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Recent Applications of Rare Earth Complexes in Photoredox Catalysis for Organic Synthesis.

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Abstract: In recent years, photoredox catalysis has appeared as a new paradigm for forging a wide range of chemical bonds under mild conditions using abundant reagents. This approach allows many organic transformations through the generation of various radical species, enabling the valorization of non-traditional partners. A continuing interest has been devoted to the discovery of novel radical-generating procedures. Over the last ten years, strategies using rare-earth complexes as either redox active centers or as redox-neutral Lewis acids have emerged. This review provides an overview of the recent accomplishments made in this field. It especially targets to demonstrate the utility of rare-earth complexes for ensuring photocatalytic transformations and to inspire future developments.

Keywords: Photocatalysis, Radicals, Rare-earth metals, Lanthanides, Lewis acid, Redox chemistry, Photocyclization

1. INTRODUCTION

Photoredox catalysis has emerged as an important platform for the formation of various chemical bonds, through the *in-situ* generation of radical species under mild conditions. [1-5] In contrast with ‘traditional’ radical chemistry, in which the radical-generation is linked to bond dissociation energy (BDE), photoredox catalysis exploits the redox properties of organic molecules for the radical-generation. In such catalysis, metal-based or organic photocatalysts, upon light excitation, can behave as both potent reductant and oxidant, activating organic substrates through single electron transfer (SET) events, resulting in the formation of radical intermediates. The increasing interest within the field has led to the development of novel radical-generating strategies, such as strategies relying on the use of rare-earth complexes (Sc, Y, Lanthanides), alone or in combination with photocatalysts. [6-10] Those complexes have been employed in photocatalytic transformations, depending on the electronic nature of the rare-earth metals, either as redox active centers or as redox-neutral Lewis acids. Indeed, some rare-earth metals are well known to have redox properties, such as samarium, europium and ytterbium, which have readily available divalent oxidation states and hence are good one-electron reducing agents in the ground state ($\text{Ln}^{3+}/\text{Ln}^{2+} = -0.3$ to -1.5 V vs NHE). [11] On the other hand, cerium(IV) compounds, especially CAN, have found use as one-electron oxidation reagents ($\text{Ln}^{3+}/\text{Ln}^{4+} = +1.6$ V vs NHE), providing functional group oxidations and

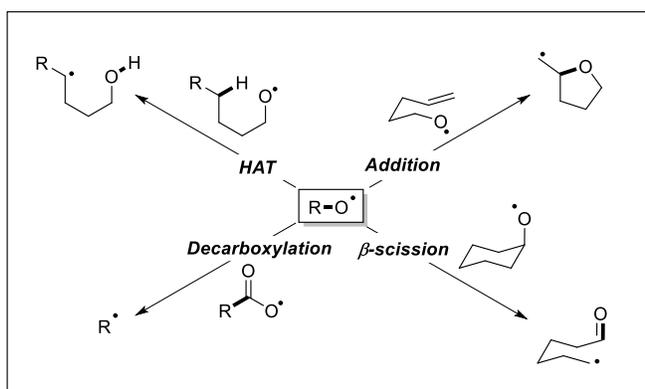
triggering radical processes. [12] The redox activities of these elements, resulted in their use as redox active centers in photochemical reactions. In contrast, other rare earth metals form predominantly trivalent redox-stable metal complexes, which are highly oxophilic and have a strong Lewis acidic character. [13-14] These properties can be fine-tuned by varying ligands, solvents and metal ion size (lanthanide-contraction). Consequently, such elements have mainly been used as redox-neutral Lewis acids unlocking various photochemical transformations.

2. RARE-EARTHS AS PHOTOCATALYTICALLY ACTIVE CENTERS

Recently, a strong interest has been devoted to the synthesis and the photochemical study of rare-earth based complexes/salts. [15-16] Interestingly, some of them have displayed remarkable photochemical behaviors, ranging from luminescence properties to photocatalytic activities. However, to date, the promotion of photoredox reactions has been exclusively described with lanthanide-based complexes or lanthanide salts. [6-8] The present review will be narrowed to the description of photocatalytic transformations. Consequently, photochemical reactions mediated by a stoichiometric amount of lanthanide would not be discussed. [17-19]

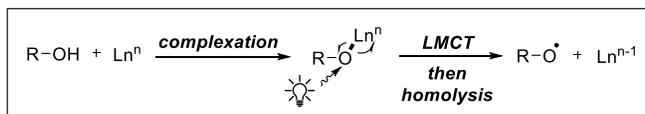
2.1 Lanthanide catalysis for the generation of O-centered radical intermediates

In recent years, lanthanides have demonstrated impressive abilities for the activation of native alcohols [20-34] and carboxylic acids, [35-38] leading respectively to the formation of alkoxy and carboxyl radicals. The formation of those radicals is particularly attractive, as they are versatile and valuable intermediates for the synthesis of a large class of compounds. While carboxyl radicals are almost exclusively involved in decarboxylative processes, alkoxy radicals are usually engaged in hydrogen atom transfer (HAT), in β -scission, or in radical addition processes (Scheme 1). [39-42]



Scheme 1. Traditional reactivity of O-centered radicals.

In contrast with conventional photoredox systems, in which the activation of organic molecules involves outer sphere electron transfers from the excited photocatalysts, the lanthanide photoredox platform mainly relies on binding processes, in which complexations of organic compounds with lanthanides are involved. For instance, alcohols and carboxylic acids can readily form complexes with lanthanides, which upon light excitation lead to the homolysis of the ligand-metal bond, resulting in the formation of the ligand-based radical and in the formal reduction of the lanthanide centers. This reactivity is based on a Ligand-Metal Charge Transfer (LMCT) (Scheme 2). [43]



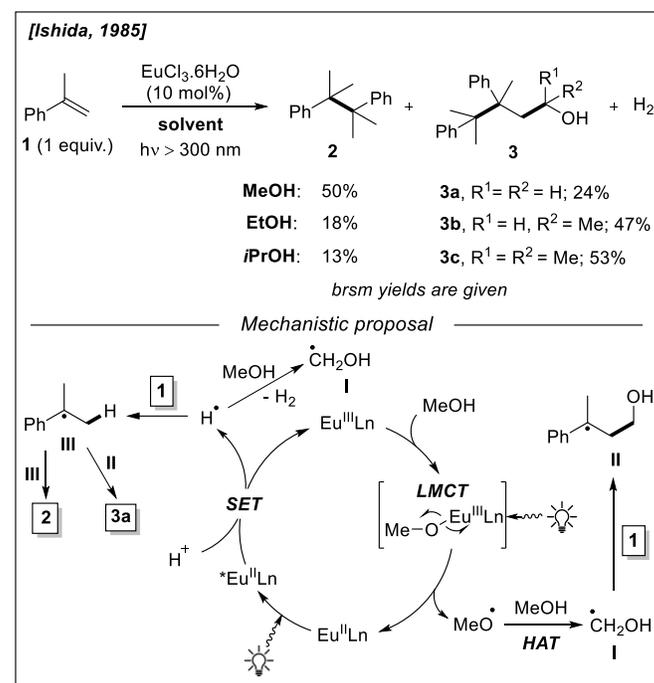
Scheme 2. LMCT mechanism with oxygenated substrates.

2.1.1 Lanthanide catalysis for the activation of alcohols

In the 1980s, the Ishida group has disclosed seminal investigations reporting that lanthanides can activate free alcohols under light irradiation. These studies have been focused on the use of Eu^{III} catalysts. [20-23]

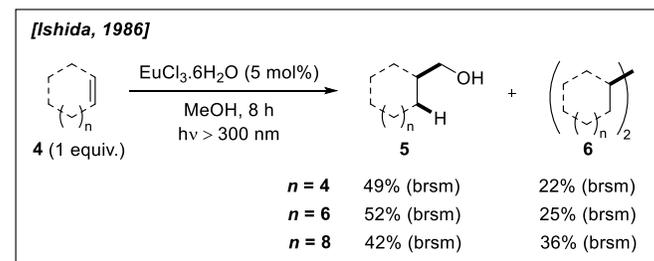
The first discovery in the field was made when a solution of 10 mol% of europium(III) chloride in methanol was irradiated with light (>300 nm) in the presence of α -methylstyrene **1**. [20] In those conditions, they observed the formation of two main compounds, which were identified as the reductive dimer of α -methylstyrene **2** and the 2:1 α -methylstyrene-methanol adduct **3** (Scheme 3). When the reaction was conducted in ethanol or in isopropanol, the same products were obtained, albeit in different ratio. To gain insight into the operative mechanism, the authors performed deuterium labeling experiments, spectrometry analyses, and monitoring of the hydrogen gas formation. The

latter allowed to propose a plausible mechanism that would involve a catalytic cycle $\text{Eu}^{\text{III}}/\text{Eu}^{\text{II}}$, in which the two europium species would be photoexcited (Scheme 3). The mechanism would start by the coordination of the methanol to the Eu^{III} species. Then, the photoexcitation of the complex would induce a LMCT process that would form the methoxy radical and the $\text{Eu}^{\text{II}}\text{Ln}$ species (Scheme 3). The methoxy radical would then initiate a HAT step, resulting in the formation of the radical **I**, which would react with compound **1**, forming the intermediate **II**. The catalytic cycle would be closed by the subsequent photoexcitation of the Eu^{II} species, followed by the single electron transfer (SET) reduction, restoring the Eu^{III} catalyst and giving rise to radical hydrogen. The latter would react with either compound **1** or methanol, affording respectively intermediate **III** or **I**. Finally, the reaction of the intermediate **II** with itself or with the intermediate **I**, would yield the final products **2** and **3a** (Scheme 3).



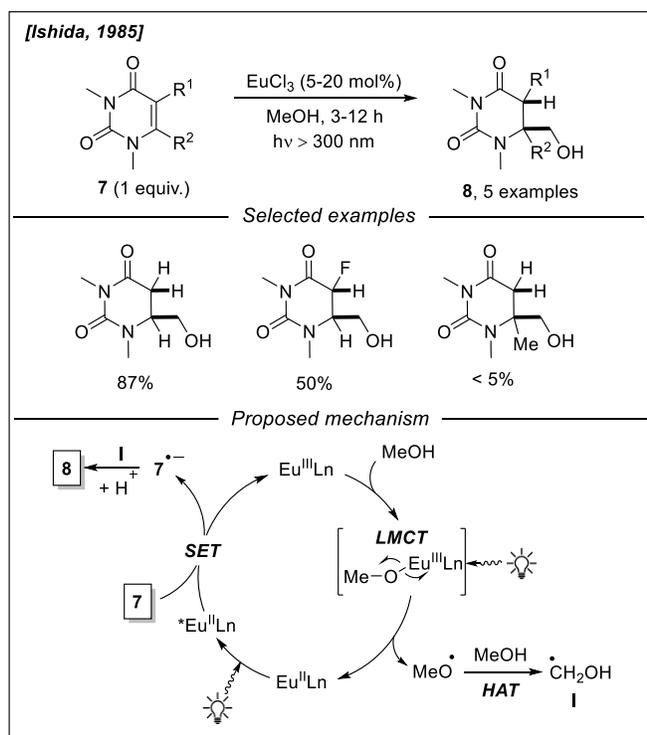
Scheme 3. First example of the photo-activation of alcohols catalyzed by europium. [20]

A year later, based on the same reactivity, the Ishida group reported the hydroxymethylation of aliphatic alkenes **4**. As previously, the reaction was found to be poorly selective leading to the formation, in modest yields, of both the dihydromer of alkenes **6** and the expected products **5** (Scheme 4). [21]



Scheme 4. Europium-catalyzed hydroxymethylation of alkenes. [21]

Finally, they have also extended the scope of the reaction to the hydroxymethylation of uracil derivatives **7** (**Scheme 5**). [22] The reaction afforded the expected products **8** in good to excellent yields with derivatives unsubstituted at the 6-position, while the reaction was ineffective with substituted substrates. For this transformation, a mechanism similar to the precedent was proposed (**Scheme 3-5**), except that, the catalytic cycle would be closed by the SET reduction of compounds **7** from the excited Eu(II) species. It should be mentioned that the reduction might occur also after the radical addition of the intermediate **I** to uracil **7** (**Scheme 5**).

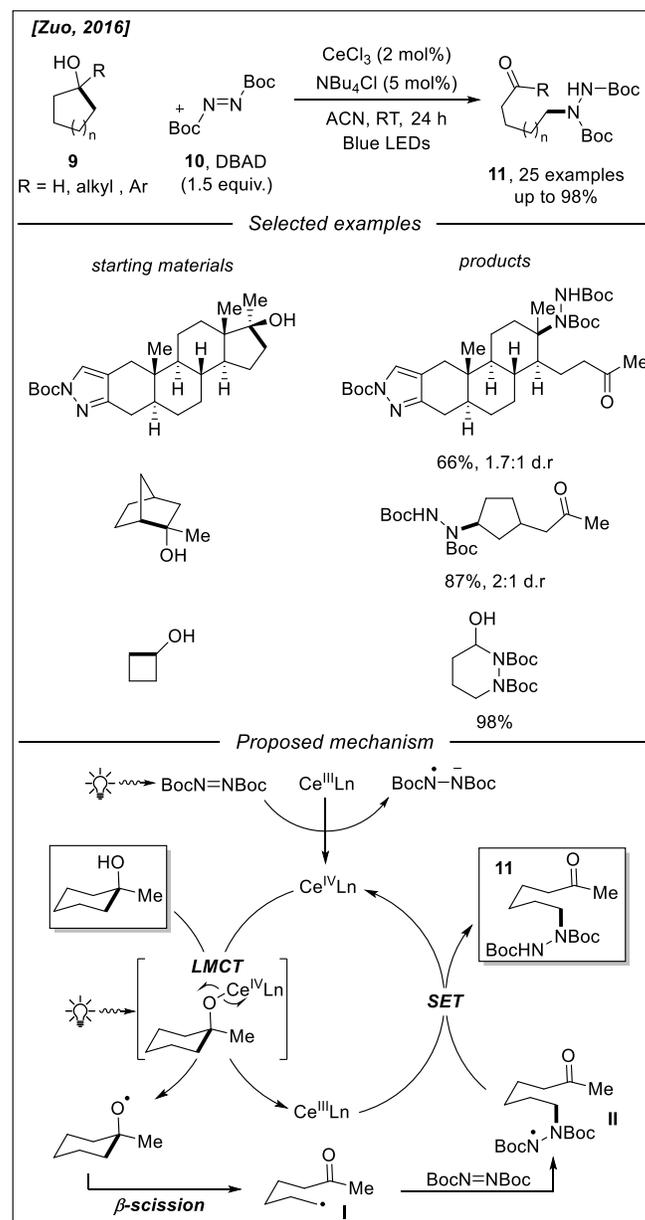


Scheme 5. Hydroxymethylation of uracil derivatives. [22]

More recently, alternatively to europium catalysis, cerium catalysis has been used for achieving the activation of alcohols. Cerium-based photocatalysis has been applied to a wide number of synthetic transformations and has proved to be a remarkable platform for accessing complex and interesting molecules.

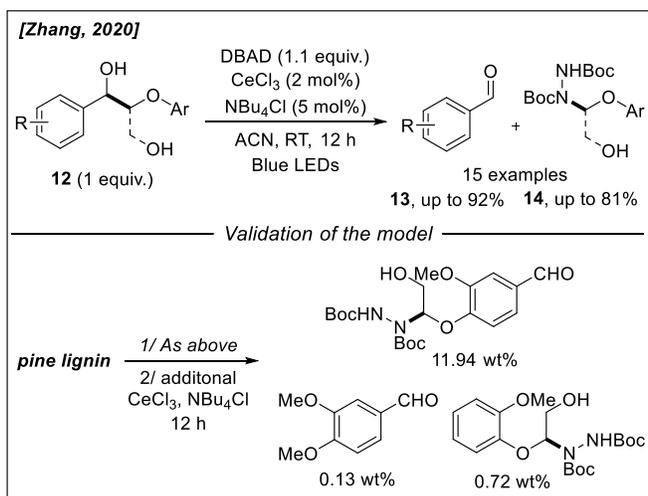
In 2016, the Zuo group firstly discovered that, under light irradiation and in presence of CeCl₃, NBu₄Cl and azodicarboxylates **10**, cyclic alcohols **9** undergo C-C bond cleavage, through β -scission, yielding to the hydrazino-carbonyl products **11** (**Scheme 6**). [24] In this protocol, a range of cyclic alcohols both secondary and tertiary were found to be suitable as substrates, giving compounds **11** in moderate to excellent yields. From a mechanistic point of view, the authors have proposed that the active Ce^{IV} species would be initially generated by the SET event involving the excited Ce^{III}-OR complex and DBAD **10**. However, advances in the field allowed updating of the initial proposed mechanism by the mechanism depicted in **Scheme 6**. The latter would start with the photoexcitation of DBAD **10**, which would oxidize the Ce^{III} precatalyst to the Ce^{IV} species. Then, the complexation of the alcohol with the Ce^{IV} would form the photoactive Ce^{III}-OR complex, which upon irradiation, would give the Ce^{III} species and the alkoxy

radical. The latter would undergo C-C bond cleavage and ring-opening providing intermediate **I** (**Scheme 6**). Finally, the reaction of compound **I** with DBAD **10**, followed by the reduction of intermediate **II**, would furnish the final molecule.



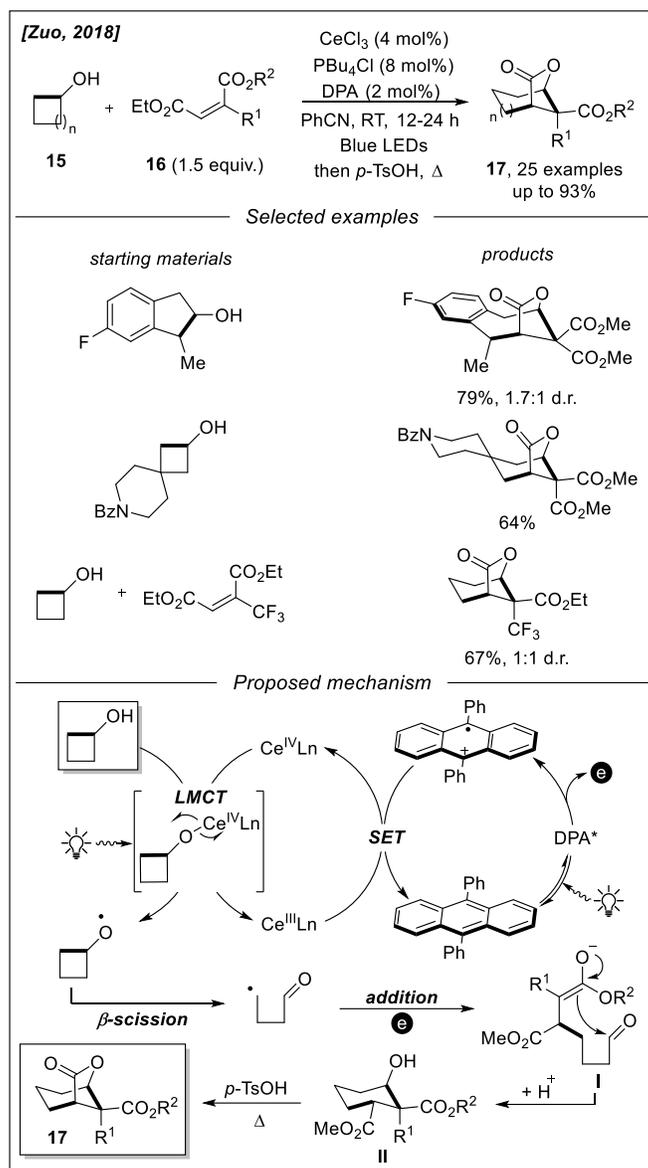
Scheme 6. Cerium catalysis for the photoinduced C-C bond cleavage. [24]

More recently, based on Zuo's work, Wang and co-workers used this reactivity for achieving the depolymerization of lignin by C-C bond cleavage (**Scheme 7**). [25] To reach this objective, they first studied the cerium photoredox system on β -O-4 linkage model substrates **12**. In this context, the reaction provided both benzaldehydes **13** and hydrazines **14** in good yields (**Scheme 7**). Finally, the reaction has been undertaken with pine lignin affording, by depolymerization, three valuable monomers in moderate global weight (11.94 wt%). It should be mentioned that this result was obtained with an additional amount of cerium catalyst system and an extended reaction time (**Scheme 7**).



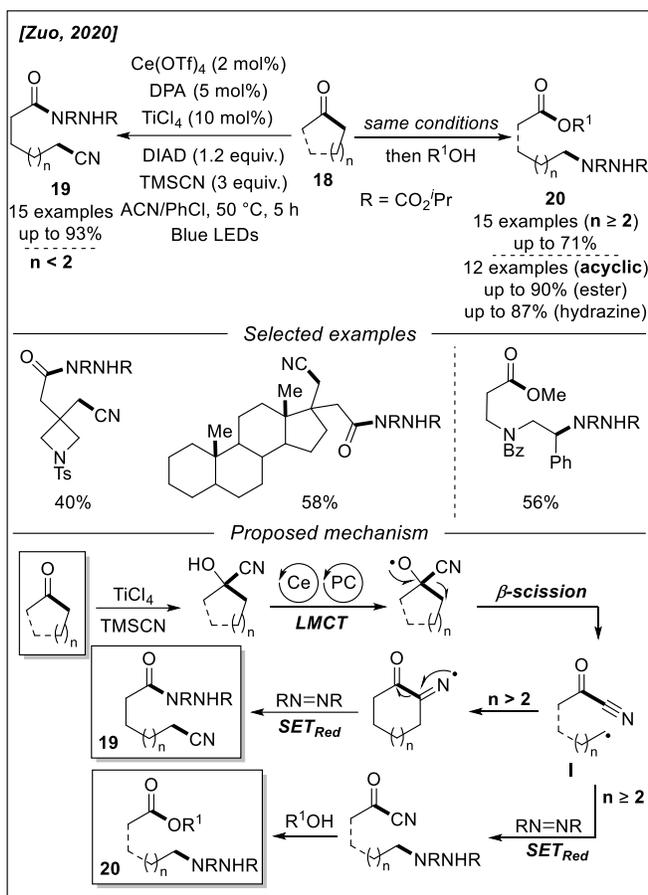
Scheme 7. Cerium-Photocatalyzed depolymerization of lignin model substrates & native lignin. [25]

Later on, the Zuo group has also exploited this reactivity for synthesizing bridged lactone derivatives **17** starting from cyclic alcohols **15** and Michael acceptors **16** by the use of a dual photoredox platform (**Scheme 8**). [26] The reaction provided access to a wide range of bridged lactones in moderate to good yields. Interestingly, in contrast with prior work reported by the group, the use of 9,10-diphenylanthracene (DPA) as photocatalyst (PC) was essential for the reaction efficiency. Without the PC, the reaction was poorly effective. Indeed, to sustain the catalytic cycle, the SET event, between the transient radical and the Ce^{III} catalyst, must be ensured to regenerate the active Ce^{IV} species (*vide supra*, **Scheme 6**). Consequently, the success of the catalysis depends on the feasibility of this SET event. Given the redox potential of the couple Ce^{III}/Ce^{IV} ($E_{1/2} = 0.40$ V *vs.* SCE in MeCN), the ground-state Ce^{III} could be oxidized by the *N*-centered radical (**Scheme 6**, intermediate **II**), while the latter cannot be oxidized by α -ester radicals ($E_{1/2} = -0.66$ V *vs.* SCE in MeCN). [43] To overcome this limitation, the Zuo group used DPA for securing both the oxidation of Ce^{III} to the Ce^{IV} and the reduction of the radical intermediate to the corresponding anion **I** (**Scheme 8**). Another strategy has been developed by the Zuo group to ensure the SET event without the use of PC and DBAD reagent (*vide infra*, **Scheme 12**). Mechanistic considerations led the authors to propose the following mechanism (**Scheme 8**). As previously, the photoinduced LMCT would lead to the homolysis of the Ce^{IV}-OR bond, forming the alkoxy radical, which by β -scission would give rise to the *C*-centered radical. Addition of the radical to the Michael acceptor would form a transient radical that would be reduced to the enolate **I** by the photoexcited DPA (**Scheme 8**). Finally, the intermolecular aldol reaction would result in the formation of the species **II**, which upon acidic/heating treatment, would give the bridged lactone.



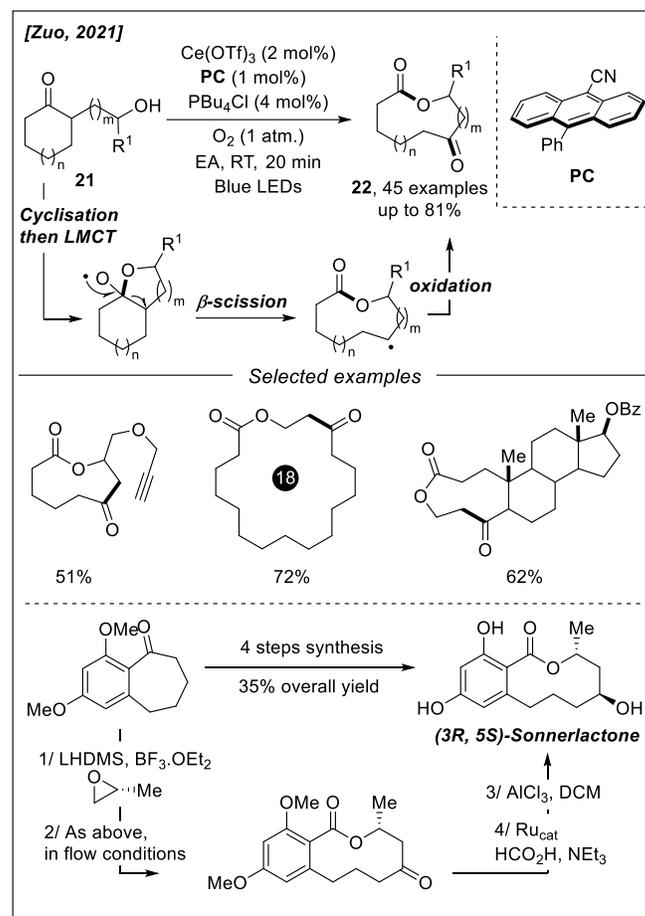
Scheme 8. Cerium-DPA dual photocatalysis for the formal cycloaddition of cyclic alcohols with alkenes. [26]

More recently, the Zuo group has developed a general procedure for the C-C bond cleavage and functionalization of ketones merging Lewis catalysis and photoredox-catalysis. [27] The strategy enabled the formation of various final compounds depending on the ring-size of the starting ketones **18**. While 4- and 5-membered cyclic ketones provide products **19**, higher membered cyclic ketones lead to the formation of compounds **20** (**Scheme 9**). The products divergence was explained by the difference in reactivity of the intermediate **I** depending on the ring-size of starting ketones (**Scheme 9**).



Scheme 9. Lewis acid/Photoredox cooperative catalysis for the C-C bond cleavage in cyclic ketones. [27]

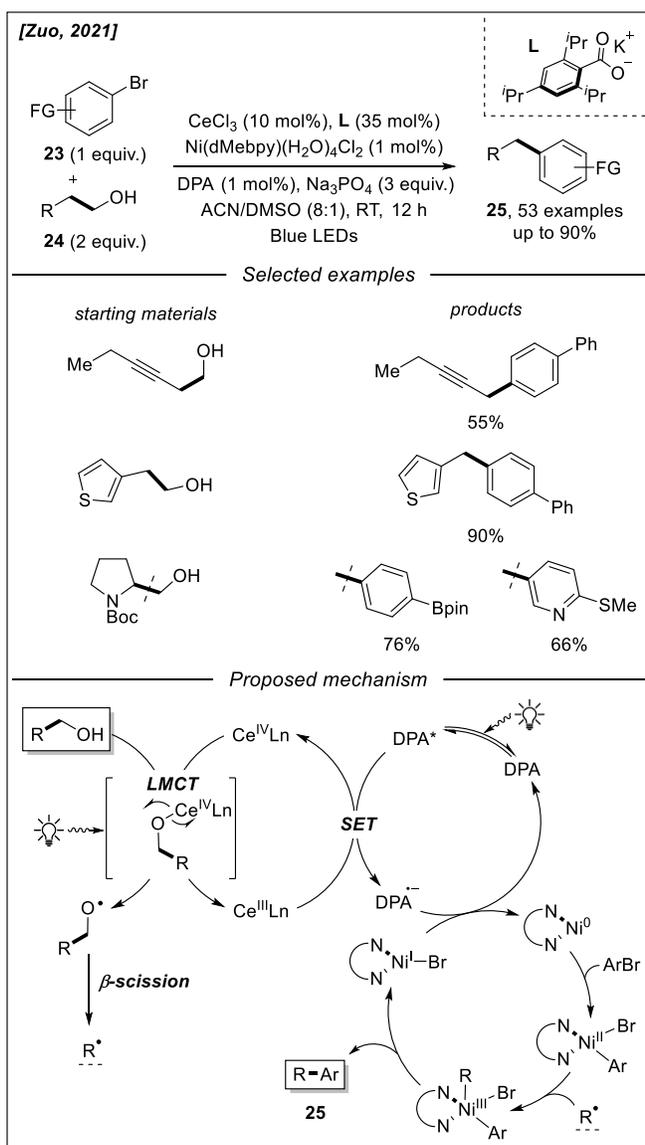
This year, Zuo and co-workers reported a ring expansion protocol of cyclic ketones under visible light irradiation and aerobic conditions, combining cerium and cyanoanthracene catalysts. [28] This elegant protocol enables the one-step synthesis of macrolactones, ranging from 9-membered to 19-membered lactones **22** in moderate to good yields, from readily available cyclic ketones **21** (**Scheme 10**). The reaction would proceed through a cyclisation mediated by cerium, followed by a LMCT step that triggered the homolysis of Ce^{IV}-OR complex, resulting in the generation of the alkoxy radical. The subsequent β -scission and oxidation with oxygen would then provide the products **22** (**Scheme 10**). This strategy might also be helpful for reducing step-synthesis for reaching some macrolactones. For instance, the authors demonstrated the utility of their procedure by synthesizing the (3R, 5S)-sonnerlactone in only 4 steps-synthesis in 35% overall yield, thereby highly improving a precedent synthesis (**Scheme 10**).



Scheme 10. Dual photocatalysis for the ring-expansion of cyclic ketones to macrolactones. [28]

In recent years, a particular interest has been devoted to the elaboration of redox-neutral coupling protocols enabling the formation of C(sp²)-C(sp³) bonds from readily available starting reagents. In this context, the photoredox/nickel dual catalysis has emerged as a powerful platform for securing the formation of such bonds under mild reaction conditions by the use of various starting materials. [44-57] Among them, alcohols have been already used and valorized, albeit in the oxalate functionalized forms. [58-64] Consequently, in 2021, the Zuo group has envisaged the feasibility to achieve such couplings by using native alcohols **24**, and they have disclosed the dehydroxymethylative arylation of free alcohols with aryl bromides **23** using a cooperative catalytic system employing cerium, DPA and nickel catalysts (**Scheme 11**). [29] Interestingly, the success of this reaction lies in the use of carboxylate salts as ligands for cerium(III) chloride. Without the use of those unconventional ligands, the reaction was ineffective. To find this class of ligands, the authors screened more than 190 ligands by using an automatic device. This survey showed that carboxylate ligands with electron-donating substituents in the ortho-position furnished the best results (**Scheme 11**). The reaction gave access to a wide range of compounds **25**, demonstrating a high functional group tolerance. However, alcohols that can be engaged in the reaction seem to be limited to substrates forming stabilized radicals such as α -O-, -N-, -vinyl or -alkynyl radicals and benzyl radicals (**Scheme 11**). Mechanistically, the reaction would proceed following the previously mentioned mechanisms, except that in this case

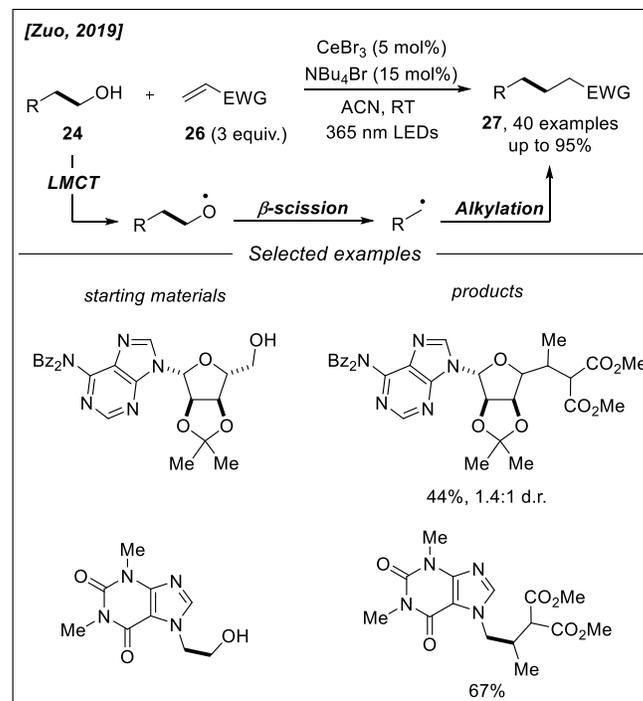
the DPA photocatalyst was used as an electron-shuttle between the cerium and the nickel catalytic cycles (**Scheme 11**). Regarding the nickel catalytic cycle, the latter would start by the oxidative addition of Ni^0 with aryl bromides, resulting in the formation of the $\text{X-Ni}^{\text{II}}\text{-Ar}$ complex, which then would trap the radical intermediate generating a Ni^{III} complex. The reductive elimination would form concomitantly products **25** and a Ni^{I} intermediate. Finally, the reduced form of DPA would reduce the Ni^{I} intermediate to Ni^0 (**Scheme 11**).



Scheme 11. Photocatalytic dehydroxymethylative arylation mediated by cerium, DPA, and nickel catalysis. [29]

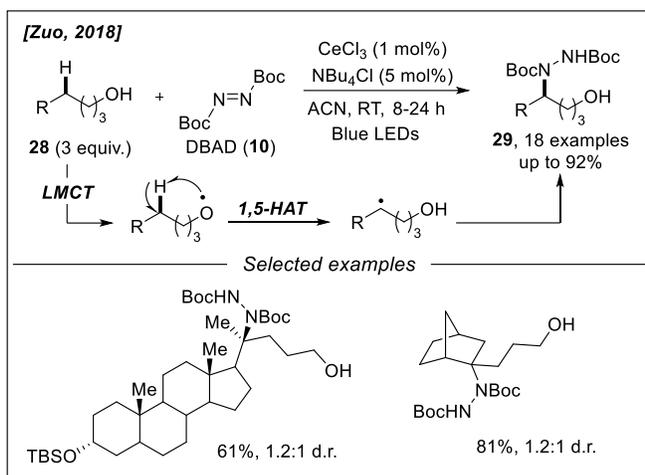
Prior to this work, the Zuo group has already reported a dehydroxymethylation of alcohols **24**, in which alkyl radicals reacted with electron-deficient alkenes **26** (**Scheme 12**). [30] In this protocol, the reaction was carried out without the use of an additional photocatalyst. Indeed, to maintain the catalytic cycle, the reaction was performed under 365 nm irradiation. This enables a double-excitation process, in which both the $\text{Ce}^{\text{IV}}\text{-OR}$ complex and the Ce^{III} are excited, ensuring respectively the LMCT step and the final SET event. Selectivity studies were conducted to demonstrate that

in the reaction the β -scission process is highly favored compared to the 1,5-HAT. The procedure has been applied to the synthesis of various substrates **27** in moderate to excellent yields, ranging from simple to complex molecules bearing, for instance, uridine or adenosine cores (**Scheme 12**).

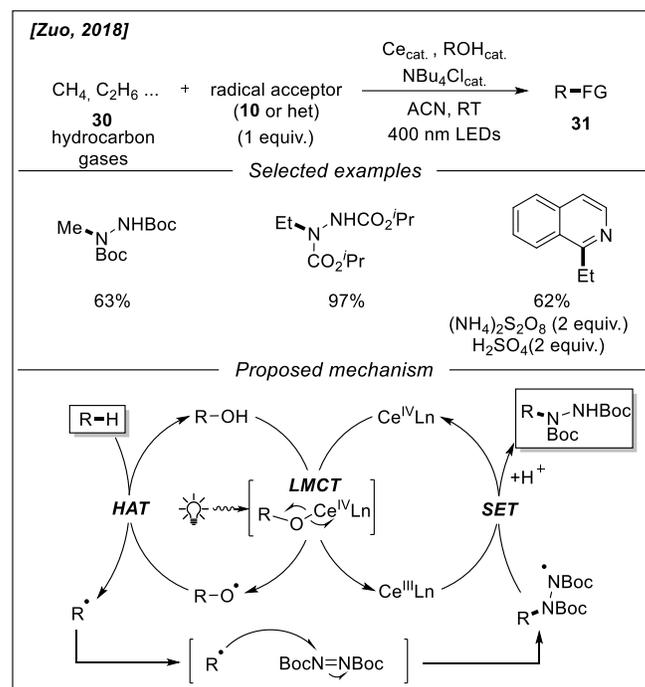


Scheme 12. Cerium-photocatalyzed dehydroxymethylation of alcohols. [30]

In parallel to the reactions involving LMCT going through β -scission processes, other cerium photochemical LMCT-based strategies involving HAT processes have been developed. For instance, the Zuo group in 2018 disclosed a method enabling the remote CH -bond functionalization of free alcohols **28**. [31] They demonstrated that alkoxy radicals, generated through LCMT under light activation and in presence of CeCl_3 and NBu_4Cl , can be engaged in a 1,5-HAT resulting in the formation of δ -C-centered radicals (**Scheme 13**). The latter would then react with DBAD **10**, giving compounds **29**. A large library of native alcohols showed to be suitable for the reaction, ranging from butanol to lithocholanyl alcohol.

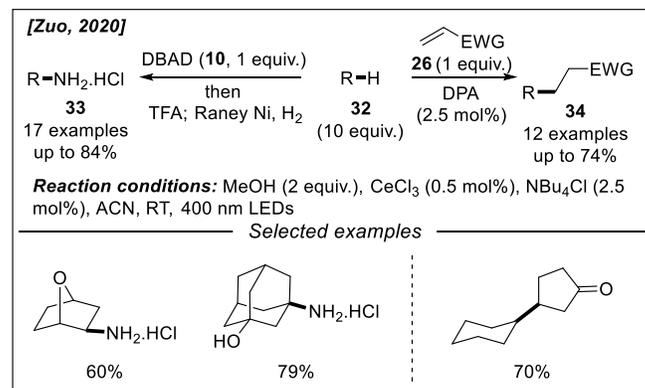
Scheme 13. Cerium-photocatalyzed δ -functionalization of alcohols. [31]

Based on such reactivity, the Zuo group have also explored the possibility to extend the reaction to intermolecular HAT. [32-33] Therefore, they developed a new and elegant reactivity concept relying on the use of a catalytic amount of free alcohols for achieving the *CH*-bond functionalization of hydrocarbon gases **30** such as methane (Scheme 14). [32] For catalyzing the reaction, simple and cheap alcohols, such as methanol, 2,2,2-trifluoroethanol (TFE) and 2,2,2-trichloroethanol (TCE), have been selected. Indeed, their alkoxy radical counterparts are strongly electrophilic and energetic, therefore able to abstract hydrogen atoms from hydrocarbon gases C-H bonds. This intermolecular HAT step would form the alkyl radical that could react with various acceptors, such as DBAD **10**, forming functionalized products **31** (Scheme 14). In comparison with intramolecular HATs, in which the selectivity is ruled by transition states, intermolecular HATs are much less selective, and often lead to mixture products. The authors were confronted to this problem while the functionalization attempts of propane and butane were undertaken. However, they also demonstrated that the selectivity of HATs could be influenced by using alcohols with divers electronic nature. For instance, they observed that methanol favors, in a general manner, HAT from the methylene C-H bonds (Scheme 14).



Scheme 14. Cerium photoredox platform used for the functionalization of gaseous alkanes. [32]

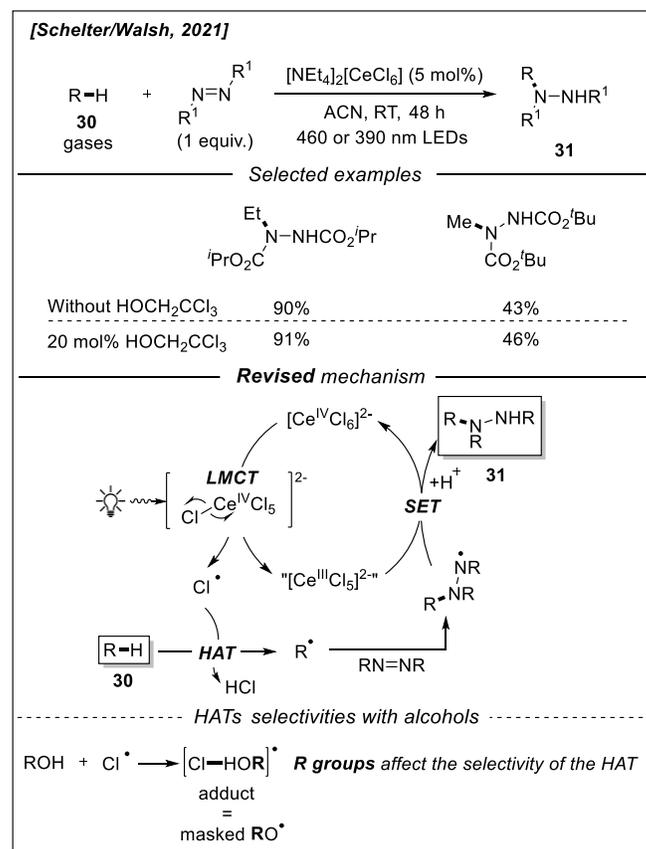
In 2020, a similar methodology was developed by the Zuo group, in which the cerium/alcohol dual catalysis was applied to the synthesis of amino-compounds **33** and molecules **34** from non-prefunctionalized hydrocarbons **32** (Scheme 15). [33] As previously discussed, the synthesis of products **34** required the use of DPA as photocatalyst. During this study, through extensive selectivity investigation, the authors defined a HAT selectivity map, which depends on the electronic nature and the steric hindrance of the alcohol HAT catalysts. For instance, methanol favors abstraction from methylene C-H bonds, whereas *tert*-butanol-catalyzed HAT from less sterically hindered C-H bond positions. On the other hand, the use of alcohols with more electrophilic behavior, such as TCE or TFE, disfavored abstraction from weaker methylene C-H bonds (Scheme 15).



Scheme 15. Cerium photoredox platform used for the functionalization of gaseous alkanes. [33]

In May 2021, Schelter/Walsh published an extensive mechanistic study aiming at improving the understanding of the reported cerium-based photochemical protocols allowing the functionalization of alkanes by HATs. [34] This recent

study has defined a new mechanistic paradigm for such reactions, in which alkoxy radicals would be unlikely formed and involved in the HAT event (**Scheme 16**). Instead, the authors proved that chlorine radicals actively participated to this HAT key step. The study started with spectroscopic analyses by recording UV-visible absorption spectra of both $[\text{NEt}_4]_2[\text{CeCl}_6]$ and $[\text{NEt}_4]_2[\text{CeCl}_5(\text{OCH}_2\text{CCl}_3)]$ ate-complexes. Then, they showed that the UV-visible spectrum of $[\text{NEt}_4]_2[\text{CeCl}_6]$ complex remained unchanged in presence of various amount of alcohols, demonstrating that the complexation of alcohols with $[\text{NEt}_4]_2[\text{CeCl}_6]$ for forming the $[\text{NEt}_4]_2[\text{CeCl}_5(\text{OCH}_2\text{CCl}_3)]$ complex is not operating. Those results are also supported by NMR studies. While kinetic studies indicated that rate of reaction depends on the concentration of both the cerium complex and alkane, the latter demonstrated a zero-order dependence on the concentration of alcohol on the reaction-rate. Then, the authors repeated the reaction depicted in the **Scheme 14**, with their reaction conditions (**Scheme 16**). They observed no significant changes of yields with the conditions employing catalytic amount of alcohol, highlighting that alcohols play no role in the reaction. Consequently, they proposed a revised mechanism, which would involve a photoinduced LMCT between chloride ligands and the cerium center, resulting in the formation of the radical chlorine and the Ce^{III} species. Then, the radical chlorine would abstract a hydrogen from the alkane **30** yielding the C-centered radical, which would give the final product **31** by an addition/protonation sequence (**Scheme 16**). Finally, the authors assumed that the difference of HAT-selectivities observed by the Zuo group by the use of various alcohols is likely due to the formation of the $[\text{ClHOR}]^{\bullet}$ radical adduct (**Scheme 16**). Those adducts can be assigned as masked alkoxy radicals, adopting similar properties. It is important to mention, in view of this preliminary mechanistic study, that 1,5-HAT and β -scission reactivities previously described might result from the formation of $[\text{ClHOR}]^{\bullet}$ radical adducts and not from the generation of alkoxy radicals.



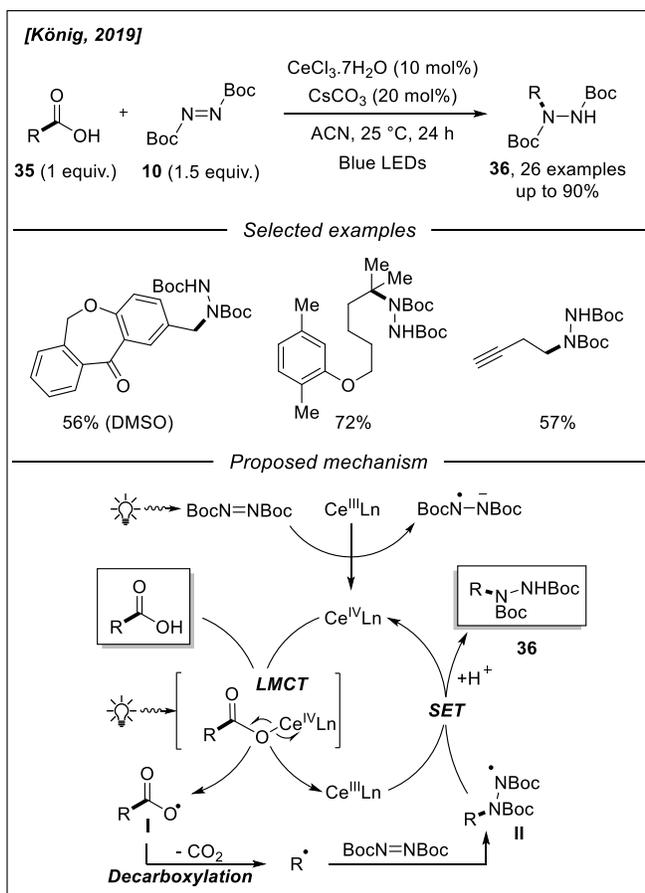
Scheme 16 Mechanistic study of the cerium photocatalyzed functionalization of gaseous alkanes. [34]

2.1.2 Lanthanide catalysis for the activation of carboxylic acids

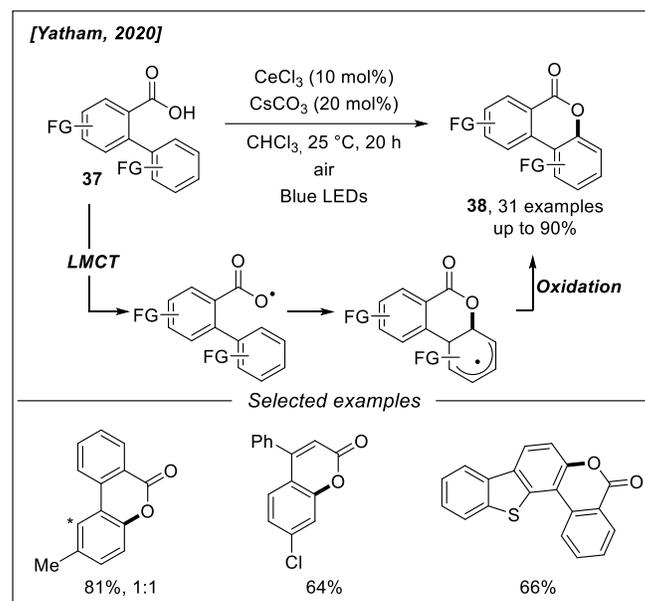
As part of the lanthanide catalysis for the generation of O-centered radical intermediates, lanthanide catalysis for the activation of carboxylic acids has been much less studied compared to processes activating alcohols. [35-38] However, such protocols are particularly interesting as carboxylic acid substrates are prevalent in nature. Moreover, this strategy might be advantageous and might constitute an alternative to the well-known photoredox activation of carboxylic acids involving outer-sphere electron transfers. [65-67] To date, only processes mediated by cerium have been disclosed for the activation of carboxylic acids. The first investigations demonstrating that cerium can be used for catalyzing decarboxylation reactions were reported by Kochi and Sheldon. [35] In this work, they showed that under light irradiation cerium(IV) carboxylate complexes can trigger the radical decarboxylation of carboxylic acids affording product mixtures through the generation of alkyl radicals.

In 2019, the König group investigated other type of decarboxylative processes by the use of a cerium catalyst (**Scheme 17**). [36] Inspired by the work from the Zuo group, they studied the decarboxylative hydrazination of aliphatic carboxylic acids **35**, in presence of DBAD **10** and catalytic amounts of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ and Cs_2CO_3 (**Scheme 17**). The reaction affords compounds **36** in moderate to good yields, and tolerates a wide variety of functional groups. As in the classical one-electron decarboxylative processes, the use of a base is mandatory for forming the active carboxylate species involved in the decarboxylation. Interestingly, in those reactions conditions only a catalytic amount of base is

required for the reaction. From a mechanistic point of view, the authors proposed that a Ce^{III} species would be oxidized to the Ce^{IV} complex by the photoexcited DBAD (**Scheme 17**). Then, the photoexcitation of the Ce^{IV} -carboxylate complex would trigger LMCT and homolysis resulting in the generation of carboxyl radicals (**I**). Next, the decarboxylation step would form *C*-centered radicals that would react with DBAD generating the intermediate **II**. The SET reduction of **II** from the Ce^{IV} would give the final compounds and restore the active catalytic species (**Scheme 17**).



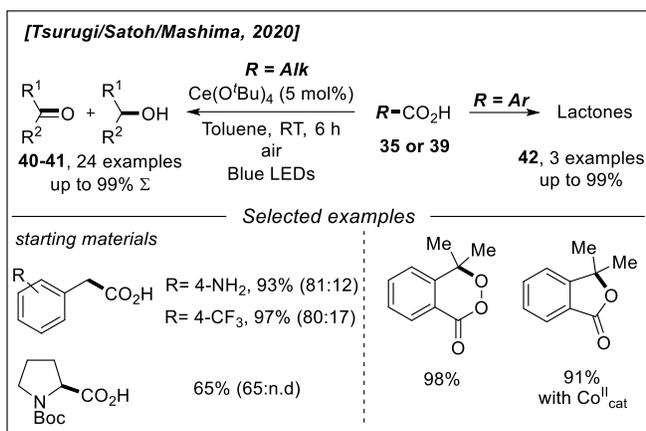
Scheme 17. Decarboxylative hydrazination mediated by the cerium photoredox platform. [36]



Scheme 18. Visible-light Cerium-catalyzed intramolecular lactonization of aryl carboxylic acids. [37]

Similarly, in 2020, Yatham and co-workers described a protocol enabling the intramolecular lactonization of aryl carboxylic acids **37** using catalytic amounts of $CeCl_3$ and Cs_2CO_3 under irradiation and air (**Scheme 18**). [37] In contrast with prior work from the König group the decarboxylation of carboxylic acids does not occur in the procedure. The difference of reactivity is explainable by the fact that the decarboxylation of aryl carboxylic acids would result in the formation of highly instable aryl radicals, whereas aliphatic carboxylic acids would form more stable alkyl radical counterparts. Therefore, the carboxyl radicals, generated after LMCT, would react in an intramolecular manner with aryl moieties. The final oxidation would provide the molecules **38** (**Scheme 18**).

The same year, Tsuguri/Satoh/Mashima published the photocatalytic decarboxylative oxygenation of aliphatic carboxylic acids **35** and the photocatalytic lactonization of aryl carboxylic acids **39** mediated by cerium catalysis in aerobic conditions (**Scheme 19**). [38] These reactions involved LMCT mechanisms enabling for the decarboxylative oxygenation process, both the formation of reduced carbon-chain ketones/aldehydes **40** and alcohols **41**. In those reaction conditions the formation of compounds **40**, compared to **41** is favored. While the lactonization reaction led to comparable lactones **32** than previously reported by Yatham with 2-aryl benzoic acids, the latter gave access to both lactones depicted in **Scheme 19** with 2-isopropyl benzoic acid. Those lactones would be formed through 1,5-HAT between carboxyl radical and the isopropyl, forming the distal *C*-centered radical. At this point, two operative pathways can be considered. Either, the radical would react with oxygen, forming an intermediate that through lactonization would yield to 6-membered lactone derivative, or the radical would be oxidized to the cation, which would react with the carboxylic acid, resulting the in the formation of 5-membered lactone. Tuning of initial reaction conditions allowed the selective formation of both molecules (**Scheme 19**).

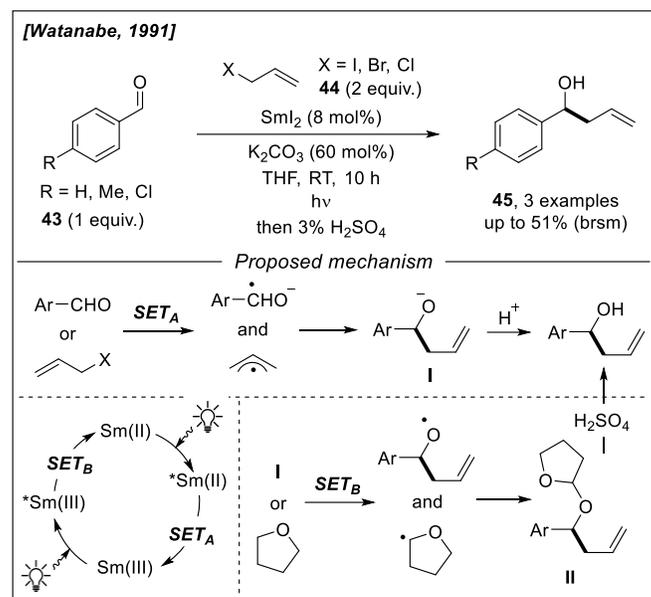


Scheme 19. Visible-light cerium-catalyzed oxygenation of alkyl carboxylic acids and lactonization of aryl carboxylic acids. [38]

2.2 Lanthanides catalysis for the activation of halides

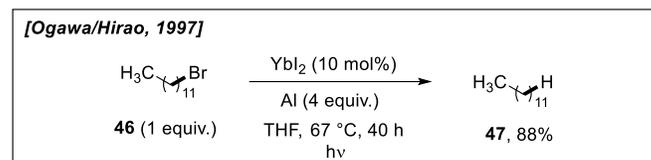
Over the years, the photocatalytic activity of lanthanides has been also exploited for the reduction of various halide substrates. [68-79] The first examples in the fields were reported in the 90s. In comparison with lanthanide catalysis for achieving the activation of alcohols or carboxylic acids, which are so far narrowed to the use of europium and cerium, lanthanide catalysis involving activation of halide species can be performed with a broader number of lanthanides.

In 1991, Watanabe and co-workers established that several trivalent or divalent lanthanides photocatalyzed the allylation of aldehydes (**Scheme 20**). [68] However, the study showed that SmI_2 was the best catalyst for the reaction, albeit the fact that only few compounds **45** were obtained in poor yields. The reaction would proceed through the photoexcitation of both divalent and trivalent samarium species (**Scheme 20**). First, the photoexcited Sm^{II} catalyst would reduce, through a SET reduction (**Scheme 20, SET_A**), either the aldehyde **43** or the allyl halide **44**, generating the Sm^{III} species and respectively the radical anion of **43**, the allyl radical. The radical-radical coupling of the two species would form the intermediate **I**, which after protonation would give the final compounds **45**. On the other side, the Sm^{III} , upon irradiation, would react, through a SET oxidation (**Scheme 20, SET_B**), either with the intermediate **I** or the THF, allowing the formation of corresponding alkoxy radical and α -oxy radical. The radical-radical coupling of the two species would form the compound **II**. The latter would then be converted to the expected product **45** by acidic treatment. It should be noticed that without the acidic treatment a mixture of compounds **II** and **44** is obtained (**Scheme 20**).



Scheme 20. Samarium-catalyzed photochemical allylation of aldehydes. [68]

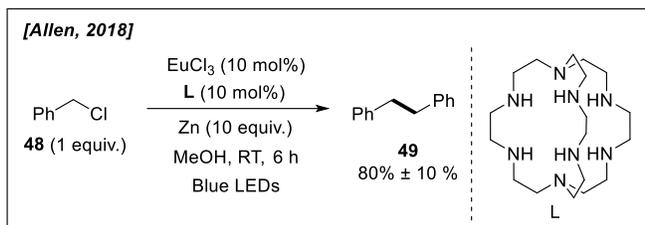
Later on, Ogawa and Hirao studied the reduction of alkyl bromides **46** to the corresponding alkanes **47** under light irradiation in the presence of YbI_2 . [69] They first investigated the reduction of various alkyl bromides with a stoichiometric amount of YbI_2 , before developing a catalytic version that relies on the use of over stoichiometric amount of sacrificial reductant, such as aluminum (**Scheme 21**). The key mechanistic step of the reaction is the photoexcitation of the ytterbium catalyst.



Scheme 21. Ytterbium-catalyzed photoreduction of alkyl bromide under light irradiation. [69]

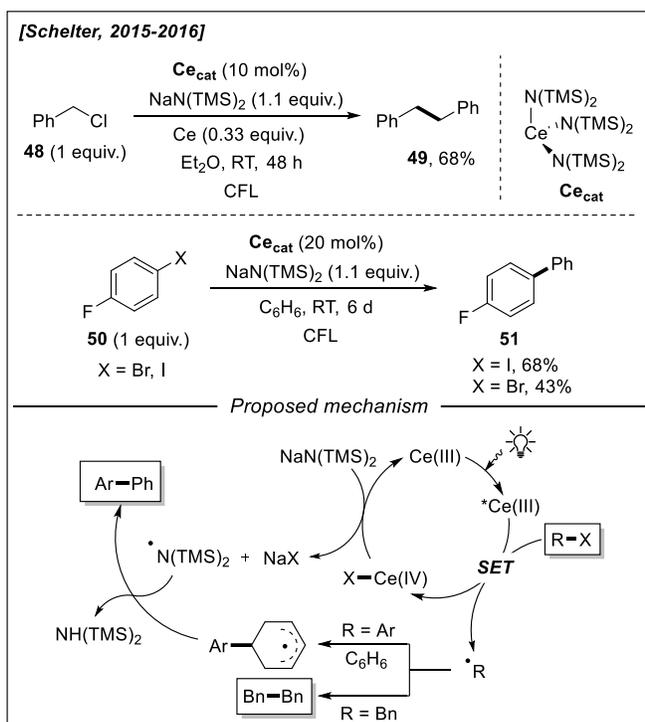
In recent years, various groups have envisaged the possibility to achieve the photoreduction of halide compounds by the use of other lanthanide catalysts, such as europium and cerium. [70-74] For instance, in 2018, the Allen group, which has a strong interest in the synthesis of divalent europium Eu^{II} complexes and their study in luminescence, [75-77] has reported the use of Eu^{II} complexes for performing the photoreduction of organic chlorides under visible-light irradiation (**Scheme 22**). [70] In this work, the excited Eu^{II} complex acts as a potent photoreductant that can activate alkyl or aryl chlorides through SET reduction, allowing respectively the formation of the dimers or the dehalogenated products in poor to good yields. Those experiments were firstly conducted with a stoichiometric amount of the Eu^{II} complex and the best results were obtained for the dimerization of benzyl chloride **48**. Then, the authors developed a catalytic version of the reduction of benzyl chloride by using zinc as sacrificial reducing agent. Control experiments supported the fact that Eu^{III} can be reduced to Eu^{II} by Zn^0 , as well as that Zn^0 could not reduce the benzyl chloride. Pleasingly, the use of Zn^0 allowed the

formation of the benzyl dimer **49** in similar yield than previously by using only 10 mol% of Eu^{III} complex (**Scheme 22**).



Scheme 22. Catalytic photoreduction of benzyl chloride mediated by Eu(II) complex. [70]

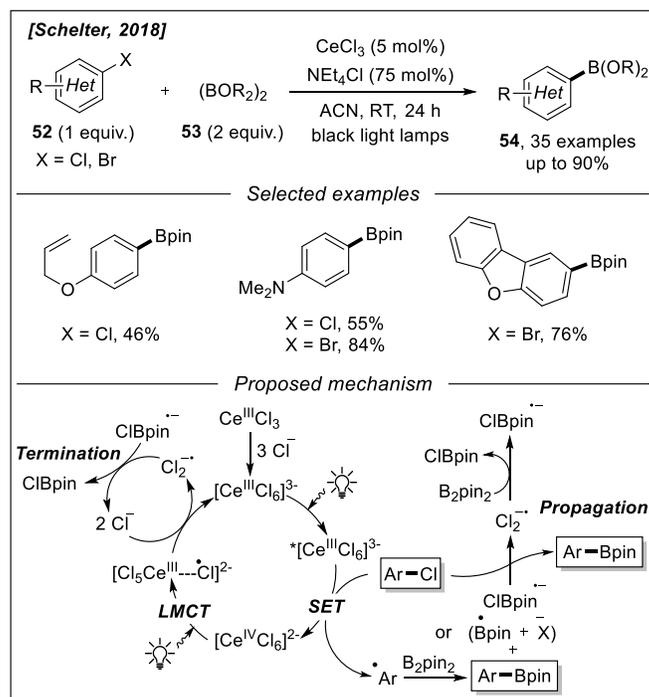
In the same vein, in 2015, the Schelter group explored the photoreduction of benzyl chloride and some aryl halides by the use of a Cerium^{III}-based photocatalyst. While the reduction of the benzyl chloride **48** led to the benzyl-dimer **49** in good yield, the reduction of aryl halides led, in benzene, to the hetero-coupled diaryl species in moderate to good yields. [71-72, 78-79] The authors proposed the mechanism depicted in **Scheme 23**. The latter would start by the photoexcitation of the Ce^{III} complex, which in the excited-state would activate organic halides through a SET reduction, providing the corresponding radicals and the Ce^{IV}-X complex. The active Ce^{III} species would be regenerated by the SET event between Ce^{IV}-X and NaN(TMS)₂, forming the corresponding aminyl radical. On the other hand, radicals generated from organic halides would either, dimerise for benzyl radicals, or form the diaryl product **51** after subsequent reactions with benzene and the aminyl radical (**Scheme 23**).



Scheme 23. Photocatalytic reduction of benzyl and aryl chlorides mediated by cerium. [71-72]

Recently, protocols for achieving the photoinduced borylation of organic compounds have gained tremendous interest. [80-81] In the part of this development, in 2018, the Schelter group published the photomediated borylation of

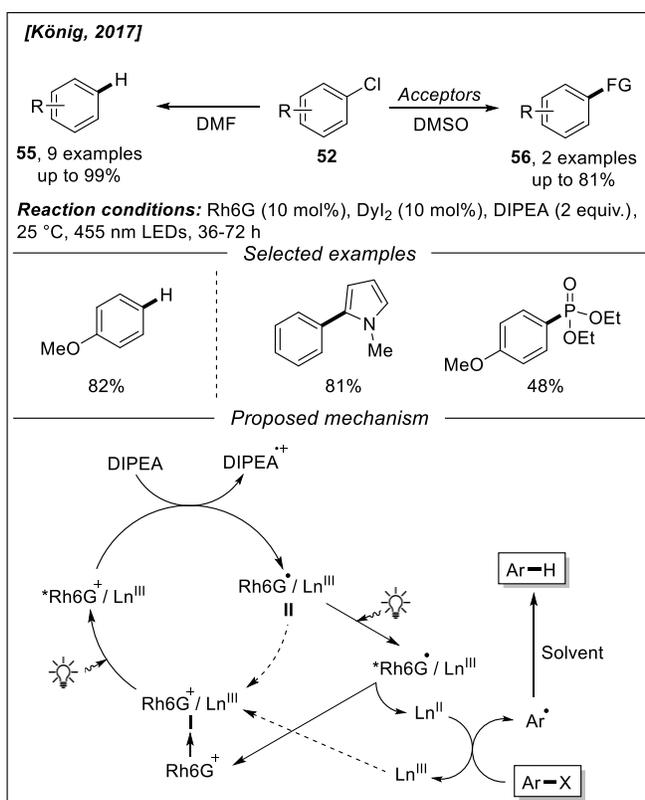
aryl halides **52** by employing a Ce^{III} catalyst (**Scheme 24**). [73] The reaction provides access to various boronate esters **54** in moderate to excellent yields. The success of this borylation process relies on the use of the combination of CeCl₃ and NEt₄Cl salts, which permits the *in situ* formation of the photochemically active [CeCl₆]³⁻ and avoids the formation of the inactive [Ce₂Cl₉]³⁻ species. The postulated mechanism would start by a SET reduction triggered by the photoexcited [CeCl₆]³⁻ complex, leading to both the generation of the aryl radical and the [Ce^{IV}Cl₆]²⁻ complex. Then, the aryl radical would react with the diboron species **53** resulting in the formation of the final product **54** and in the formation of the ClBpin[•] species. The radical propagation would start by a reaction of ClBpin[•] with the starting materials **52**, generating another molecule of **54** and Cl₂^{•-}. Cl₂^{•-} would reduce compounds **53** forming again the ClBpin[•]. Finally, the termination step would proceed by quenching of ClBpin[•] with Cl₂^{•-}, resulting in the formation of ClBpin[•] and two chloride atoms (**Scheme 24**). On the other side, the authors proposed that the initial [CeCl₆]³⁻ complex was restored through a photoinduced LMCT mechanism involving chloride and the [Ce^{IV}Cl₆]²⁻ complex.



Scheme 24. Cerium-photocatalyzed borylation of aryl halides. [73]

To complement the protocols using lanthanides as potent photoreductants upon light irradiation, the König group has developed a method that combines the use of lanthanides and PC, in which the complex of both molecules enables the reduction of aryl chlorides under light exposure (**Scheme 25**). [74] Various combinations of Rhodamine 6G (Rh6G) and lanthanides, notably neodymium and thulium, proved to be effective for the reduction of chlorobenzene **52**. However, the best results were obtained with the combination Rh6G/DyI₂. The extensive mechanistic study allowed the authors to propose a plausible mechanism relying on a Metal Ion Coupled Consecutive Photoinduced Electron Transfer (MCconPET) (**Scheme 25**). The latter would start by the complexation of Ln^{III} to Rh6G forming the corresponding complex **I**. The photoexcited complex **I**, would be reduced

by DIPEA leading to the complex **II**. Then the complex **II** would be excited, [82] allowing the reduction of Ln^{III} to Ln^{II} . This step might be considered as photoinduced LMCT. Finally, the Ln^{II} species would reduce the aryl chloride, resulting in the formation of the aryl radical that would give either the product **55** through hydrogen abstraction from the solvent or the products **56** in the presence of acceptors (Scheme 24). It should be mentioned that control experiments proved that both Rh6G and lanthanide were essential for the reaction efficiency.

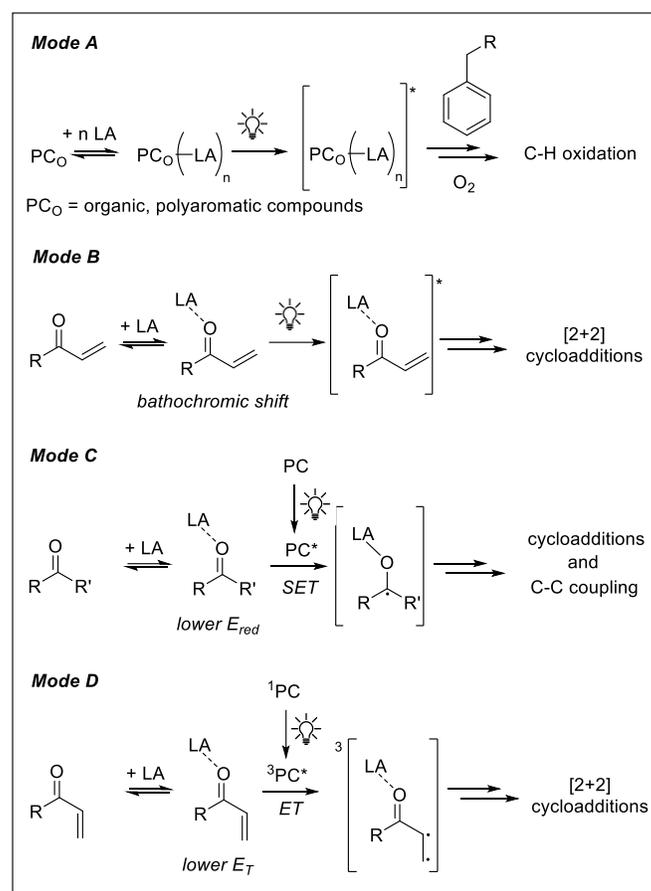


Scheme 25. Cerium-photocatalyzed reduction of aryl chlorides. [74]

3. RARE-EARTHS AS REDOX-NEUTRAL LEWIS ACIDS IN PHOTOCATALYTICAL TRANSFORMATIONS

3.1 Introduction

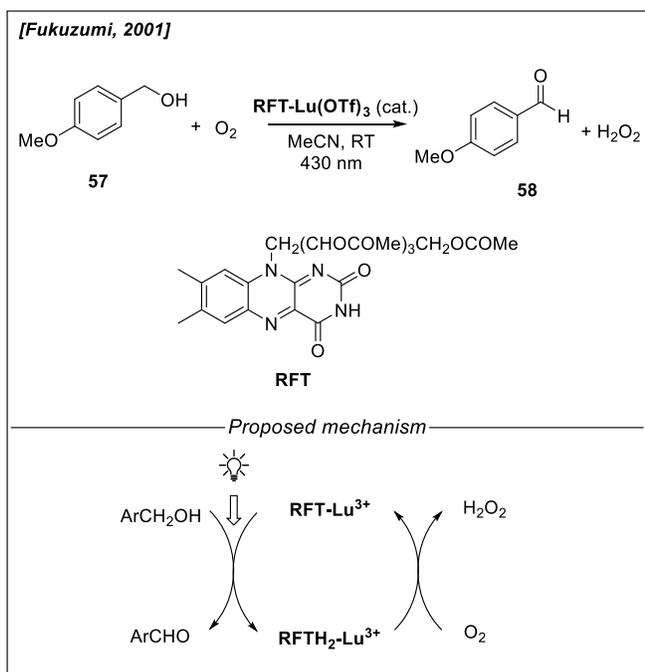
Dual activation modes in photoredox chemistry have recently emerged as an important research area.[83-85] Redox-inactive Lewis acids have attracted particular attention as they can influence photocatalytical transformations in different manners (Scheme 26).[9,10] The Lewis acid can bind to the photocatalyst (in its ground or excited state) to improve its redox properties in the excited state and enable reactions which are impossible with the photocatalyst alone (Mode A). Alternatively, the Lewis acid can bind to the substrate leading to three distinct cases: either the Lewis acid changes the light absorbing properties of the substrate for direct photoexcitation without additional photocatalyst (Mode B) or it facilitates the substrate reduction by a photocatalyst (Mode C) or it lowers the triplet energy of the substrate enabling efficient energy transfer from the photocatalyst (Mode D). In all cases of substrate coordination, chiral Lewis acids have been shown to control the regio and/or stereoselectivity of the reaction process.



Scheme 26. Influence of Lewis acids on photoredox processes.

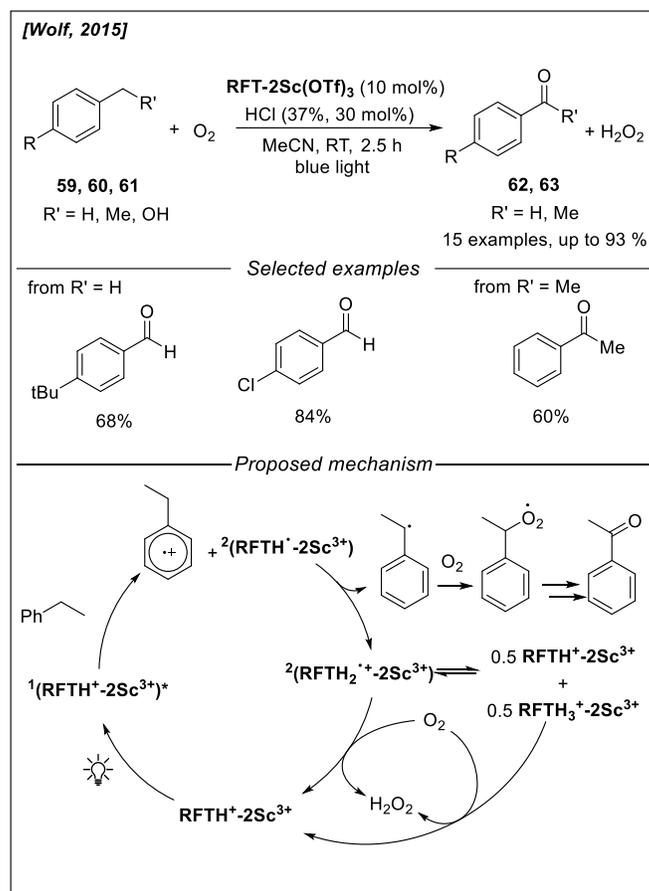
3.2 C-H bond oxidation processes (Mode A)

Flavins have long been studied in photoredox catalysis for their interesting redox-properties.[86,87] Following the seminal work by Fukuzumi and Tanaka on the use of flavin analogue-metal ion complexes (Mg^{2+} , Zn^{2+}) as efficient photocatalysts in alcohol oxidation reactions,[88] it was shown that rare earth metals could also complex flavin analogues to even further increase their redox activity.[89] Coordination of $\text{Sc}(\text{OTf})_3$ to riboflavin tetraacetate (**RFT**) (Scheme 27) resulted in the formation of a 2:1 complex (**RFT-2Sc³⁺**), which led to a considerable blue shift of the fluorescence maximum and a shortening of the fluorescence lifetime compared to metal-free **RFT**. La^{3+} also afforded a 2:1 complex, whereas Yb^{3+} and Lu^{3+} gave 1:1 complexes. The redox potential of the singlet excited state reached 2.45 V (vs. SCE in acetonitrile) for the **RFT-2Sc³⁺** complex, compared to 2.25 V for **RFT-Yb³⁺**, 2.06 V for **RFT-Mg²⁺** and 1.67 V for **RFT** alone. It could then be shown that the **RFT-Lu(OTf)₃** complex was an efficient catalyst for the photocatalytic oxidation of p-methoxybenzyl alcohol **57** using oxygen under visible light irradiation. The formation of the corresponding aldehyde **58** and H_2O_2 in high yields showed evidence for the efficient recycling of the **RFT-Lu³⁺** complex according to Scheme 27. In addition, the presence of Lu^{3+} also prevented the photodegradation of **RFT**.



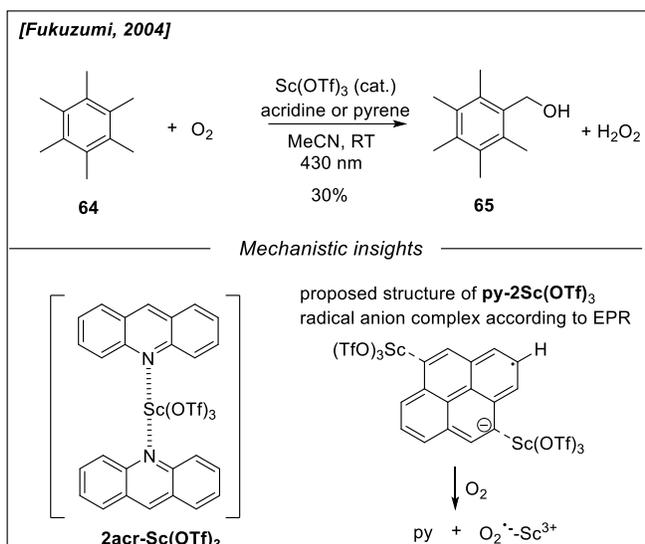
Scheme 27. Flavin-rare earth complexes for photocatalytic oxidations.[89]

Along this line, the Wolf group showed in 2015 that the riboflavin tetraacetate-scandium complex **RFT-2Sc(OTf)₃** was an efficient catalyst for the photocatalytic oxidation of various alkylbenzene derivatives and benzyl alcohols **59-61** in air providing the corresponding aldehydes **62** or ketones **63** in good to high yields (Scheme 28).[90]. It was found that in the presence of HCl (30 mol%) the reaction proceeded four times faster. From a mechanistic point of view, it was suggested, based on Fukuzumi's proposal [89,91], that after the one-electron transfer from the protonated, photoexcited $^1(\text{RFTH}^+-2\text{Sc}^{3+})^*$ complex to the aromatic substrate a proton transfer would occur to yield the benzyl radical and a $^2(\text{RFTH}_2^+-2\text{Sc}^{3+})$ complex. The benzyl radical would further react with dioxygen to yield the hydroperoxide radical and finally yield the carbonyl compound. The catalytic cycle would be closed by slow oxidation of $^2(\text{RFTH}_2^+-2\text{Sc}^{3+})$ with dioxygen to provide H_2O_2 and regeneration of **RFTH⁺-2Sc**. Alternatively, $^2(\text{RFTH}_2^+-2\text{Sc}^{3+})$ could disproportionate to **RFTH⁺-2Sc** and **RFTH₃⁺-2Sc**, the latter which would react with O_2 to H_2O_2 and regenerate the catalytic species.



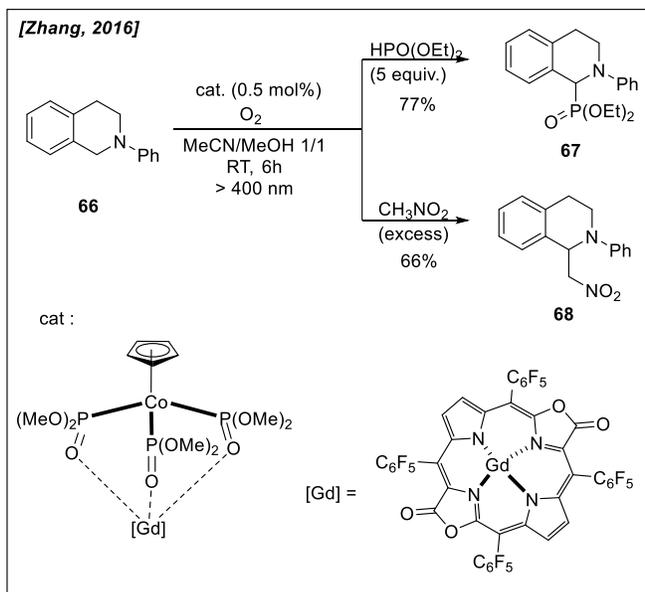
Scheme 28. Flavin-rare earth complexes for photocatalytic C-H bond oxidations.[90]

The Fukuzumi group showed in 2004, that other organic molecules, such as acridine (**acr**) or pyrene (**py**), could also complex Sc^{3+} ions to promote photoinduced electron transfers.[91] Interestingly, whereas acridine forms a 2:1 complex with Sc^{3+} in acetonitrile (**2acr-Sc(OTf)₃**), pyrene is only complexed by two Sc^{3+} ions in its excited state, as shown by EPR studies, forming the excimer **py-2Sc(OTf)₃**. Both systems were studied in the photooxidation of hexamethylbenzene **64** providing pentamethylbenzyl alcohol **65** in modest 30% isolated yield due to overoxidation of the product (Scheme 29). An important mechanistic intermediate, the $[\text{O}_2^{\cdot-}-\text{Sc}^{3+}]$ radical anion complex, was identified by EPR studies, which after protonation eventually disproportionates to yield O_2 and H_2O_2 .



Scheme 29. Acridine and pyrene scandium complexes for photocatalytic C-H oxidation of hexamethylbenzene.[91]

In 2016, Zhang and coworkers reported on the application of Gd-porpholactones as efficient singlet oxygen photosensitizers enabling several C-H bond oxidation reactions. The coupling of tertiary amine **66** with diethyl phosphite and the oxidative aza-Henry reaction provided good yields of the corresponding products **67** and **68**, respectively (**Scheme 30**).[92] In the key step, the photochemically produced singlet oxygen oxidizes the amine to an iminium ion intermediate.



Scheme 30. Gd-porpholactones for photocatalytic C-H oxidations.[92]

3.3 Cycloaddition reactions

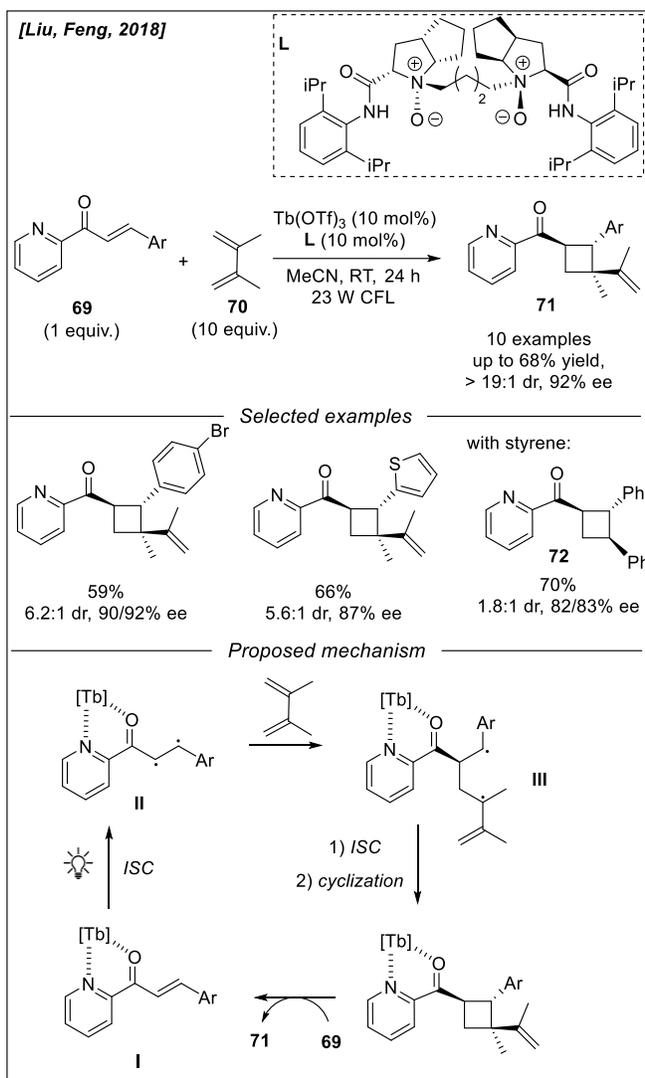
3.3.1 [2+2] photocycloaddition reactions

Light-induced [2+2] cycloaddition reactions of olefins are among the most widely studied photochemical reactions.[93-96] They either occur by direct light absorption of the organic substrates (mainly UV light) or are mediated under milder conditions (visible light) using photocatalysts.

3.3.1.1 Lewis acids as sole photocatalysts (Mode B)

Chiral Lewis acids have recently been shown to provide access to enantioselective [2+2] photocycloadditions through direct coordination to one of the organic reaction partners. The resulting bathochromic shift of the substrate-Lewis acid adduct allows to suppress unselective background reactions upon irradiation in the visible-light region. Leading work in this field was based on chiral aluminum,[97] iridium or rhodium complexes.[98]

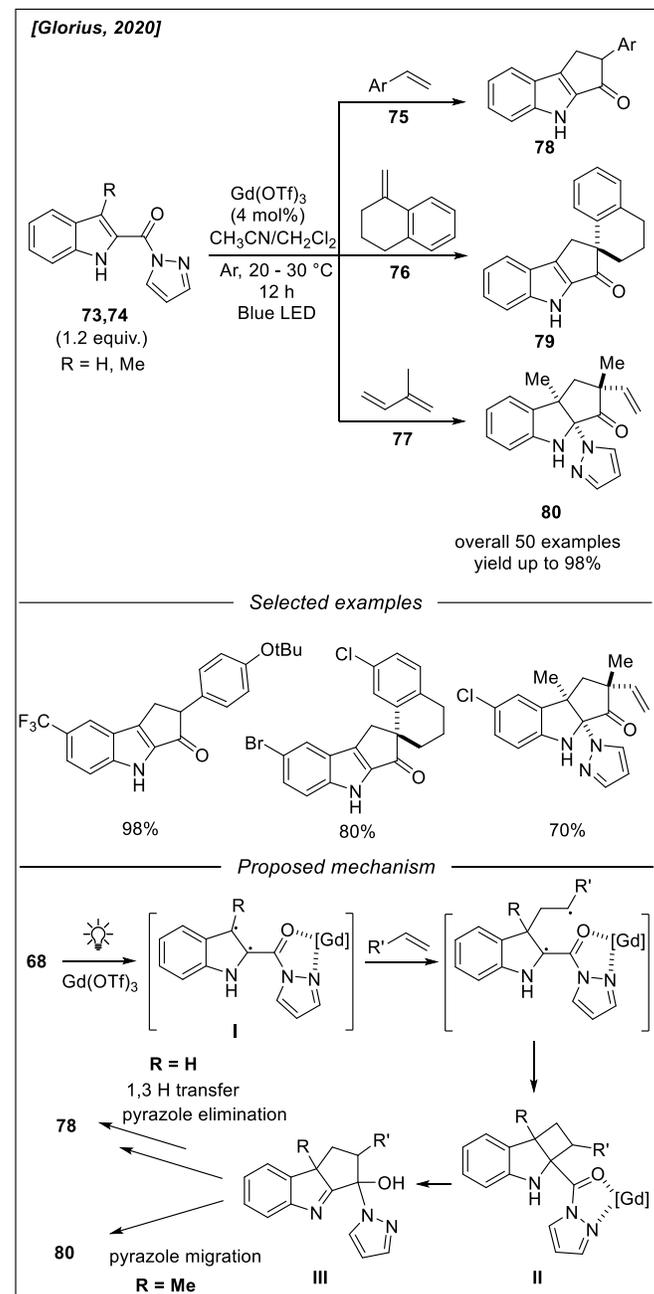
In 2018, Liu and Feng reported on the use of a Lewis acidic terbium complex bearing a chiral tetradentate N,N'-dioxide ligand (**L**) in the visible-light enantioselective [2+2] cycloaddition between 2-alkenylpyridines **69** and dienes **70** (**Scheme 31**).[99] Numerous enantioenriched cyclobutanes **71** could be synthesized in good yields and with high diastereo and enantioselectivity. The reaction could also be extended to alkenes as coupling partners, providing for example cyclobutane **72** in the case of styrene. The pyridine nitrogen atom was essential for the reaction to occur, a 2'-hydroxychalcone did not react under these conditions. For the mechanism, it was suggested that the initially formed Tb-2-alkenylpyridine complex **I** would be excited under visible light and form the diradical **II** after inter-system-crossing (ISC). This intermediate would be attacked by the alkene from the α -Re face providing the new diradical species **III** which after ISC would cyclise to the cyclobutane product **71**. The formation of **II** was supported by the observed Tb luminescence. A crystal structure of the **L**-Tb(OTf)₃ complex was obtained which provided a possible explanation for the observed diastereoisomer.



Scheme 31. Intermolecular enantioselective [2+2] photocycloaddition using a chiral $\text{Tb}(\text{OTf})_3$ complex as photocatalyst.[99]

A $\text{Gd}(\text{OTf})_3$ -catalyzed [2+2] photocycloaddition/ring-expansion sequence involving indoles and alkenes was described in 2020 by the Glorius group (**Scheme 32**).[100] When the colourless indole derivative **73** bearing a pyrazole moiety as traceless directing group was mixed with colourless $\text{Gd}(\text{OTf})_3$ a yellow solution resulted indicative of a bathochromic shift of the substrate-Lewis acid adduct. Excitation of this complex under blue light in the presence of styrene derivatives **75** or **76** afforded cyclopenta[b]indole products **78** and **79** as single regioisomers. The reaction also proceeded with the methyl-substituted indole derivative **74** and isoprene **80**, affording selective 1,2 addition to furnish product **81**, still containing the pyrazole group. Mechanistically, excitation of the Gd -substrate adduct would provide a long-lived diradical species **I**, which would undergo a stepwise [2+2] cycloaddition with the alkene to provide the cyclobutene intermediate **II**. Spontaneous semipinacol rearrangement of **II** would yield the cyclopentanol species **III** which could either undergo a 1,3-H transfer and pyrazole elimination to give **78** or pyrazole migration would

occur in the case of the 3-methyl-substituted indole leading to **81**.

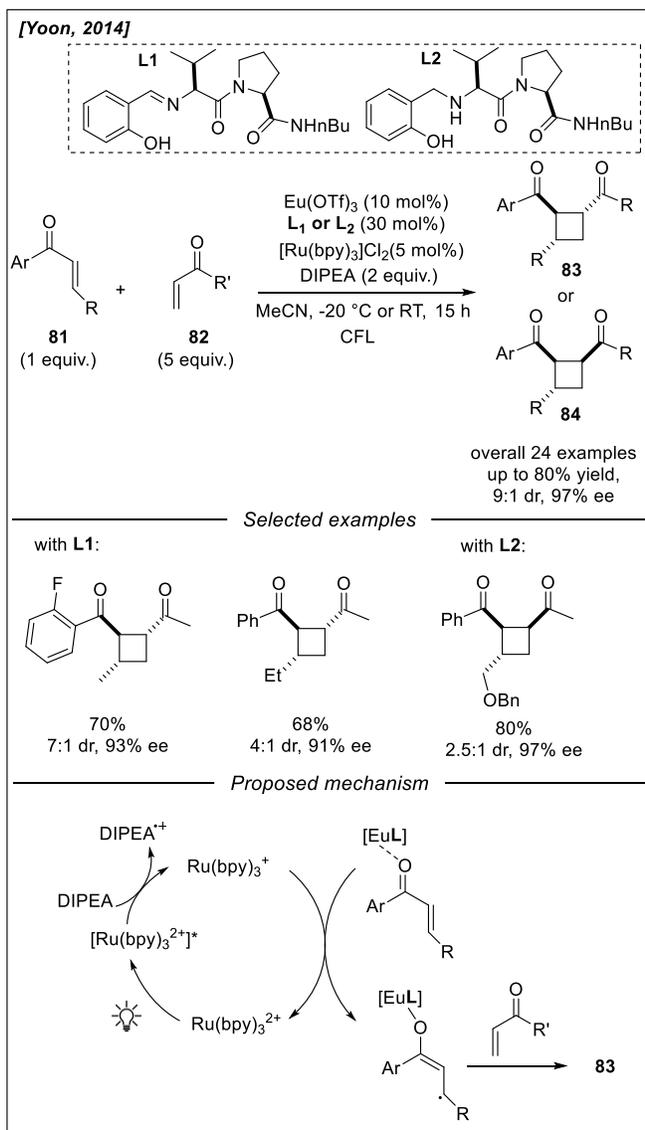


Scheme 32. Intermolecular [2+2] photocycloaddition/ring expansion using $\text{Gd}(\text{OTf})_3$ as photocatalyst.[100]

3.3.1.2 LA + PC (Mode C + D)

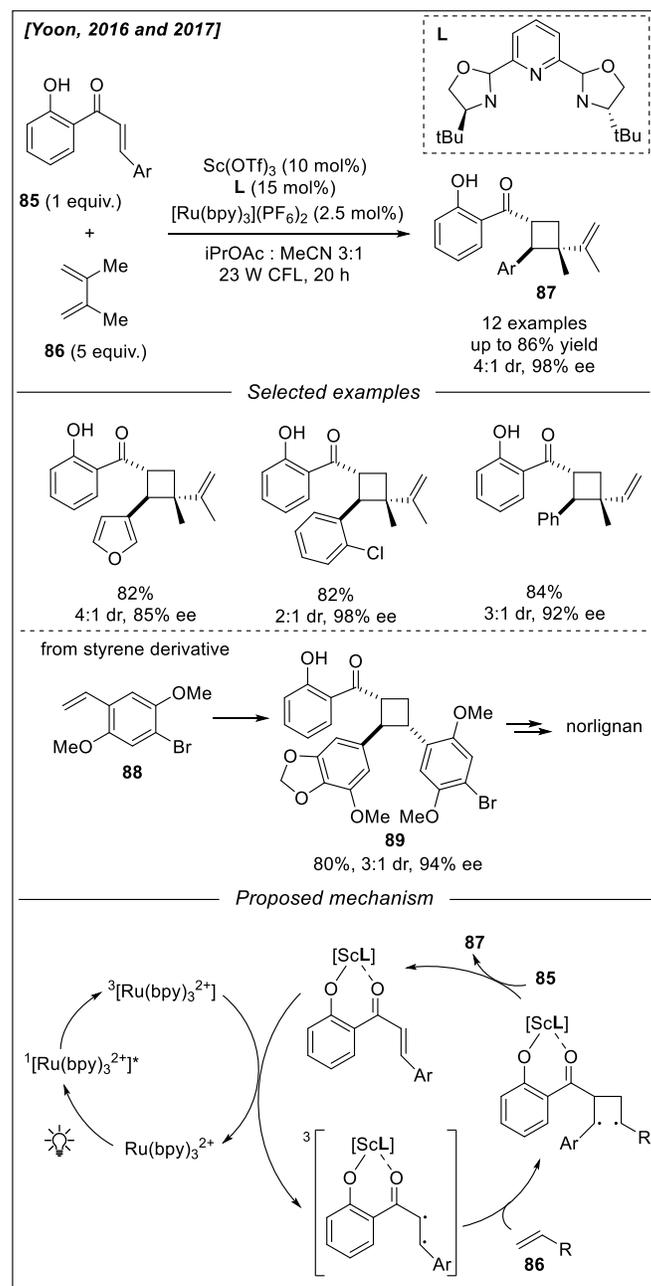
The highly enantioselective intermolecular [2+2] photocycloaddition of two enone derivatives was reported by Yoon in 2014 (**Scheme 33**).[101] The association of $\text{Eu}(\text{OTf})_3$ with a chiral Schiff base dipeptide ligand (**L1**) turned out to be most efficient for the enantioselective synthesis of 1,2-trans-cyclobutane derivative **83** from the starting enones **81** and **82** under visible-light photoredox catalysis. The success of this reaction relies on the absence of reactivity of the two substrates under visible light without the Lewis acid coordination, hence preventing undesired non-stereoselective side reactions. Note that using an excess of **82** diminished the formation of possible homocoupling products. Reduction of the ligand **L1** with NaBH_4 provided

amine ligand **L2** which could also be successfully employed in this transformation, affording the 1,2-cis-cyclobutane product **84** in high yields and ee. This result shows the independence of the photocatalyst and the chiral Lewis acid catalyst opening up a wide range of possible dual catalyst combinations. From a mechanistic point of view, the coordination of the chiral Lewis acid to substrate **81** would enable its reduction by a photogenerated Ru(I) catalyst to the radical anion, followed by stepwise [2+2] cycloaddition with **82**.



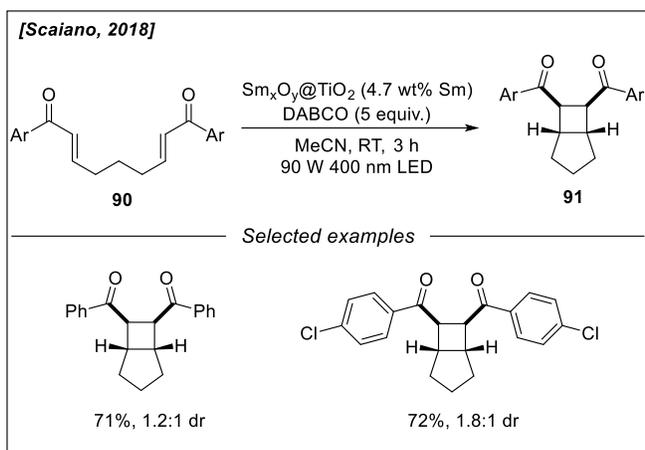
Scheme 33. Enantioselective [2+2] cycloaddition of enones.[101]

In another seminal contribution to the field of enantioselective [2+2] photocycloaddition reactions, Yoon and coworkers showed that the coordination of a chiral Sc(OTf)₃ complex to 2'-hydroxychalcone **85** lowered the triplet energy of this substrate to enable efficient energy transfer from an excited triplet photocatalyst resulting in the reaction with diene **86** to yield the cyclobutane **87** in high yield and excellent ee (**Scheme 34**).^[102] This work was further extended to styrenes, such as **88**, as coupling partners providing access to interesting building blocks, e.g. **89**, for natural product synthesis such as norlignan, artochamin and lindleyanin.^[103]



Scheme 34. Enantioselective [2+2] cycloaddition via triplet energy transfer.^[102,103]

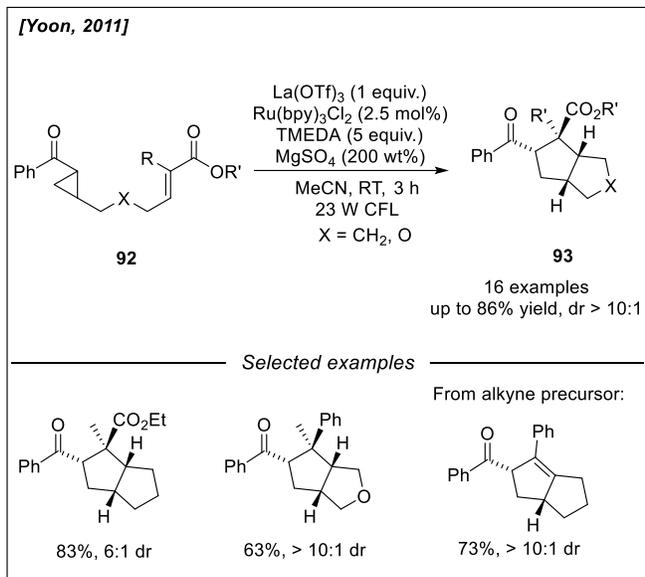
The use of a bifunctional nanocomposite material consisting of titanium dioxide decorated with samarium oxide nanoparticles in a heterogeneous [2+2] photoaddition reaction was shown by Scaiano in 2018 (**Scheme 35**).^[104] The reaction of **90** under visible light in the presence of catalytic amounts Sm_xO_y@TiO₂ and an excess of DABCO provided the cyclized products **91** in good yields but low diastereoselectivity. Previously, Yoon had reported the corresponding homogeneous reaction using the dual catalyst system LiBF₄/[Ru(bpy)₃]²⁺ with comparable yields.^[105] Note that the heterogeneous catalyst could be reused at least three times without significant alterations in the reaction outcome.



Scheme 35. Intramolecular heterogeneous [2+2] cycloaddition.[104]

3.3.2 Other photoaddition reactions (Mode C)

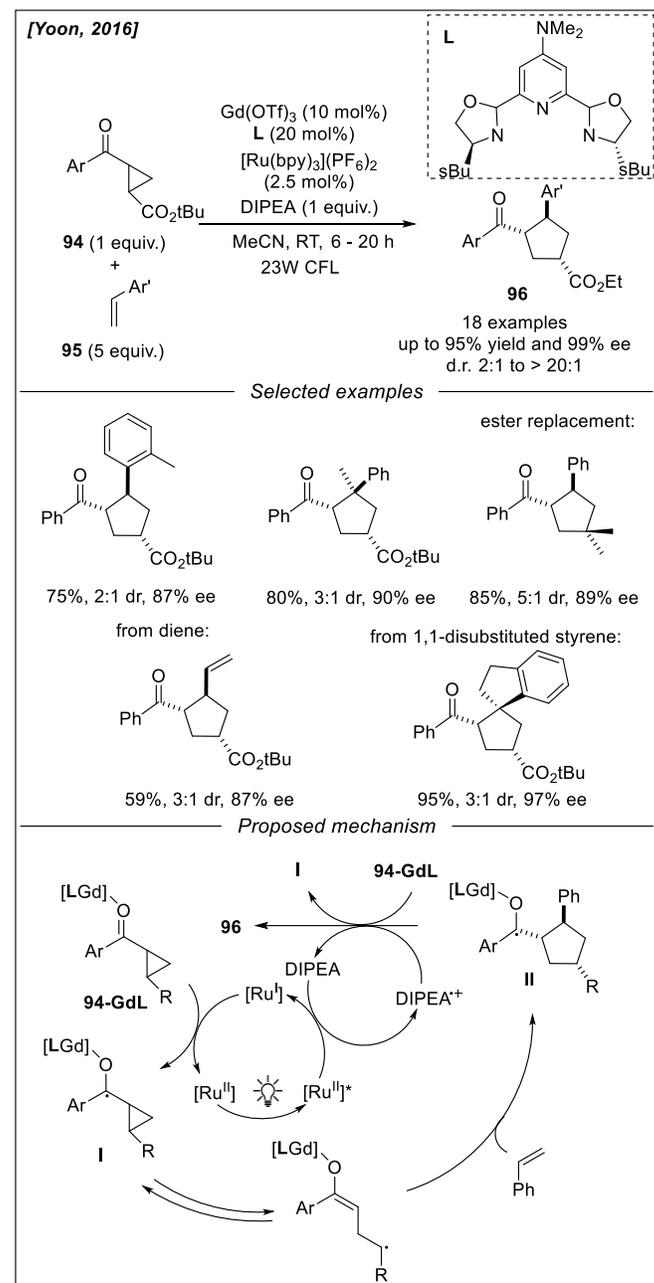
A first example of the combination of rare-earth Lewis acids with a transition-metal based photocatalyst for a [3+2] photocycloaddition was reported by Yoon and coworkers in 2011.[106] Irradiation of the cyclopropyl precursor **92** containing an α,β -unsaturated ester group in the presence of an equimolar amount of $\text{La}(\text{OTf})_3$, catalytic $\text{Ru}(\text{bpy})_3\text{Cl}_2$ and an excess of TMEDA and MgSO_4 afforded the bicyclic product **93** in high yield and with good diastereoselectivity (Scheme 36). The reaction displayed good functional group tolerance and a variety of precursors could be employed, including ether linkages and alkynes.



Scheme 36. Intramolecular [3+2] cycloaddition.[106]

Subsequently, the same group reported an intermolecular enantioselective version of this [3+2] photocycloaddition starting from the cyclopropyl precursor **94** and various alkenes **95** (Scheme 37).[107] In order to achieve high enantioselectivity in the cyclopentane product **96**, the chiral pybox ligand (**L**) with the electron-donating dimethylamino group was employed in combination with $\text{Gd}(\text{OTf})_3$ in catalytic amounts. Variations on the styrene moiety were tolerated and dienes could also be employed. In the cyclopropane substrate various aryl groups were possible and the ester group could be replaced with one or two alkyl

groups, still providing high yields and ees. A first important step in the mechanistic proposal is the coordination of the chiral Lewis acid to the carbonyl group (**94-GdL**), which allows its reduction by the in-situ generated $\text{Ru}(\text{I})$ photocatalyst via SET to provide ketyl radical **I**. Reversible cyclopropane ring-opening and slow stepwise cycloaddition with styrene derivatives would lead to the ketyl radical **II** which could provide the final product **96** either by reduction of another Gd-coordinated starting complex or by a chain terminating reduction of the amine radical cation.



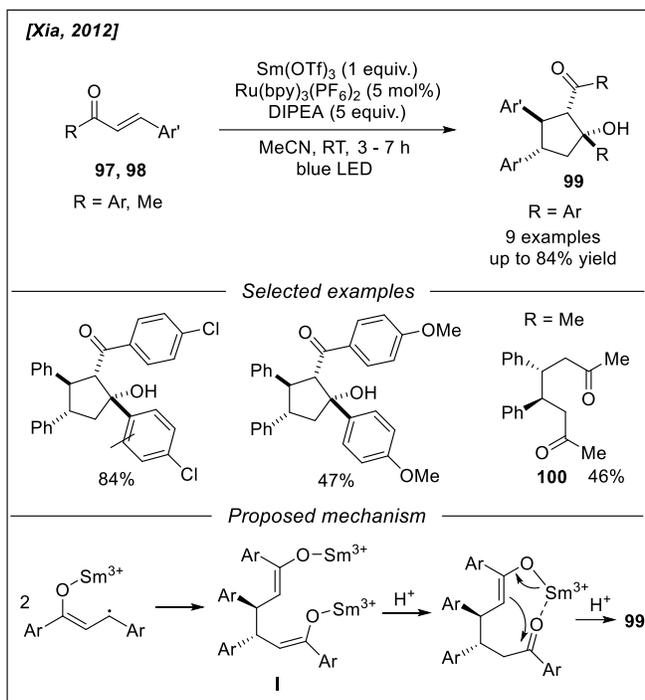
Scheme 37. Intermolecular enantioselective [3+2] cycloaddition.[107]

3.4 Reductive coupling of electrophiles (Mode C)

In 2012, the reductive coupling and cyclization of chalcones under dual Lewis acid photoredox catalysis was reported (Scheme 38).[108] The reaction of chalcones **97** ($\text{R} = \text{Ar}$) in the presence of one equivalent $\text{Sm}(\text{OTf})_3$ and catalytic Ru photocatalyst afforded the cyclopentanols **99** in

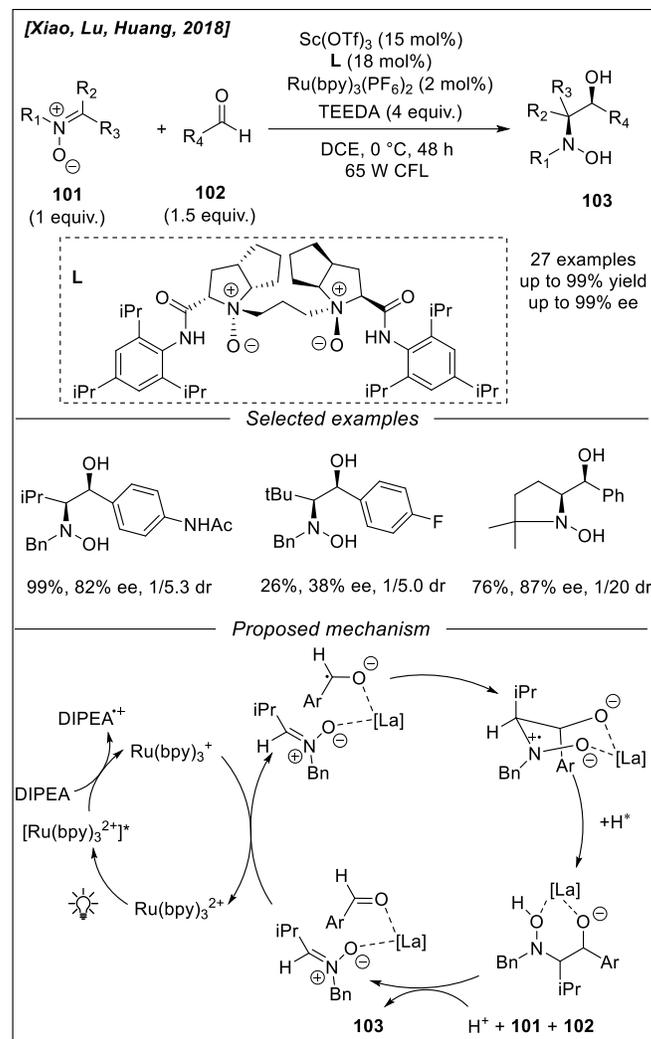
moderate to good yields, depending on the electronic character of the aryl substituents. The cyclisation was not observed for acetone derivatives **98** (R = Me) but only reductive coupling occurred to the linear dimer product **100**. The key intermediate in this reaction, the dianionic complex **I**, obtained from the dimerization of photogenerated radical-anion, would undergo sequential protonation and intramolecular aldol cyclisation.

In 2018, Scaiano showed that this reaction was also feasible under heterogeneous conditions using the bimetallic $\text{Sm}_x\text{O}_y/\text{TiO}_2$ photocatalyst (see **Scheme 35**) providing better yields in certain cases compared to the homogeneous reaction.[104] In addition, the bimetallic system could be reused at least 5 times without any loss of activity.



Scheme 38. Reductive coupling and cyclization of chalcones.[108]

In 2018, a convergent synthetic pathway to enantiopure vicinal amino alcohols using dual chiral Lewis acid/photocatalysis conditions was described (**Scheme 39**).[109] The reaction of nitrones **101** with aldehydes **102** in the presence of Ru photocatalyst, chiral Sc(OTf)₃(N,N'-dioxide) catalyst and TEEDA as co-reductant under CFL exposure at 0 °C provided a large variety of vicinal aminoalcohols **103** with good to very high yields and good to excellent enantioselectivity. Different alkyl substituents on the nitron moiety as well as various aryl/heteroaryl groups on the aldehyde were tolerated. Only the very bulky t-butyl group (R₂ on nitron) led to strongly diminished yields and ee. Mechanistic investigations using radical clock experiments, cyclic voltammetry and DFT calculations provided evidence that the reaction would start by SET from the photogenerated Ru(I) to the Lewis acid bound aldehyde. The corresponding ketyl radical would add onto the nitron via a six-membered transition-state favored by the concomitant coordination of the nitron to the Lewis acid. Hydrogen abstraction from DIPEA by the N-radical intermediate would provide the Lewis acid bound product.

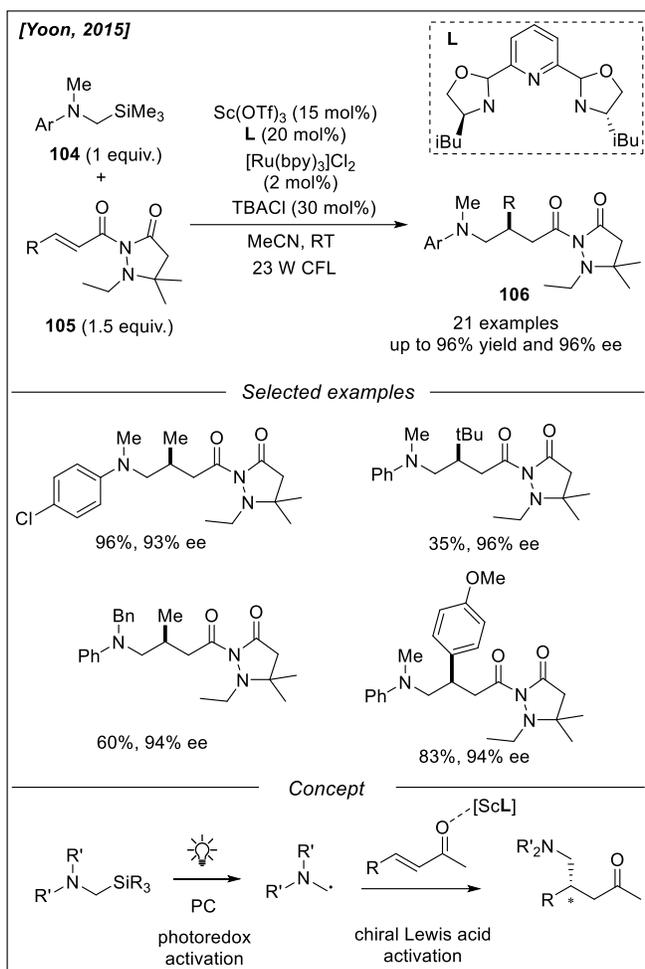


Scheme 39. Reductive coupling of nitrones with aldehydes.[109]

3.5 Functionalization of C=C bonds (mainly Mode C)

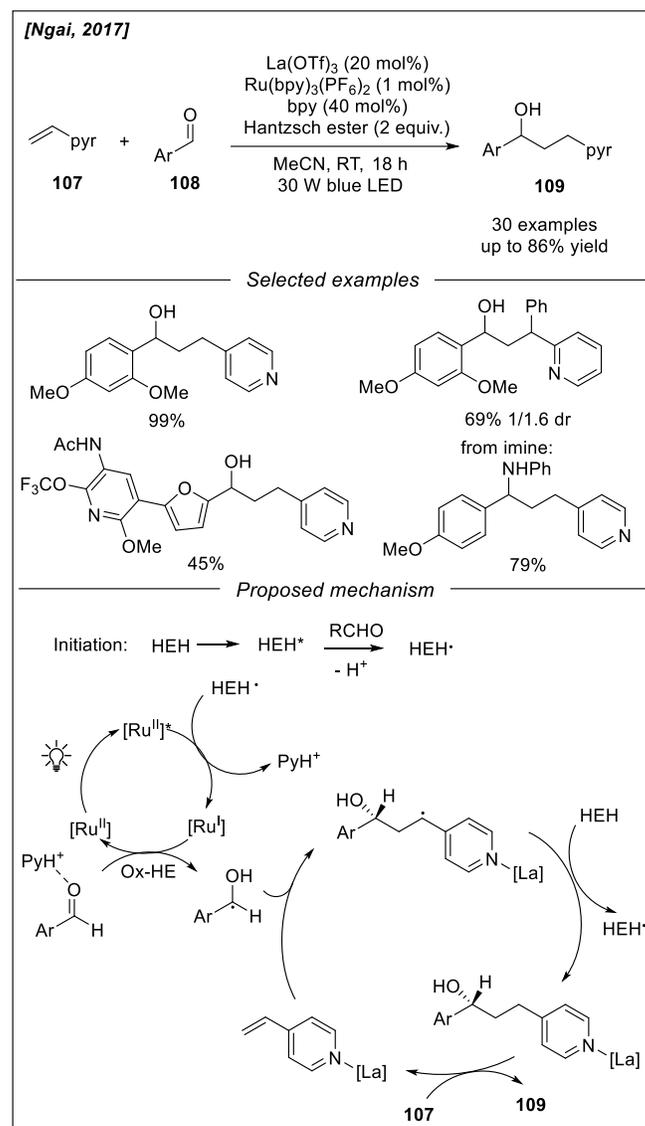
3.5.1 Formal hydrofunctionalizations

A cooperative photoredox and Lewis acid catalysis approach was designed for the highly enantioselective addition of photogenerated α -amino radicals to Michael acceptors using a chiral Sc complex and a Ru photocatalyst under CFL exposure (**Scheme 40**).[110] In contrast to the previously described modes of action A-D (see **Scheme 26**), in this example the Lewis acid does not influence directly the photoredox process, but its coordination to the carbonyl compound renders the Michael acceptor more electrophilic and creates a chiral environment for the radical attack. Furthermore, the addition of TBACl was crucial for obtaining very high ees, which was related to a rate-accelerating effect of the enantioselective pathway over a racemic background reaction by increasing the turnover of the Lewis acid catalyst. It was shown that structurally diverse α -silylamines **104**, containing at least one electron-neutral or electron-poor aryl group reacted with the Michael acceptor **105** to the final γ -aminocarbonyl adduct **106** in high yields and very high ees. Alkyl and various aryl groups were tolerated on the Michael acceptor without altering the reaction outcomes.



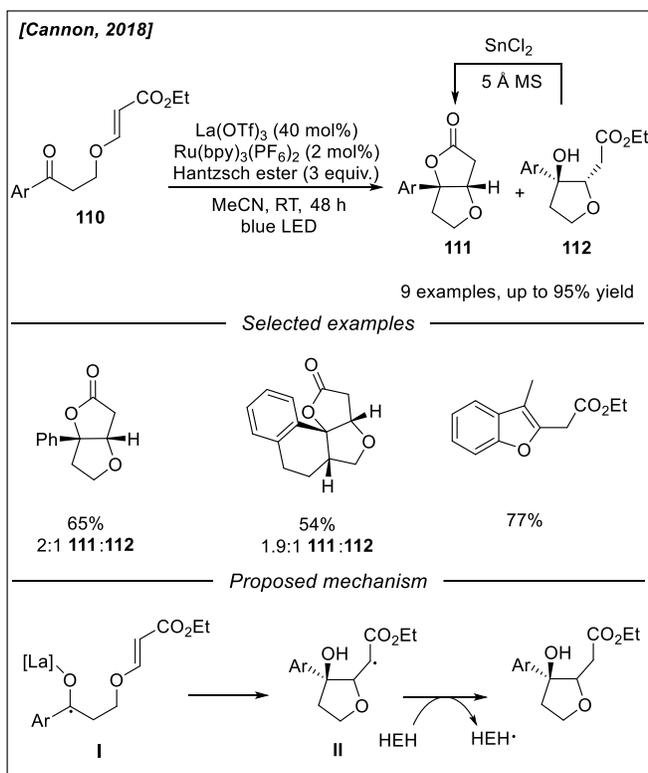
Scheme 40. Enantioselective conjugate additions of α -amino radicals.[110]

An efficient, highly β -selective coupling of alkenylpyridines with aldehydes or imines was proposed in 2017 by the Ngai group (**Scheme 41**).^[111] The reaction of 4-alkenylpyridine **107** with a wide range of aldehydes **108**, including complex substrates such as sugar, peptide or natural product derivatives, under dual Lewis acid/photoredox conditions provided selectively the linear coupling products **109** in moderate to excellent yields. The Hantzsch ester (HEH) was used as a stoichiometric reductant and the bpy ligand increased the solubility of the La(OTf)₃ in MeCN. Extension of this methodology to 2-alkenylpyridine derivatives and different imine coupling partners was achieved. In the postulated mechanism, the Hantzsch ester would be photo-excited to HEH* and react via SET with an aldehyde and after proton transfer to form the radical HEH[•]. This species would reduce the photoexcited *[Ru(bpy)₃]²⁺ to the highly reducing Ru(bpy)₃ and generate a pyridinium ion PyH⁺. An aldehyde would be activated by this PyH⁺ via hydrogen bonding and reduced to the ketyl radical species I by the Ru^I complex. Radical addition on the Lewis-acid activated alkenylpyridine and reduction by Hantzsch ester would provide the Lewis acid bound alcohol.



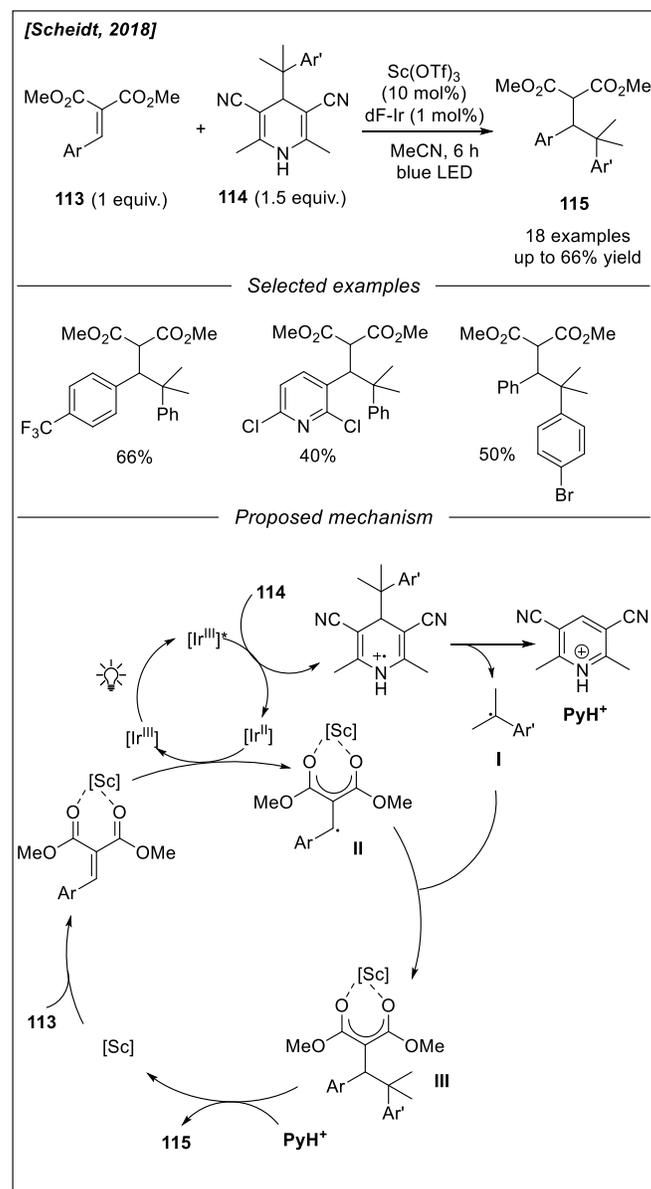
Scheme 41. β -selective coupling of alkenylpyridines with aldehydes.[111]

The Hantzsch ester was also efficiently employed in the dual Lewis acid/photoredox catalyzed synthesis of 2,6-dioxabicyclo[3.3.0]octan-3-ones (**Scheme 42**).^[112] The exposure of vinylogous carbonates **110** to blue light in the presence of catalytic La(OTf)₃, Ru photocatalyst and three equivalents of HEH provided a mixture of desired bicyclic product **111** and trans-tetrahydrofuran **112**. Compounds **111** result from the cyclisation of the initially formed cis-tetrahydrofuran product. Note that epimerization of trans-THF **112** with SnCl₂ over molecular sieves provided product **111** in high yields. Mechanistically, it was proposed that the Lewis-acid bound vinylogous carbonate would be reduced to the ketyl radical anion I by a photogenerated Ru(I) species in analogy to **Scheme 41**. After cyclization by addition onto the double bond, the resulting radical species II would be reduced by H-transfer from HEH.



Scheme 42. Addition of ketyl radicals to vinyllogous carbonates.[112]

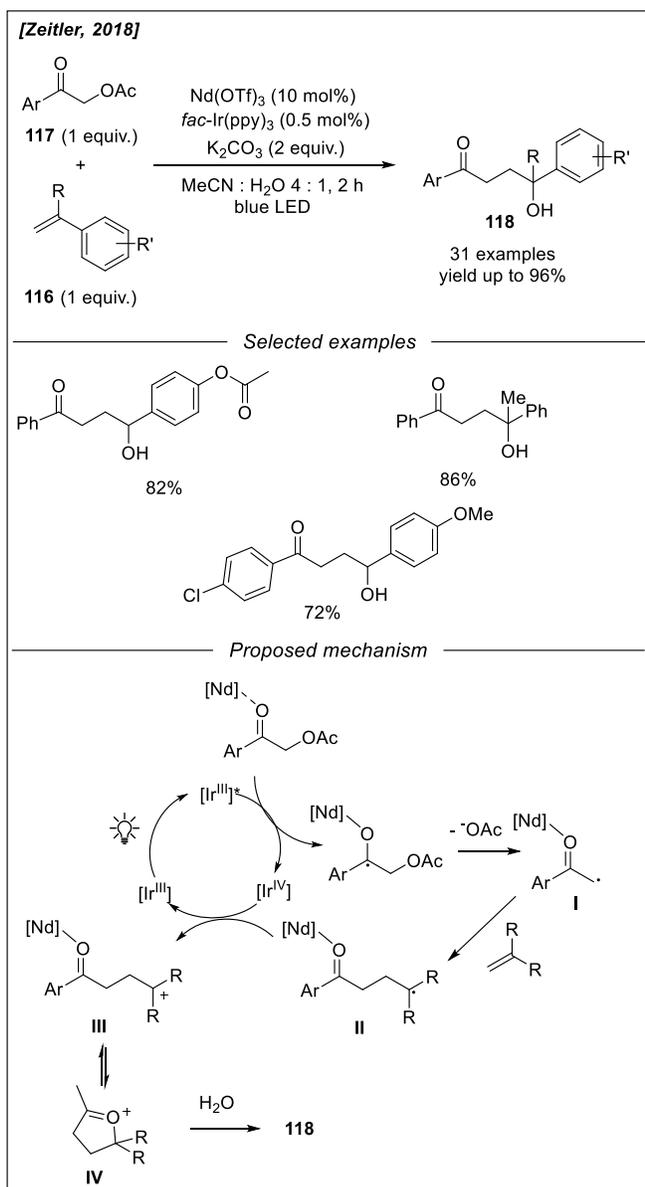
In 2018, the Scheidt group showed that tertiary benzyl radicals generated from Hantzsch ester derivatives could be successfully employed in the intermolecular reductive coupling with arylidene malonates employing Lewis acid/photoredox catalysis (**Scheme 43**). [113] Initially, it was observed that coordination of Sc(OTf)_3 to arylidene malonate shifted the reduction potential by over 1 V from -1.57 V to -0.37 V vs SCE. Consequently, combining **113** with nitrile Hantzsch ester derivatives **114** in the presence of Sc(OTf)_3 and dF-Ir photocatalyst in MeCN and irradiation under blue light provided the reductive coupling products **115** in moderate to good yields with a variety of aryl groups on the starting materials. Concerning the mechanism, the benzyl radical **I** and PyH^+ would be generated after SET from the excited Ir(III) catalyst to starting **114**. The resulting Ir(II) complex would reduce the Sc-bound arylidene malonate to provide the radical anion **II** which after radical-radical coupling with **I** would give the Sc-enolate complex **III**. Finally, protonation with PyH^+ would afford product **115**.



Scheme 43. Alkylation of arylidene malonates.[113]

3.5.2 1,2-difunctionalization of styrenes

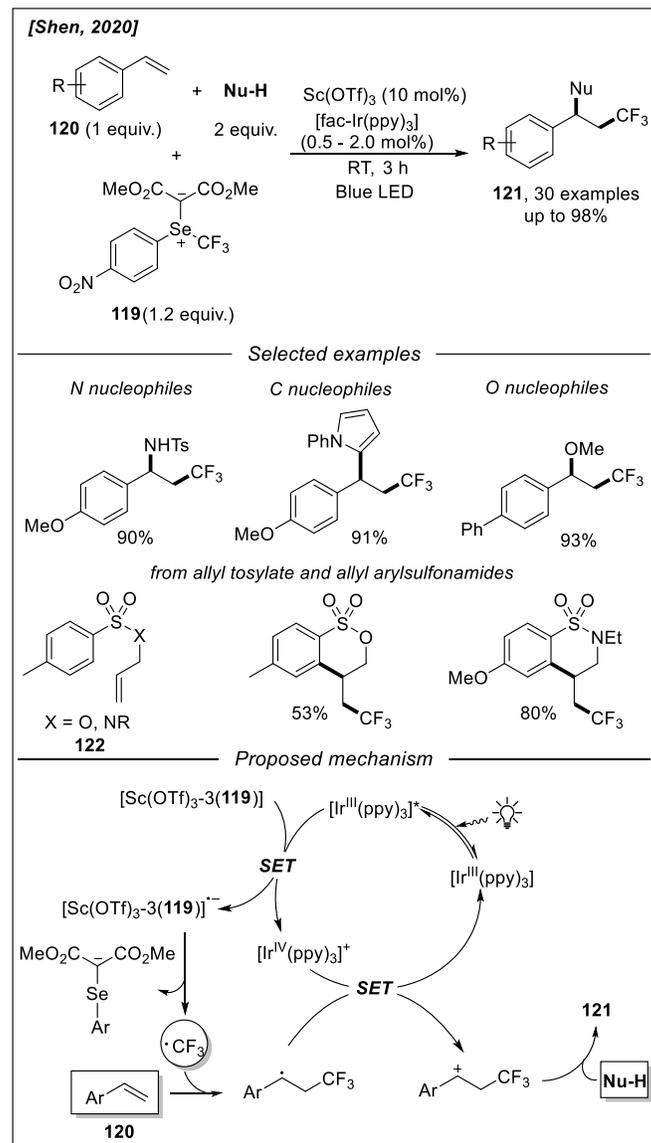
The cross-coupling of styrene derivatives **116** with radicals derived from α -acetoxy acetophenone **117** in water under blue light in the presence of Nd(OTf)_3 and Ir-photocatalyst provided γ -hydroxyketones **118** in high yields (**Scheme 44**). [114] Variations were tolerated on the acetophenone and the styrene aryl groups and 1,1-disubstituted styrenes gave tertiary alcohols in high yields. Electrochemical studies showed the LUMO-lowering effect of Nd-coordination to **117** in MeCN/water mixture, changing the reduction potential from -1.54 V (without Nd) to -1.27 V vs SCE. An oxidative quenching cycle was proposed starting with the reduction of Nd-bound **117** by a photoexcited Ir(III) species. After C-O bond cleavage the alpha-radical species **I** would add onto the styrene leading to a new benzylic radical **II** which would be oxidized by an Ir(IV) species. The cationic compound **III**, in equilibrium with the oxonium form **IV**, would react with water to the final product **118**.



Scheme 44. Cross-coupling of α -carbonyl acetates with styrenes.[114]

The crucial role of $\text{Sc}(\text{OTf})_3$ in the trifluoromethylative difunctionalization of styrenes under photocatalysis was reported by Shen in 2020. Reaction of the selenium ylide based trifluoromethylating agent **119** with *p*-methoxystyrene **120** and tosylamine as nucleophile (**Nu-H**) under blue light in the presence of an Ir photocatalyst provided only a poor yield of product **121** (**Scheme 45**).^[115] In contrast, addition of 10 mol% of $\text{Sc}(\text{OTf})_3$ increased the yield from 13 to 96% under otherwise identical conditions. This reaction could then be extended to a wide range of nitrogen, oxygen and carbon nucleophiles and various electron-rich styrene derivatives. In the case of water as nucleophile, 2 equivalents of $\text{Sc}(\text{OTf})_3$ were necessary. Similar reaction conditions also allowed the trifluoromethylative cyclisation reaction of *N*-allyl arylsulfonamides and allyl tosylate **122**. Extensive mechanistic studies supported by DFT calculations and ESI-MS provided evidence for the exothermic formation of a $[\text{Sc}(\text{OTf})_3 \cdot 3(\mathbf{119})]$ complex which would be more readily reduced via SET to the radical anion than free **119** (-0.70 V

vs -1.07 V (calculated)). Mesolytic cleavage of the resulting radical anion would provide the CF_3 radical, a process exergonic by around 6 kcal/mol, compared to the homolytic cleavage of the Se- CF_3 bond in **119**, endergonic by 24 kcal/mol. The generated CF_3 radical would then add onto the styrene **120** and the newly created radical would be oxidized via SET by an Ir(IV) species to the cationic compound followed by reaction with the nucleophile to afford **120**.

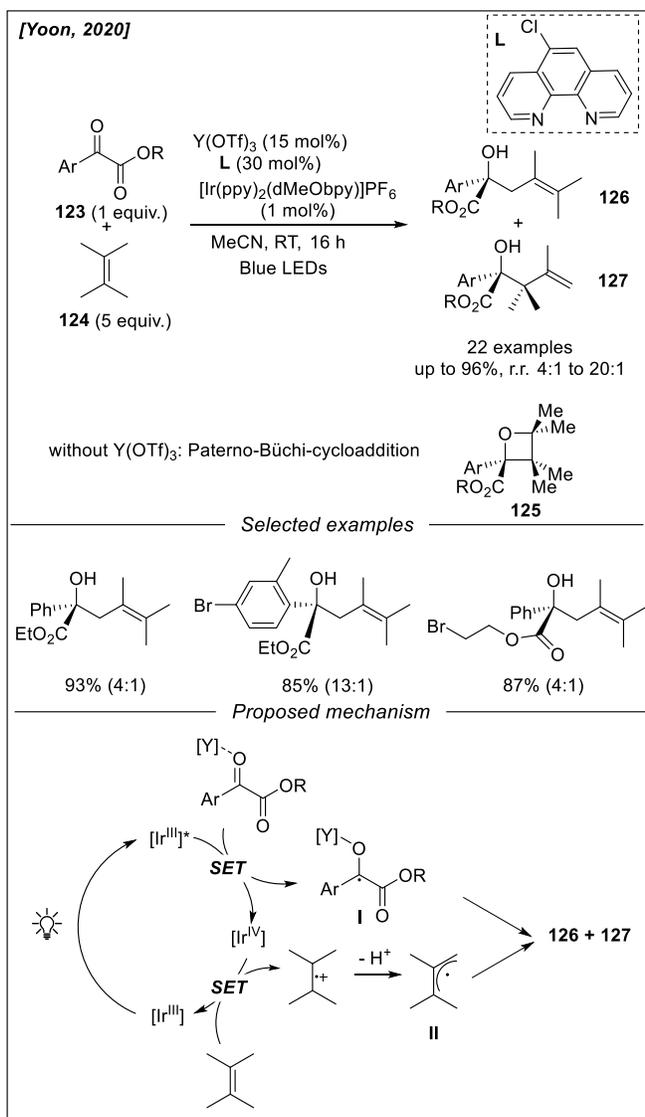


Scheme 45. Trifluoromethylative difunctionalization of styrene.[115]

3.6 Miscellaneous

The reactivity of a large variety of α -ketoesters **123** with tetramethylethylene **124** under photocatalytic conditions was investigated (**Scheme 46**).^[116] Exposure of these reagents to blue light in the presence of an iridium photocatalyst provided the Paterno-Büchi-cycloadduct **125**. The formation of this product could be explained by triplet sensitization of the α -ketoester followed by [2+2] photocyclisation. In contrast, addition of catalytic amounts of $\text{Y}(\text{OTf})_3$ complexed with 5-chlorophenanthroline modified completely the reaction outcome, favoring a photoredox process over an energy transfer process. The two

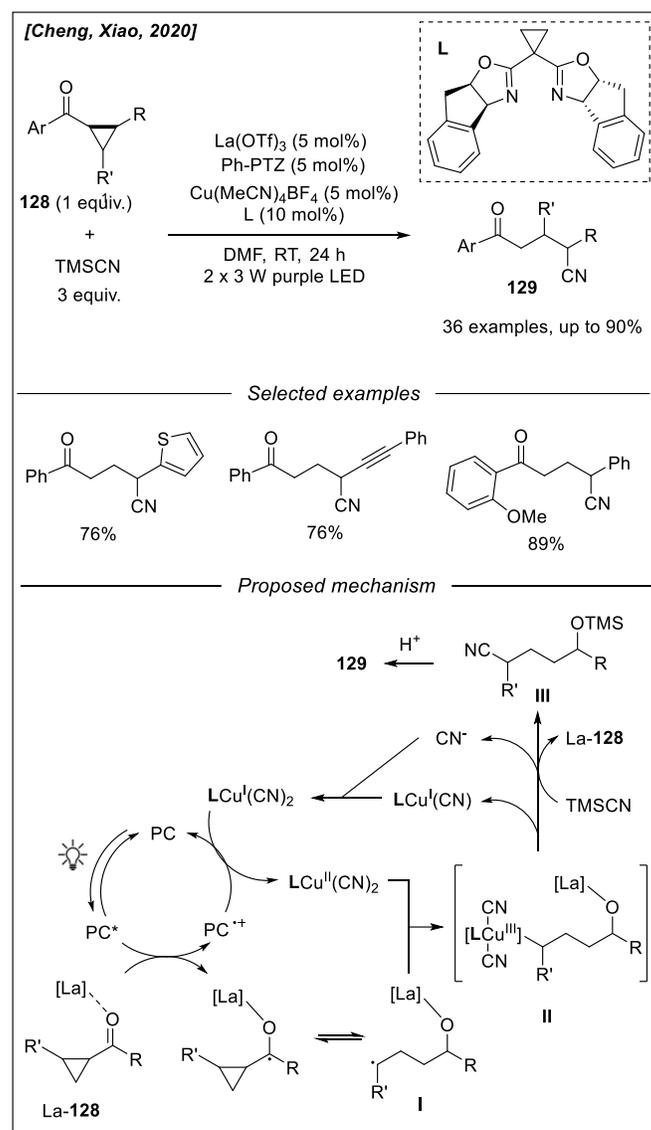
regioisomeric allylic functionalization products **126** and **127** were obtained in good yields and ratios from 4:1 to over 20:1 depending on the aryl group substituents. In the mechanistic proposal, the Y-coordinated α -ketoester would be reduced by the photochemically excited Ir(III) complex leading to ketyl radical complex **I** and an Ir(IV) complex. The latter would oxidize tetramethylethylene **124** via SET to the corresponding radical cation, which upon deprotonation would form the allyl radical **II**. Combination of the two radical species would afford the two regioisomeric products **126** and **127**.



Scheme 46. Allylic functionalization of alkenes with α -ketoesters.[116]

The synthesis of γ -cyanoketones **129** via ring-opening cyanation of cyclopropyl ketones **128** with TMSCN using a triple catalytic system was reported by Cheng and Xiao in 2020 (Scheme 47).[117] The combination of the organic photocatalyst Ph-PTZ together with the Lewis acidic $La(OTf)_3$ and a cationic copper(I) salt in the presence of a C_2 -symmetric bisoxazoline ligand provided access to a wide range of γ -cyanoketones in good yields after irradiation with purple LEDs. Various aryl groups on the ketone and the cyclopropyl moiety as well as unsaturated fragments (vinyl, alkynyl groups) on the cyclopropyl ring were tolerated under

these reaction conditions. It was proposed that after La-coordination to the ketone the corresponding complex would be reduced by the excited photocatalyst and ring opening would follow to provide the homoallylic radical **I**. The latter would be reduced by an in-situ photochemically generated $Cu(I)(CN)_2$ complex to form an intermediate $Cu(III)$ complex **II**. Reductive elimination and reaction with TMSCN would afford the silyl enol ether product **III** and regenerate a $Cu(I)CN$ species. Finally, hydrolysis of **III** would furnish product **129**.



Scheme 47. Triple catalysis to access γ -cyanoketones.[117]

Conclusion

In conclusion, rare earth metals can behave in photochemical reactions as either redox active centers or redox-neutral Lewis acids in a dual photocatalysis approach. While their redox properties have allowed the activation of native alcohols, carboxylic acids and halides compounds, their Lewis acid features have enabled the activation of a plethora of carbonyl-containing compounds, their nitrogen counterparts and even a selenium ylide. To date, many questions remain to be answered concerning the exact

mechanism of lanthanide photocatalysts and their extension beyond the mainly employed Ce and Eu catalysts. The factors governing the Lewis acid photoredox approach are also not fully elucidated, as it has been shown that a wide range of rare earths can function as Lewis acid partner. The combination of new chiral ligands with rare earth metals could also open up new synthetic possibilities. Finally, the development of photochemical reactions merging redox and Lewis acidity characters of rare earth metals would be beneficial for achieving radical transformations in an enantioselective manner without the use of an external PC.

CONSENT OF PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no competing financial interest.

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LIST OF ABBREVIATIONS

brsm: Based on recovered starting materials

BDE: Bond Dissociation energy

HAT: Hydrogen Atom Transfer

SET: Single Electron Transfer

LMCT: Ligand-Metal Charge Transfer

PC: PhotoCatalyst

LED: Light-Emitting Diode

CFL: Compact Fluorescence Lamp

RT: room temperature

ACN: acetonitrile

TFE: 2,2,2-trifluoroethanol

TCE: 2,2,2-trichloroethanol

ET: energy transfer

ISC: Inter-system-crossing

Ph-PTZ: 10-phenyl-10H-phenothiazine

TEEDA: tetraethylethylenediamine

HEH: Hantzsch ester

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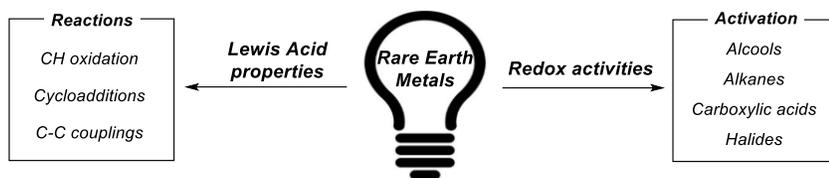
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GRAPHICAL ABSTRACT AND CAPTION



Synthetic strategies using rare-earth complexes as either redox active centers or as redox-neutral Lewis acids in photoredox catalysis.