Then, photoinduced electron transfer occurs and the alkyl radical generated undergoes combination with its chiral enamine radical cation partner in the solvent cavity of their origin[20]. The mechanism described can be seen in figure 5.

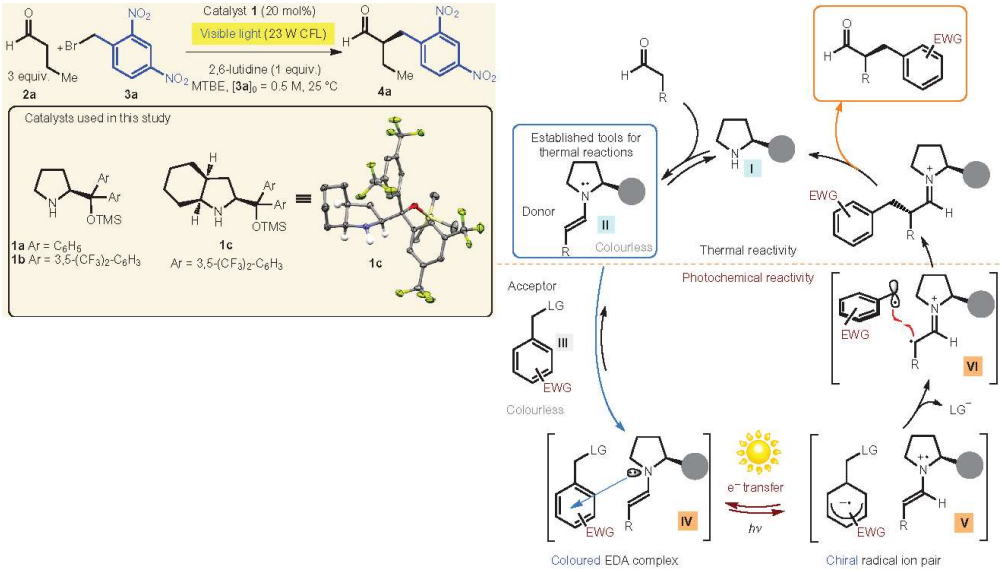

Figure 5: Mechanistic proposal for the photochemical organocatalyzed direct a-alkylation of aldehydes and ketones[20].

Furthermore, the same group described and effective alternative for the direct functionalization of simple ketones. As in the case of aldehydes, the process is a molecular aggregation which occur in the ground state upon association of the transiently generated electron-rich enamine EDA complex (the donor, formed from the condensation of an aldehyde or

ketone and a chiral amine) with the electron-accepting alkyl bromide. The mechanism of this asymmetric alkylation of cyclic ketones with alkyl bromides, leading to the formation of α-alkylated products[22], follow the same guidelines as in figure 5.

Alternatively, enamines can also reach an electronically excited state upon simple light absorption and then to act as effective photosensitizers and not are limited to form ground state EDA complexes[23]. This absorption leads to a chain propagation mechanism illustrated in figure 6. The two blended processes in the way enamine can act are compared in figure 7.

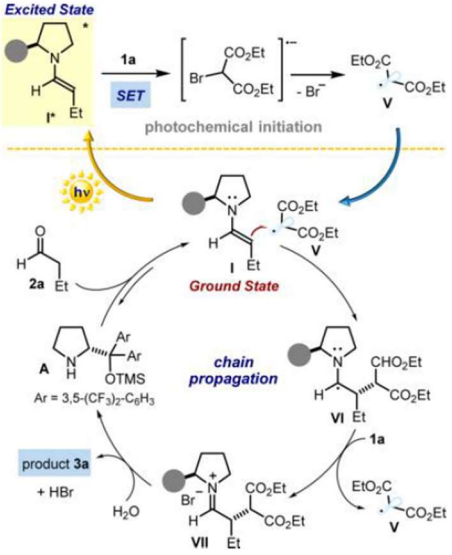

Figure 6: Mechanism of enamines in the ground and excited states[23].

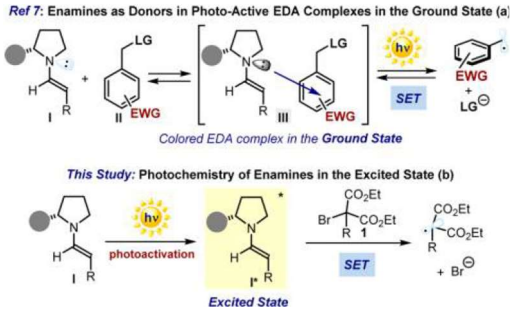

Figure 7: Mechanisms that enamines can use to drive the photochemical generation of radicals; a) by inducing ground state EDA complex formation; b) acting as a photosensitizer upon direct photoexcitation[23].

A few years later, Alemán and co-workers developed a photoaminocatalyst, composed by 4-imidazolidinone because it was the one employed in alkylation of aldehydes in most of dual catalytic systems and it possess two groups that could allow the incorporation of two different units; one photocatalytic unit and a group for the modulation of the steric hindrance of the aminocatalyst. The photoredox properties came from the thioxanthone, a photo-organocatalyst which is combined with the amino-organocatalyst, imidazolidinone.

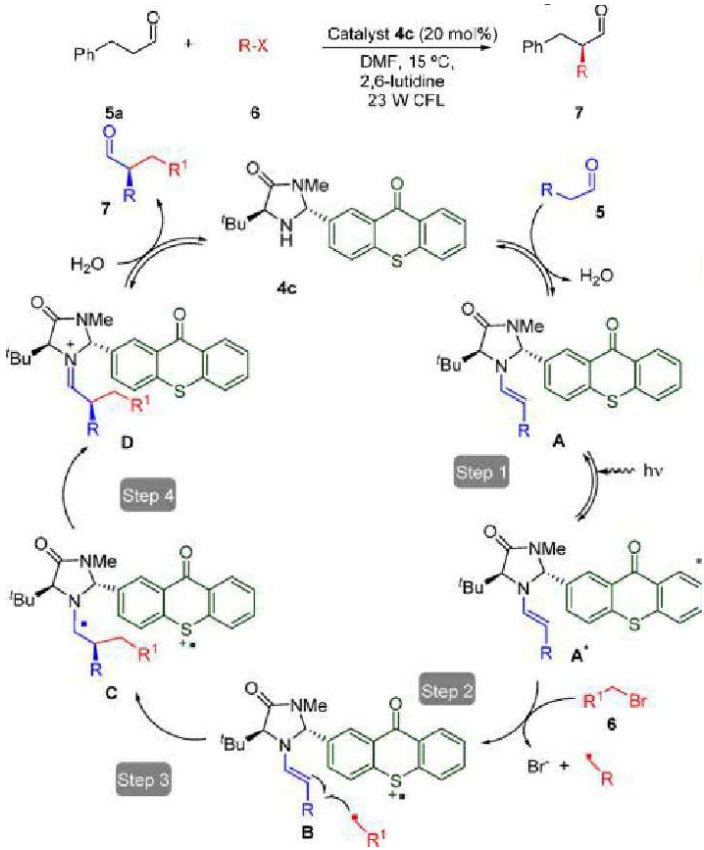

Figure 8: Proposed mechanism for the α-alkylation of aldehydes in accordance with the original mechanism proposed by MacMillan[4].

The first proposal was according to the original mechanism proposed by MacMillan and others. In figure 8 is outlined the mechanism for the photoalkylation of aldehydes. The reaction starts with the condensation of catalyst 4c with aldehyde 5 to give the first enamine intermediate A.

The thioxanthone moiety of intermediate A can absorb light to reach excited intermediate A* (step 1). It is well-known that thioxanthones can promote a SET. Therefore, this excited intermediate A* can reduce the bromoalkane derivative 6 (step 2) through a SET reduction, to give intermediate B and the alkyl radical. Then, the alkyl radical is added to the nucleophilic enamine B to yield α-amino radical C that can be intramolecularly oxidized by the thioxanthone radical cation. Finally, the resultant iminium D is hydrolyzed to give the final α-alkylated aldehyde 7.

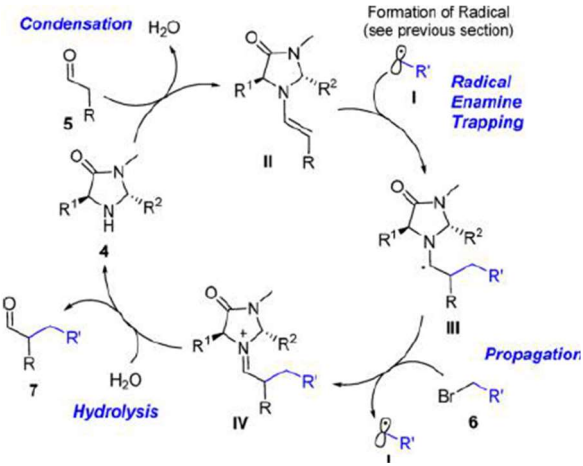

Figure 9: Accepted radical chain propagation process for the α-alkylation of aldehydes[4].

Then, the initiation step under bifunctional catalysts proceeded toward the tioxanthone was also conclude. In this radical I is trapped by enamine II to form α-amino radical III that can be oxidized by bromo derivative 6. Next, the generated iminium ion IV is hydrolyzed to recover catalyst 4. Therefore, the generation of additional radical species to react with II, via the initiation process, is unnecessary because propagation of the process can take place (6 to I)[4].

6.3. METAL-LEWIS ACID CATALYSIS

Initially, Meggers and co-workers developed asymmetric photoredox transition-metal catalysis, an issue that has been acutely explored afterwards and lots of examples and applications are reported nowadays. They envisioned the combination of the facts that photosensitizers are typically based on transition-metal complexes and that chiral transition-metal complexes are on type of asymmetric catalysts in one single transition-metal based catalyst acting in photoredox and in asymmetric catalysis processes.

6.3.1. Iridium

At first, the study was conducted by chiral-at-metal iridium (III) complex coordinated by two achiral bidentate ligands and two additional labile acetonitriles that gave acces to Lewis acid metal centre (figure 10). These chiral Lewis acid were designed to intertwin chiral enolate catalysis with photoredox radical ion chemistry when activating α,β-unsatured 2-acyl imidazoles.

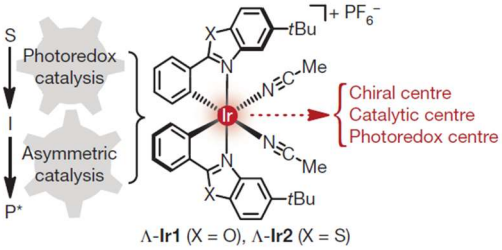

Figure 10: Chiral iridium complexes.

S, substrate; I, intermediate; P*, non-racemic chiral product. The complex acting in the plausible mechanism has X = S because an increased steric hindrance thanks to longer C – S bonds that positions the two tert-butyl groups somewhat closer to the exchange labile acetonitrile ligands than if it is oxygen[24].

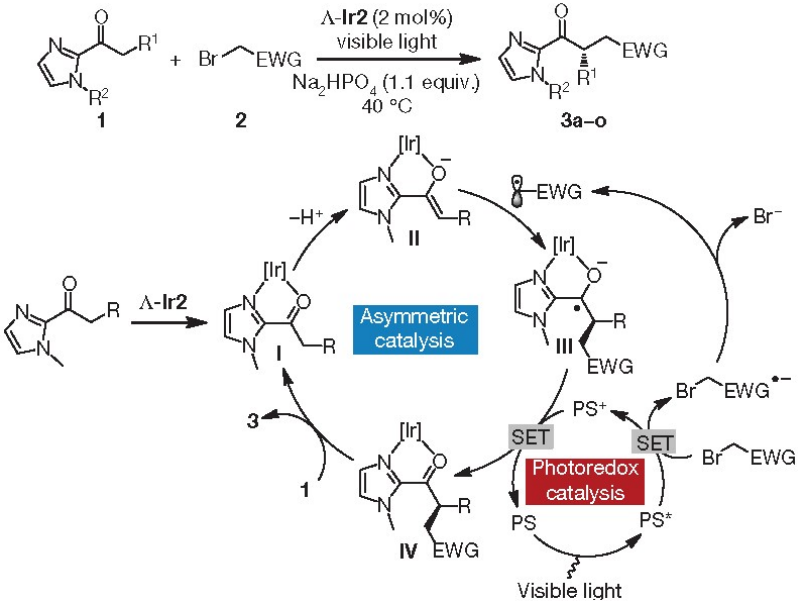

Figure 11: Plausible mechanism for a combined photoredox and asymmetric catalysis; photosensitizer is in the form of enolate complex II[24].

The mechanism, illustrated in figure 11, initiates with the coordination of 2-acyl imidazoles to the iridium catalyst, followed by the formation of a nucleophilic iridium (III) enolate complex upon deprotonation. Herein, a photo-reductively generated electrophilic radical is added to the electron rich metal-coordinated enolate double bond affording and iridium-coordinated ketyl radical that will be oxidized to a ketone by single electron transfer. Finally, iridium catalyst is regenerated and released upon exchange with unreacted starting materials and following by a new catalytic cycle[24].

Keeping track of previous work, Meggers and co-workers developed an oxidative coupling of 2-acyl-1-phenylimidazoles with tertiary amines providing aminoalkylated products. The previous α-alkylation of 2-acyl imidazoles consisted in a reductive activation, instead the reaction being reported now occurs through oxidative chemistry. Moreover, against the preceding consideration for the pioneer transformation, in this case the catalyst with sulfyde in lieu of oxygen results less efficient because of the reactions nature.The catalytic cycle is initiated upon coordination of the 2-acyl imidazole substrate to the iridium complex in a bidentate fashion under release of the two labile monodentate acetonitrile ligands to provide the substrate coordinated intermediate. The subsequent reversible deprotonation in the α-position of the carbonyl group affords the nucleophilic iridium enolate intermediate, which reacts with an electrophilic iminium ion that is generated by an iridium-photosensitized oxidation of the α-silylamine with oxygen serving as the terminal oxidant according to the shown and generally accepted photoredox catalysis cycle. The addition of the iminium ion to the iridium enolate complex occurs in a stereocontrolled fashion dictated by the metal-centered chirality and provides the iridium-coordinated product, which is subsequently released as the product upon coordination to a new substrate molecule, thereby initiating a new catalytic cycle[25].

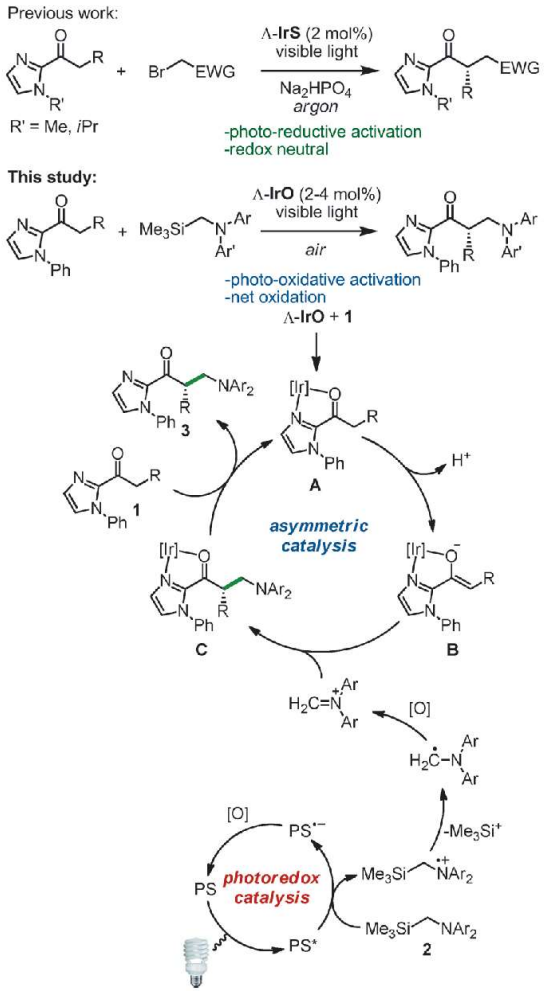

Figure 12: Plausible mechanism for the photoinduced asymmetric catalysis. PS: iridium photosensitizer; [O]: oxidant in form of molecular oxygen and superoxide anion[25].

Another reaction tested by Meggers' group has been the thrichloromethylation of 2-acyl imidazoles and 2-acylpyridines. This mechanism, shown in figure 13, not differs appreciably from the previous one (figure 12). In the same role, the perfluoroalkylation of 2-acyl imidazoles with perfluoroalkyl iodides at the α-position of the carbonil groups, a redox-neutral and electron-catalysed reaction, goes ahead the same steps in the reaction[26]. In these reactions, the intermediate iridium (III) enolate complex, which is expected to act as the chiral reaction partner for the electron-deficient radicals, acts simultaneously as the active photosensitizer.

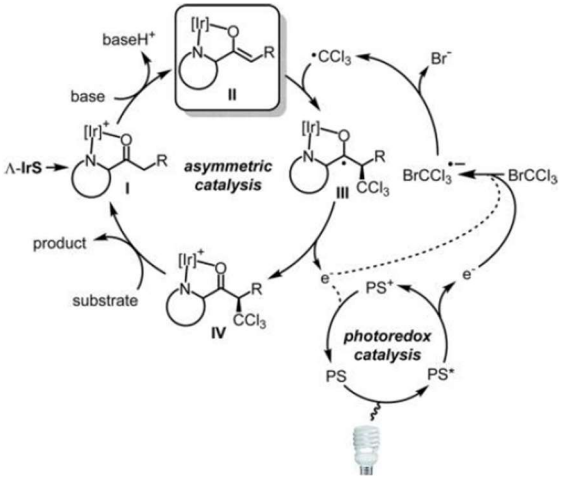

Figure 13: Putative mechanism for the visible-light asymmetric catalysis. PS, photosensitizer in the form of enolate intermediate II[26].

Next, 1,2-amino alcohols were synthesized from trifluoromethyl ketones and tertiary amines with high enantioselectivities using, alike before, iridium that catalyses the electron transfer reaction between a donor substrate and a catalyst-bound acceptor substrate that apparently is followed by a sterecontrolled radical-radical recombination. As we can see in figure 14, it starts with the photoactivation of the iridium-coordinated trifluoromethyl ketone (step 1), which induces a single electron transfer from a tertiary amine, thereby generating an amino radical cation aside from a reduced iridium complex, which can be described as an iridium-coordinated ketyl radical (step 2). This is followed by a proton transfer (step 3) and a radical–radical cross-coupling between the electronrich α-aminoalkyl radical and the electron-deficient ketyl radical (step 4), which is stereochemically controlled by the chiral iridium complex. Finally, the product is replaced by new substrate (step 5)[10].

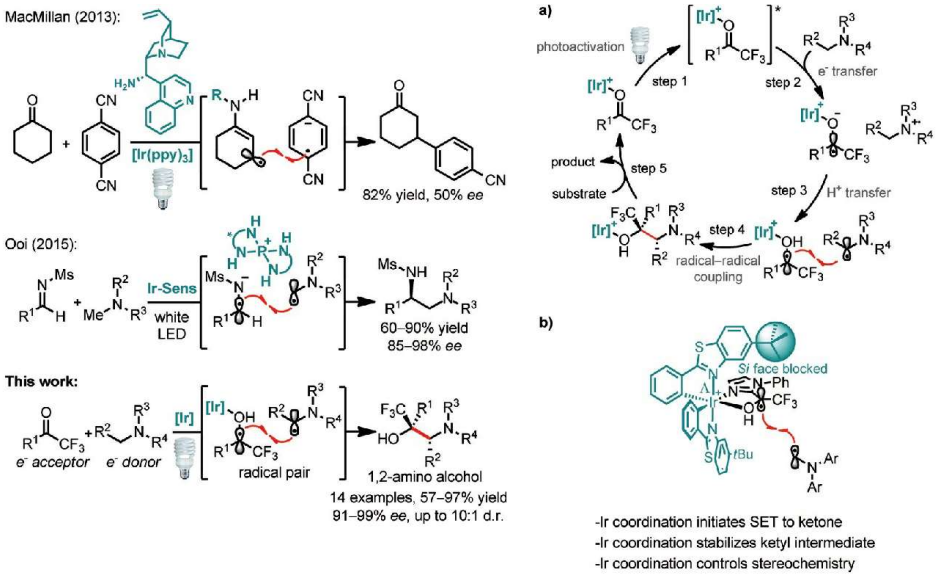

Figure 14: Mechanism for the visible-light-activated catalytic asymmetric process. a) Catalytic cycle. b) Model for the asymmetric induction in the course of the radical–radical recombination shown for selected substrates[10].

The catalytic asymmetric β-C−H functionalization of carbonyl compounds that is based on weakening of the β-C−H bond upon catalyst-induced enolate formation and visible light induced single electron transfer was also developed by Meggers. A subsequent proton transfer then sets the stage for a stereocontrolled radical−radical recombination under control of the chiral catalyst. It is worth noting that a related iridium complex, which is known to enable photoactivated enolate photoredox chemistry, failed to promote this. Visible light and oxygen-free conditionals are devised to be essential for this transformation. Taken together, all mechanistic studies with rhodium catalysts, it is consistent that the role of the Rh catalyst as both a chiral Lewis acid and light-harvesting antenna which will suppress direct photoactivation of the dicarbonyl reaction partner and promote an electron- and proton-transfer (net hydrogen atom transfer) initiated by photoactivated Rh-enolate Rh-II[27].

As yet, in all the published cases, an in situ substrate coordinated iridium intermediate, with or without following deprotonation, served as the active photoredox mediator/catalyst by tuning the UV/Vis-absorption spectrum and the redox potential of the intermediate iridium species. For the case that concerns us now, the employed catalyst is a bis-cyclometalated iridium that provides access to useful chiral building blocks like carbocycles, 2,3-disubstituted indoles and

functionalized alcohols. The intermediate is not isolated for this reaction since the single catalyst is mediating two mechanistically different reactions simultaneously[28]. In order to complement this experiment and to provide diverse chiral alcohols with formation of a new C-C bond and establishing one or more chiral centers, the same group of Meggers tried to establish the same procedure but executing first the photoredox reaction followed by an asymmetric transfer hydrogenation[29].

6.3.2. Rhodium

In contrast to bis-cyclometalated iridium complexes which are well established photoredox sensitizers, this is not the case for the analogous rhodium complexes. Notwithstanding the aforementioned, rhodium complexes have been established as Lewis acid asymmetric catalysts for some applications likewise the activation of 2-acyl imidazoles through two point binding, asymmetric Michael additions (electrophile activation) as well as asymmetric α-aminations (nucleophile activation). In these cases, the rhodium catalyst is found to be overall superior to its iridium congener[16]. Emphasizing the first item, where a chiral-at-rhodium complex is capable of catalysing the amination of 2-acyl imidazoles through the formation of a coordinated rhodium enolate, asymmetric cross-coupling of two Csp^3-H groups with molecular oxygen as the oxidant has also been proved to work well under rhodium catalysis[30]. In figure 15 the mechanism of this reaction, applicable to the others with rhodium as catalyst, is illustrated.

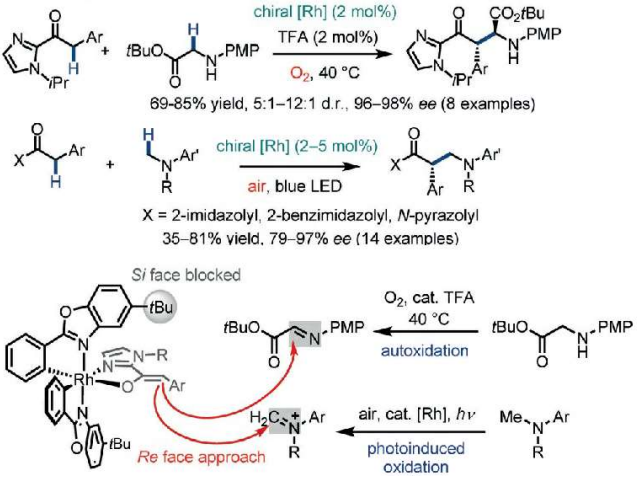

Figure 15: Mechanism for the catalytic asymmetric cross-dehydrogenative couplings with molecular oxygen[30].

By the other hand, rhodium complexes have also been used with other photosensitizers in order to make possible a photoredox asymmetric catalysis. For example, a reaction that has been studied, the addition of alkyl radicals to alkenes, is initiated by the now well-established photosensitized oxidative conversion of organotrifluoroborates to carbon-centered radicals, which in turn add to N,O-rhodiumcoordinated 2-acyl imidazole or N-acyl pyrazole substrate thereby generating the secondary radical intermediate II, which is subsequently reduced by SET to a rhodium enolate, which upon protonation by water provides rhodium-bound product[31]. This course of reaction is very similar to the α-alkylation of 2-acyl imidazoles and the thrichloromethylation of 2-acyl imidazoles and 2-acylpyridines.

Furthermore Kang demonstrated an efficient strategy for the addition of α-amino radicals generated from tertiary amines to Michael acceptors catalysed by a chiral-at-metal rhodium complex. In this case, the catalyst is N,O-rhodium-coordinated complex instead of rhodium metal free[32]. The steps overall are related in figure 16. The addition starts with the coordination of Substrate 1 with the rhodium complex in a bidentate fashion to generate intermediate I. Then, the N,O-rhodiumcoordinated α,β-unsaturated 2-acyl imidazole complex (intermediate I) is photoexcited and reduced by tetrahydroisoquinoline 2, thus generating an α-amino radical, which subsequently added to intermediate I to generate the secondary radical intermediate II. Intermediate III (rhodium enolate), which is generated from intermediate II via a SET process, results in rhodium-coordinated product IV by protonation with H^+. The desired product is released via the replacement of the coordinated product IV by 1a[32].

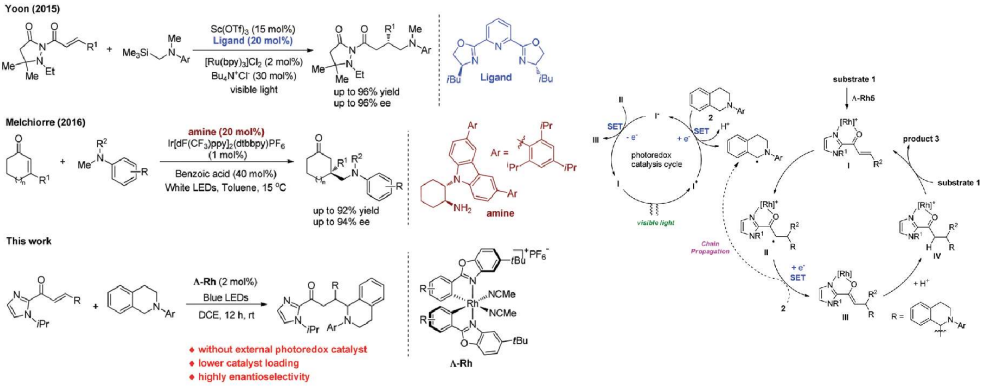

Figure 16: Proposed mechanism for the addition of α-amino radicals generated from tertiary amines to Michael acceptors[32].

6.3.3. Copper

Leaving aside the advances related before, the first to develop a light-promoted enantioselective C-N cross-coupling by a copper (I) catalyst containing a chiral phospine ligand was Fu and his laboratories; never before copper had been established as a bifunctional catalyst. An outline of a possible mechanism for photoinduced copper-catalyzed C-N couplings of alkyl halides is illustrated in figure 17. Irradiation of a copper-nucleophile complex (A) could lead to an excited-state adduct (B) that would then engage in electron transfer with the alkyl halide (R-X) to generate an alkyl radical; next, bond formation between the nucleophile and the radical (Nu-R) could occur through an innersphere pathway involving a copper-nucleophile complex (C)[33].

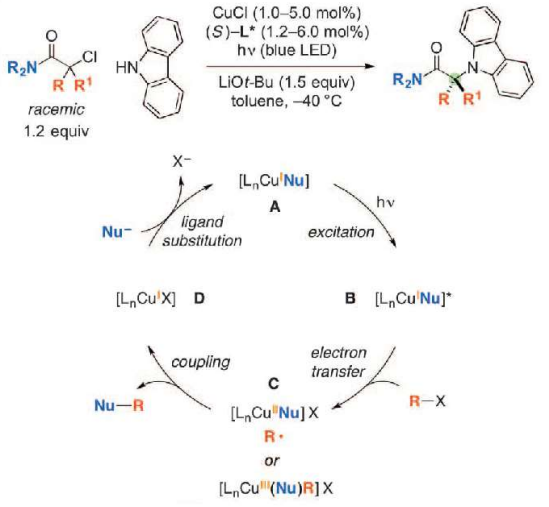

Figure 17: Outline of a possible pathway for photoinduced copper-catalyzed C-N crosscouplings of alkyl halides. For simplicity, all copper complexes are illustrated as neutral species, and all processes are depicted as being irreversible; X may be serving as an inner- or an outer-sphere ligand [Ln denotes additional ligand(s) coordinated to copper][33].

Beside the aspects of relatively shorter excited state lifetimes and weaker visible-light absorption, an inherent drawback of copper complexes as photoredox catalysts is that the low reduction potentials of Cu(II) to Cu(I) might impede the closure of a photocatalytic cycle. Very recently, an appealing strategy involving light-accelerated homolysis has been developed to address this problem. So that copper(II) bisoxazoline complexes (Cu-BOX) have been disclosed as asymmetric/photoredox catalysts for the alkylation of imines.

As we can see in figure 18, catalyst Cu(II)−L oxidizes the trifluoroborate substrate 2 to the radical A through a ligand exchange/light accelerated homolyses process. On the other hand, imine substrate 1 or 4 undergoes fast ligand exchange with Cu(II)−L and affords the intermediate complex B. The nucleophilic alkyl radical A proceeds with radical addition to the carbon an nitrogen double bond of complex B in an enantioselective fashion and transformation to radical C. Reduction of C by Cu(I)−L affords monocationic complex D, followed by protonation and ligand exchange to release chiral product 3 or 5 and regenerated intermediate complex B. The effective asymmetric induction can be explained by radical attack from the sterically less hindered side of the copper-coordinated imine. Result of this experiment it is clear that a ligand exchange/light-accelerated homolysis pathway might be engaged to overcome the low oxidizability of the Cu(II) complexes[5].

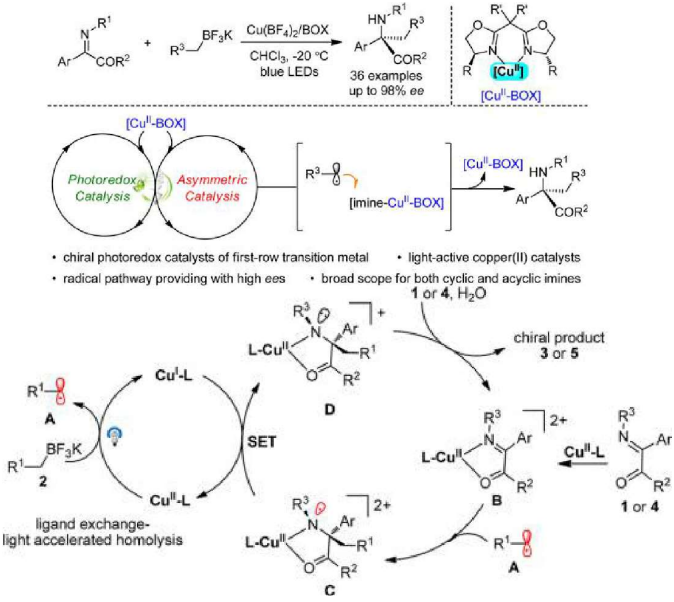

Figure 18: A Proposed Reaction Mechanism for the alkylation of imine[5].

6.3.4. Nickel

Although they are inexpensive and well-compatible in photochemical reactions, nickel complexes themselves have been less reported as photoredox catalysts. In this case the study turns around the photoredox reactions of α,β-unsaturated carbonyl compounds and tertiary/secondary α-silylamines.

The reaction proceeds with N-acyl pyrazole substrate that undergoes fast ligand exchange with the chiral nickel catalyst and affords the intermediate complex. On the other hand, the photon-absorbing nickel complex Ni–L1 or Ni–L1–1 is activated by visible light, and then oxidizes α-silylamine by SET to generate silylamine cation radical and the reduced radical (only Ni–L1 as the photocatalyst is shown in the figure). Subsequent desilylation of B led to the formation of the nucleophilic α-aminoalkyl radical, which undergoes radical addition to the carbon double bond of complex A in an enantioselective fashion and transformation to radical species. Reduction of these by strong reductant radical produces anion E, followed by protonation to afford neutral complex F. Finally, substitution with 1 released chiral product 3 and regenerated intermediate A[34]. The mechanism is outlined in figure 19.

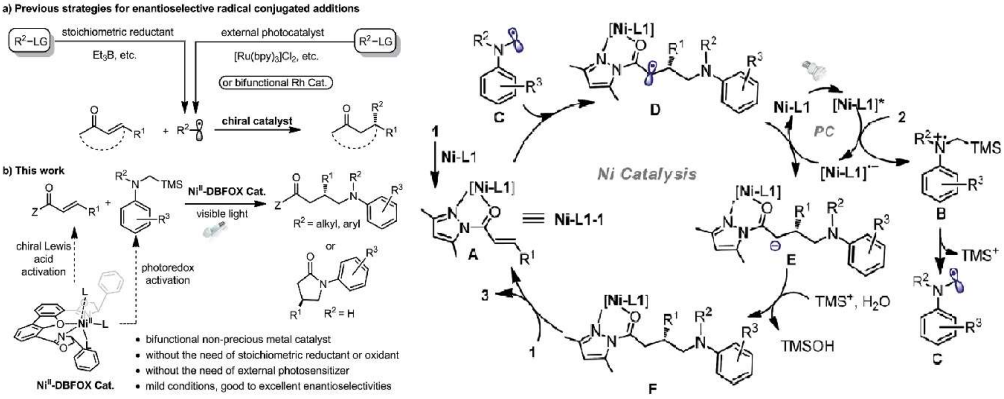

Figure 19: A proposed reaction mechanism for the nickel-catalyzed enantioselective photoredox reaction of α,β-unsaturated carbonyl compounds and α-silylamines[34].

Considering the steric hindrance created by the tridentate and bidentate coordination, nickel center does not interact directly with the free carbon radicals in the nickel catalysis cycle. The metal instead serves as a Lewis acid to activate the electrophilic N-acyl pyrazole through a bidentate coordination. To sum up, a range of α,β-unsaturated N-acyl pyrazoles containing aliphatic, aromatic or electron-donating substituents at the β-position were well tolerated[34].

6.3.5. Nanomaterial

In 2018 Scaiano and Hodgson reported an efficient nanocomposite acting as a Lewis acid catalyst and formed by samarium oxide nanoparticle (a nanostructured semiconductor) decorated with titanium or ceria dioxide (Lewis acidic nanoparticles).

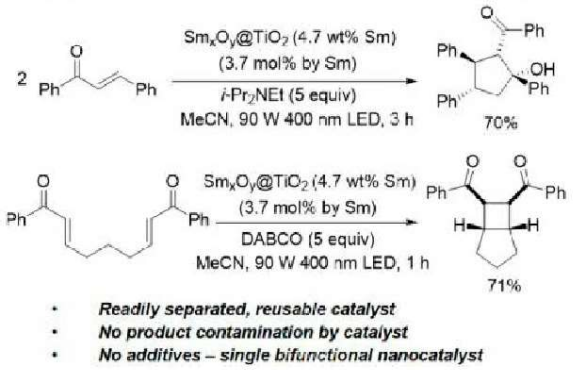

Figure 204: Proposed mechanism for the heterogeneous net reductive photoredox-Lewis acid catalytic reductive cyclization of trans-chalcones[35].

This catalyst performed the photoreductive cyclization and [2+2] photocycloaddition chemistry reactions; shown in figure 20. For the first, the net reductive mechanism (figure 21) begins with coordination of two molecules of substrate to a single Sm_xO_y nanoparticle on the catalyst surface such that the two reactants come into close proximity. As in the homogeneous analogue, photoexcitation of the catalyst and two SET events are followed by radical−radical coupling to form a new carbon−carbon bond. Subsequent monoprotonation of the dienolate followed by intramolecular aldol addition furnishes the substituted cyclopentanol product. Interestingly, the Lewis acid samarium triflate has been proposed to take on multiple roles in the homogeneous catalytic version of this system. In addition to stabilizing the radical anion intermediate, it has been reported that a single Sm(III) atom facilitates the ring-closing final step by coordinating to both the enol and carbonyl functionalities of the dienolate, rendering the reaction highly selective toward the thermodynamically favored stereoisomer.

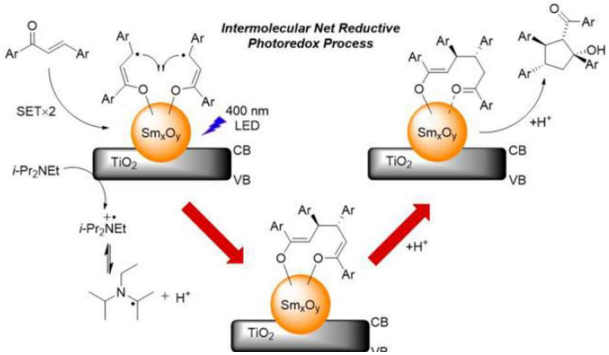

Figure 21: Proposed mechanism for the heterogeneous net reductive photoredox-Lewis acid catalytic reductive cyclization of trans-chalcones[35].

Secondly, a similar mechanism was proposed for the heterogeneus catalytic intramolecular [2+2] photocycloaddition of symmetric bis(enones) (figure 22). It consists in a SET from the photoexcited nanocomposite catalyst to the Lewis acid-activated substrate forms the key radical anion intermediate stabilized by the Lewis Acidic Sm_xO_y nanoparticles. Subsequent intramolecular Michael addition leads to closing of the five-membered ring followed by cyclobutanation to afford the samarium-coordinated ketyl radical, which then gives up an electron to yield the cycloadduct 5 (one diastereomer shown for clarity). Unlike the photoreductive cyclization of chalcones then, the intramolecular [2 + 2] photocycloaddition of bis(enones) is a net neutral redox process and the possibility of a chain component in the overall mechanism should not be ignored[35].

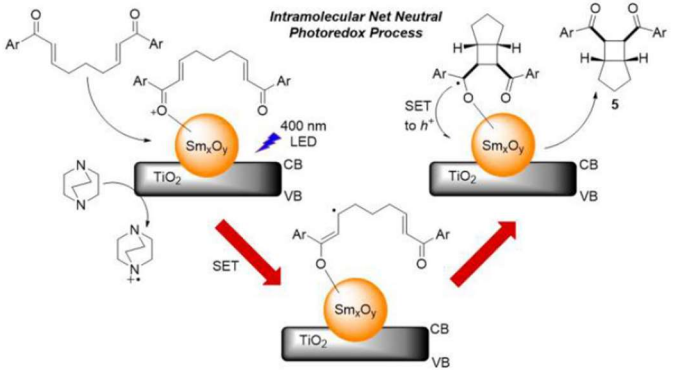

Figure 22: Proposed mechanism for the heterogeneous net neutral photoredox-LA dual catalytic intramolecular [2 + 2] photocycloaddition of symmetric aryl bis(enones)[35].

This emerging class of nanomaterials harnesses the Lewis acidity of the lanthanide, eliminates product contamination by the catalyst, and can be excited with visible light.

7. CONCLUSIONS

By one hand asymmetric catalysis is seen as one of the most economical strategy to synthetize enantiomerically pure small molecules. On the other hand, visible light has been recognized as an environmentally friendly and sustainable form of energy for triggering chemical transformations. Moreover, photoredox catalysis provides the generation of highly reactive radical intermediates with often unusual or unconventional reactivities. Overall, in asymmetric photoredox catalysis the photoactivated sensitizers (or the bifunctional catalyst with photoexcitation) initiate a SET from or to a closed-shell organic molecule to produce radical cations or radical anion whose reactivities are then exploited.

Generally, the catalyst is a metal complex or an organic molecule which can be photoexcitated as well as can control stereoselectivity across different types of asymmetric catalysis likewise Lewis acid catalysis, enamine catalysis, photoaminocatalysis and hydrogen bond catalysis.

Lewis acid catalysis through chiral-at-metal complexes such as iridium, rhodium, copper ad nickel is the field that has been most explored. The iridium catalysts are more abundant than others of other metals; however these catalysts overall have been demonstrated to catalize enolate reactions, Michael additions, cycloadditions, asymmetric hydrogenations, asymmetric transfer hydrogenations, and a variety of different photoredox reactions.

Nevertheless in recent years photoaminocatalysis or Lewis acid with a nanomaterial as center of chirality, have also been related and greatly proved to conduct a chemical transformation with the desired enantioselectivity.

To sum up, this advances allow it to forge a green, sustainable and economical chemistry without forgetting enantioselective propierties.

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9. ACRONYMS

SET: single electron transfer

PET: photoinduced electron transfer

EDA: electron donor-acceptor

EWG: electron-withdrawing group

LG: leaving group

BOX: bisoxazoline complexes

APPENDICES

APPENDIX 1: TABLE DATA

YEAR	AUTHOR	BIFUNCTIONAL CATALYST	ASYMMETRIC CATALYSIS	CHEMICAL TRANSFORMATION	REFERENCE
2005	Bach	organocatalyst	Hydrogen Bond catalysis	conjugate additions of α-amino alkyl radicals to enones	8
2013	Melchiorre	enamine-derived EDA complex	Enamine catalysis	α-alkylation of aldehydes and ketones	20
2014	Meggers	iridium complex	Lewis Acid catalysis	α-alkylation of 2-acyl imidazoles	24
2015	Meggers	iridium complex	Lewis Acid catalysis	oxidation of 2-acyl-1-phenylimidazoles with tertiary amines	25
2015	Meggers	rhodium complex	Lewis Acid catalysis	amination of 2-acyl imidazoles	16, 30
2015	Melchiorre	enamine-upon direct photoexcitation	Enamine catalysis	α-alkylation of aldehydes and ketones	22, 23
2016	Meggers	iridium complex	Lewis Acid catalysis	thrichloromethylation of 2-acyl imidazoles and 2-acylpyridines	9, 26
2016	Meggers	iridium complex	Lewis Acid catalysis	α-amination of trifluoromethyl ketones	10
2016	Meggers	rhodium complex	Lewis Acid catalysis	addition of alkyl radicals to alkenes	31
2016	Fu	copper complex	Lewis Acid catalysis	C-N cross-coupling	33
2017	Meggers	iridium complex	Lewis Acid catalysis	β-C−H functionalization of carbonyl compounds	27
2017	Kang	rhodium complex	Lewis Acid catalysis	addition of α-amino radicals to Michael acceptors	32
2018	Meggers	bis-cyclometalated iridium	Lewis Acid catalysis	chiral building blocks like carbocycles	28, 29
2018	Gong	copper(II) bisoxazoline complex	Lewis Acid catalysis	alkylation of imines	5

2018	Gong	nickel complex	Lewis Acid catalysis	photoredox reaction of α,β-unsaturated carbonyl and α-silylamines	34
2018	Scaiano	Nanocomposite	Lewis Acid catalysis	photoreductive cyclization and [2+2] photocycloaddition	35
2018	Alemán	Photoaminocatalyst	Enamine catalysis	photoalkylation of aldehydes	4