This document is the Accepted Manuscript version of a Published Work that appeared in final form in ChemCatChem, copyright © Wiley, after peer review and technical editing by the publisher. To access the final edited and published work see https://doi.org/10.1002/cctc.202200916

## Ligand-to-Metal Charge Transfer (LMCT) Photochemistry at 3d-Metal Complexes: An Emerging Tool for Sustainable Organic Synthesis

Fabio Juliá\*<sup>[a]</sup>



Dr. F. Juliá Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology 43007 Tarragona (Spain) E-mail: fajulia@iciq.es https://www.iciq.org/research/research\_group/dr-fabio-julia

Abstract: Despite the rich photochemistry of 3d-metal complexes, the utilization of excited-state reactivity of these compounds in organic synthesis has been historically overlooked. The advent of photoredox catalysis has changed the perception of synthetic chemists towards photochemistry, and nowadays the potential of photoinduced, outersphere single-electron transfer events is widely recognized. More recently, an emerging new mode of photoactivation has taken the spotlight, based on an inner-sphere mode of reactivity triggered by population of ligand-to-metal charge-transfer (LMCT) excited states. Contrarily to photoredox, LMCT-activation does not rely on matching redox potentials, offers unique reactivity profiles and is particularly well suited on Earth-abundant metal complexes. Those appealing features are propelling the development of methods using this blueprint to generate highly reactive open-shell species under mild conditions. The aim of this contribution is to provide a didactical tool for the comprehension of this emerging concept and facilitate the development of new synthetic methodologies to achieve sustainable chemical transformations.

## 1. Introduction

[a]

The interaction between light and first-row transition metal complexes lies at the very heart of important biological processes that sustain life in our planet. Indeed, the chain of reactions that enables the transformation of light into chemical energy proceeding during photosynthesis in plants and bacteria is intimately related to 3d-metalloproteins such as ferredoxin (Fe), plastocyanin (Cu), water oxidation cofactors (Mn) or Rieske protein (Fe).<sup>[1,2]</sup> Not surprisingly, the photochemistry of metal complexes of the 3d block is rich and has been extensively studied for over 70 years.<sup>[3–7]</sup> In fact, as undergraduates we learn about the rich photophysics and photochemistry of 3d-metal complexes in Inorganic Chemistry courses but, remarkably, the utilization of excited-state reactivity of Earth-abundant metals in organic synthesis has been historically overlooked.

Although organic photochemistry has a long history,<sup>[8,9]</sup> the advent of photoredox catalysis in the last decade has changed the perception of synthetic chemists towards photochemistry,[10-14] and nowadays the extraordinary power of light as clean, selective, and yet powerful source of energy to carry out chemical reactions is widely recognized in the field of organic synthesis and has been embraced by the community.[15-17] The main conceptual advantages offered by this enabling technology are the possibility of generating highly reactive radical species under mild conditions by simply shining light into chemical reactions, and the access to distinct reactivity modes that are unreachable in the ground state. Importantly, technical development of tunable, safe and broadly available light sources has contributed to boost the rapid adoption of photochemistry in synthetic methodologies and, thus, the key role of this technical development cannot be unappreciated. [18,14] Now that photoredox is a mature field, there are some efforts to replace high-performance catalysts typically based on the

precious metal iridium by others that use more abundant metals<sup>[19-21]</sup> or are purely organic molecules.<sup>[22-24]</sup> First-row transition metals are generally cheap and abundant, so performing catalysis with them activated by visible light is highly attractive towards the goal of developing sustainable synthetic methods.<sup>[25-28]</sup> However, the substitution of iridium or ruthenium by 3d-metal complexes as photocatalysts goes beyond a simple economical or sustainability purpose, and opens new opportunities given by the more labile character or first-row metal complexes. Thus, the exploration of Ni, Cu or Fe complexes as photocatalysts offers a rich mechanistic landscape with applications in cross-coupling reactions and the generation of open-shell species. These aspects have recently propelled chemists to turn their attention towards the direct photoexcitation of metal complexes with synthetic purposes, exploiting reactivities beyond the well-established outer-sphere single-electron transfer (SET) events that conform the basis of photoredox catalysis.<sup>[29-33]</sup> Indeed, many elementary steps of organometallic chemistry such as oxidative addition, reductive elimination, *β*-hydride elimination or bond homolysis can be enabled or accelerated under light irradiation, exploiting the distinct reactivity of metal complexes in the excited states. Among them, one of the most generalized strategies is the population of ligand-to-metal charge-transfer (LMCT) excited states of metal complexes to generate open-shell species that can be used in radical reactions.

In this review are described the most relevant aspects of this reactivity mode and their application in organic transformations, covering both seminal reports and recent progress of synthetic photochemical reactions based on the population of LMCT excited states at first-row transition metal complexes. This work provides a detailed and updated discussion focused only in 3d-metal block complexes, complementing a recent minireview by Reiser, Bhattacharyya and coworkers<sup>[34]</sup> and those covering cerium-catalyzed reactions involving LMCT excited states.<sup>[35–37]</sup> The overarching goal of this contribution is to provide an instructive tool for non-specialists, with the aim of stirring the curiosity of the reader and motivate further exploration of this emerging and promising field to develop future sustainable methodologies.

Fabio Juliá obtained his PhD at the University of Murcia (Spain) under the supervision of Pablo González-Herrero, working on the synthesis and photophysical studies of organometallic platinum complexes. He was then a postdoctoral researcher in the group of Daniele Leonori (University of Manchester, UK), using photoredox catalysis to assemble C–N bonds and develop halogen atom transfer reactions. Later he moved to the group of Tobias Ritter at Max Planck Institute



(Germany), working on late-stage functionalization and C-H functionalization reactions. In 2021 he started his independent career at

ICIQ (Spain) as Group Leader Junior, where he is focused on developing new and sustainable synthetic tools by combining Earth-abundant metal complexes and photochemistry.

## 2. Understanding LMCT reactivity

#### 2.1. Photophysical aspects and structural requirements

To design photoactive systems with LMCT reactivity it is necessary to understand the photophysical and photochemical properties of this type of excited states.[38-42] LMCT states are the result of an electronic transition from a filled orbital that is largely based on a ligand to an empty orbital of the metal center (Scheme 1A). Since the empty metal orbital (d\*) must be relatively low in energy to be accessible, this type of excited states are characteristic of complexes bearing electrophilic, high-valent metal centers. Some archetypal examples within the 3d-block are Ti(IV), Fe(III) or Cu(II), among others. On the other hand, since the ligand act as the internal source of electrons in this electronic transition, the presence of electron-rich  $\sigma$  or  $\sigma\text{+}\pi\text{-}\text{donor}$  ligands such as halides, carboxylates or azide are also favorable for the appearance of LMCT transitions at relatively low energies. Regarding structural aspects, LMCT transitions involve the population of an antibonding orbital  $(d^*/d\sigma^*)$  at expense of electronic density of a ligand  $(p/\pi)$  or a metal-ligand  $(d\sigma)$  bond. As a result, the bond order of one or several M-L (M: metal, L: ligand) bonds decreases, which makes them more labile and facilitates their cleavage. This behavior, which is translated in a dissociative potential energy surface (Scheme 1B), often confers this type of excited states a non-emissive nature that is a consequence of their innate tendency to undergo non-radiative deactivation via bond dissociation.<sup>[43-45]</sup> As such, these excited states are not suitable for their detection via fluorescence/phosphorescence

emission spectroscopy due to their short lifetimes and very low emission quantum yields, and are generally characterized using ultrafast transient absorption spectroscopy. LMCT are, accordingly, the inverse situation of long-lived, highly emissive metal-to-ligand charge-transfer (MLCT) states that are predominant in photoredox catalysts, involving electron-rich metal centers and  $\pi$ -acceptor ligands that are generally not dissociative. It is however worth noting that not all LMCT states possess a dissociative character and, in fact, some emissive LMCT excited states have been reported in highly robust or rigid complexes where the population of d\* bonds is not causing important structural deformations that can result in the relaxation to the ground state.<sup>[46-48]</sup>

In terms of overall reactivity, LMCT states represent an interesting platform for the transformation of nucleophilic entities into openshell species via coordination to a metal center and subsequent photoexcitation (Scheme 1C). Since the resultant products are a 1e<sup>-</sup>-reduced metal complex and a radical, LMCT photoreactivity is often simplified as the homolytic cleavage of a M–L bond.

## 2.2. Mechanistic features of LMCT reactivity: a comparison with photoredox catalysis

With the aim of providing a clear understanding from the perspective of a synthetic chemist, below is compared the mode of action of LMCT reactivity in the generation of radicals with the more established photoredox catalysis.

Photoredox catalysis is based on the ability of a given photocatalyst (**PC**) to become a powerful redox agent (oxidant or reductant) upon absorption of light (Scheme 2A).<sup>[10,49]</sup> The resultant excited-state species (**PC**\*) may participate in bimolecular reactions via SET events with a given substrate, provided that the individual redox potentials are matched and, thus, the reaction is thermodynamically feasible. These reactions generally proceed via *outer-sphere* mechanism, *i.e.* without pre-association of the two reactants, and without involving significant chemical changes in the structure of the photocatalyst beyond the accommodation of an extra/deficient electron.



Scheme 1. (A) Photophysics and photochemistry of LMCT states. (B) Dissociative energy profile of LMCT states. (C) Overall chemical process via photoinduced LMCT homolysis.

However, a redox match is not the only requisite in these processes, because the diffusion through the solvent and subsequent encounter of both species must happen before SET. For this reason, **PC\*** not only has to be a good oxidant/reductant, but must also be long-lived enough to diffuse through the solvent ( $k_{\text{diff}} \sim 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ ). As a rule of thumb, an excited state with a

lifetime of <1 ns is generally unable to participate in efficient bimolecular quenching and therefore is not well-suited to act as photoredox catalyst.<sup>[38,49]</sup> Analogously, in those reactions involving photoinduced generation of radicals via LMCT reactivity (Scheme 2B) there is also a net SET between a metal, which act as an oxidant, and a given substrate that is oxidized ( $M^n + L^- \rightarrow$  $\mathbf{M}^{n-1} + \mathbf{L} \cdot$ ). However, contrarily to photoredox, in this case the SET event proceeds via inner-sphere mechanism, triggered by population of the LMCT excited state after absorption of light. While this prerogative requires that substrate L must be able to coordinate to  $\mathbf{M}^n$  in the ground state, it ensures an effective preassociation of the two reactive species before light excitation. This key feature enables that even LMCT states with very short lifetimes ( $\tau$ <1 ns) can still engage in efficient reactions because they are not subject to diffusion-controlled kinetics to encounter the substrate. In addition, rules of outer-sphere SET do not apply anymore, so matching the redox potentials of  $\mathbf{M}^n$  and  $\mathbf{L}^-$  is not relevant and the net oxidation of challenging substrates (e.g. Cl- $\rightarrow$  CI•,  $E_{ox}$  > +1.2 V vs SCE) with weakly oxidizing metals (e.g.  $\rm Cu^{2+} \rightarrow \rm Cu^{+}$  ,  $\it E_{\rm red}$  = +0.50 V vs SCE;  $\rm Fe^{3+} \rightarrow \rm Fe^{2+}$  ,  $\it E_{\rm red}$  = +0.53 V vs SCE) can be achieved with this strategy.<sup>[50,51]</sup>



Scheme 2. Comparison between photoredox (A) and LMCT (B) as reactivity platforms for the generation of radicals.

The differences between photoredox and LMCT are not only restricted to the generation of the radical species, but also have an influence on its subsequent reactivity. Indeed, the photoinduced homolysis of the M-L bond is often reversible, and this characteristic can be exploited to enable interesting applications. For example, the decarboxylation of alkyl carboxylates is well-established and provides a reliable way to access alkyl radicals via photoredox catalysis,[52-55] however, the analogous decarboxylation of benzoic acids is significantly more challenging (Scheme 3A). This disparity is a consequence of the slower rate of CO<sub>2</sub> extrusion ( $10^9 \text{ M}^{-1} \text{ s}^{-1}$  for alkyl,  $10^6 \text{ M}^{-1} \text{ s}^{-1}$  for aryl) on the carboxyl radical,[56-59] which results in inefficient generation of aryl radicals that is overpowered by other faster side reactions, such as hydrogen atom transfer (HAT) or back electron transfer from PC<sup>-</sup> generating a deactivated, ground-state photocatalyst (PC). Interestingly, recent works by the Ritter and MacMillan groups have shown how LMCT activation at Cu(II) can overcome this challenge, enabling radical decarboxylative functionalization of benzoic acids.[60-63] The explanation of this distinct behavior has its roots in the reversible nature of the Cu-O homolysis step, providing an efficient stabilization of the benzoyl radical within the solvent cage and allowing an effective subsequent decarboxylation. On the other hand, the reversible homolysis of Co(III)-C bonds has allowed Leonori and coworkers to modulate the regioselectivity of the desaturation of alkyl radicals towards the site-selective synthesis of olefins (Scheme 3B).<sup>[64]</sup> In this case, a reversible trap-release sequence of alkyl radicals by cobaloxime complexes enables the control of the subsequent HAT step, which is the selectivity-determining step of the reaction, by tunning the electronic and steric properties of the cobaloxime catalyst. Finally, since many metal complexes can trap carbon radicals at almost diffusion-controlled rates this also opens a gateway for their generation and subsequent transformation in versatile organometallic species in a single catalytic manifold, [63,65,66] something that is nowadays generally approached by the combination of two catalysts in metallaphotoredox catalysis.[11,67] Overall, these features showcase how the LMCT manifold not only is a sustainable and effective alternative to established photoredox catalysis, but also offers a number of unveiled opportunities unlocked by the distinct reactivity modes based on inner-sphere chemistry.



Scheme 3. Reactivity features and synthetic opportunities of LMCT reactivity.

# 3. Synthetic uses of LMCT reactivity in organic synthesis

This section summarizes a collection of relevant applications of LMCT reactivity in organic transformations, organized according to the nature of the photochemically active metal complex. Accordingly, Cu(II), Fe(III), Ni(III), Co(III), Ti(IV) and V(V) systems are discussed below. Even though LMCT processes on other 3d-metal complexes such as Cr(III)<sup>[39,68]</sup> or Mn at different oxidation states<sup>[69–71]</sup> are known in the literature, these systems have not been broadly applied so far in synthetic settings and will not be covered in this review.

#### 3.1. Reactions mediated by Cu(II) complexes

Irradiation of Cu(II)-X complexes is one of the oldest platforms used for the generation of X• via LMCT excited states. In particular, the formation of chlorine radicals (Cl-) is arguably the most frequently exploited reactivity since its report by Kochi in 1962.<sup>[72]</sup> This seminal work summarized the observations on the reaction of CuCl<sub>2</sub> with different organic substrates under light irradiation (Scheme 4). The photoreduction of  $Cu(II) \rightarrow Cu(I)$  was observed when this cupric salt was dissolved in certain organic solvents after irradiation with the whole spectrum of a mercury lamp (UV+visible range). The addition of LiCI was found beneficial to dissolve anhydrous CuCl<sub>2</sub>, presumably due to the formation of anionic species [CuCl<sub>n</sub>]<sup>Z-</sup>. The authors proposed a reactivity initiated by homolysis of the Cu(II)-CI bond into Cu(I) and CI as the responsible for the photoreduction process. Moreover, the diminished photoreduction in MeCN or AcOH was pointed out as an indication of the reversibility on CI. generation, in view of the low reactivity of these solvents towards chlorine radicals in comparison with the fast rebound with Cu(I) to re-form the initial Cu(II) chloride. Instead, those solvents presenting structural features that are highly reactive towards CI+, such as C-H bonds activated towards HAT or alkenes via radical addition, promote metal photoreduction efficiently. Overall, these stoichiometric experiments, including the oxidation of alcohols or chlorination of ethers and olefins, paved the way for the use of LMCT excitation in copper(II) chlorides in modern methodologies.



Scheme 4. Seminal work on LMCT reactivity of CuCl<sub>2</sub>.

Indeed, in 2020 Wan and coworkers built up on these results to develop a method for the catalytic vicinal dichlorination of alkenes (Scheme 5).<sup>[73]</sup> Stoichiometric HCI was used as the terminal source of chloride, while turnover is possible via Cu(I) oxidation under air atmosphere. The use of chlorine radicals in synthesis is often hampered by the need for harsh conditions on their generation, such as the use of corrosive Cl<sub>2</sub> under UV-light irradiation or the challenging Cl<sup>-</sup>  $\rightarrow$  Cl• oxidation ( $E_{ox} > +1.2$  V vs SCE). Contrarily, in this work the inner-sphere oxidation of chloride mediated by Cu(II) during LMCT excitation allows the smooth production of this reactive species from simple chloride sources, using visible light at room temperature. The authors propose that Cl•, detected by high-resolution mass spectroscopy (HRMS) after trapping with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl

(TEMPO), reacts with alkenes to give chloroalkyl radicals that, in turn, abstract a chlorine atom from CuCl<sub>2</sub> to yield dichlorinated products. Thus, in this mechanism Cu(II) chloride complexes formally transfer two CI• to the olefin sequentially, the first in the form of a free radical after LMCT-homolysis and the second via halogen-atom transfer (XAT) to carbon radical intermediates. The methodology works generally well with a broad substrate scope, featuring both inactivated and activated (styrenes) olefins containing (hetero)arenes and multiple polar functional groups including amino, carboxylic acid, thioester or sulfonamide, among others. For styrenes, superstoichiometric amounts of CuCl<sub>2</sub> were required under inert atmosphere to achieve good results.



Scheme 5. Vicinal dichlorination of alkenes mediated by CuCl<sub>2</sub>.

The ability of Cu(II) chlorides to generate CI• upon light irradiation was next applied to C-H functionalization by the group of Rovis (Scheme 6).<sup>[50]</sup> Owing to the strength of the H–Cl bond (BDE = 103 kcal/mol) and its polarized character, Cl• is able to undergo HAT from inactivated Csp<sup>3</sup>–H bonds (for example, in cyclohexane BDE = 100 kcal/mol<sup>[74]</sup>) leading to alkyl radicals. Rovis and coworkers used this blueprint to develop C-H alkylation of alkanes by means of a Giese reaction, i.e. the fast and efficient addition of nucleophilic C-radicals to electron-deficient olefins such as Michael acceptors. In this case, there is no need for an external, sacrificial oxidant since the electrophilic a-EWG-alkyl radical (EWG: electron-withdrawing group) intermediate is proposed to carry out the  $Cu(I) \rightarrow Cu(II)$  oxidation, leading to a Cu(II) enolate that is hydrolyzed by HCI closing the catalytic cycle on copper. Accordingly, both CuCl<sub>2</sub> and chloride can be used in catalytic amounts, thus representing an overall redox neutral transformation. The authors also found that the addition of LiCl improved the yield of the reactions. This effect was rationalized by the improvement of solubility, but the impact on the speciation of the active Cu species was also discussed, based on a previous report by Mereshchenko.<sup>[44]</sup> Thereby, the addition of increasing amounts of chloride can tune the major species in solution in the direction  $[Cu(NCMe)_3CI]^+ \rightarrow [Cu(NCMe)CI_3]^-$ [CuCl4]<sup>2-</sup>,  $\rightarrow$ impacting the overall efficiency of the process. A scope comprising cyclic and acyclic alkanes, ethers, esters, amides, free carboxylic acids, aldehydes and silanes as substrates was shown. The observed regioselectivities among different C-H bonds towards HAT are the expected for the participation of electrophilic Cl•, activating preferentially more hydridic (i.e. electron-rich) C-H bonds in preference to those that are acidic.<sup>[75,76]</sup> This effect can be readily seen in the functionalization of ethers selectively at the  $\alpha$ -O position or the lack of reactivity of acidic, alpha-to-carbonyl C-H bonds. With respect to the olefin partner, classical Michael acceptors such as acrylates, vinyl sulfones or enones were used, as well as one example with azodicarboxylate to form C-N bonds. Notably, when endocyclic acceptors were used unusually high levels of diastereoselectivity were observed, which is rationalized by the formation of the Cu(II) enolate intermediate that can be protonated stereoselectively.



Scheme 6. Giese-type C-H alkylation photocatalyzed by CuCl<sub>2</sub>.

The decarboxylation of carboxylic acids under UV light irradiation in presence of Cu(II) salts has been known for 50 years,[77-81] but it was not until 2021 when the first synthetic methodologies exploiting this reactivity emerged. Interestingly, while decarboxylation of aliphatic carboxylic acids via LMCT irradiation was attained before employing Fe(III)<sup>[82]</sup> or Ce(IV)<sup>[83]</sup> catalysts, the considerably more challenging decarboxylation of aryl carboxylic acids was first unveiled by Ritter and coworkers, who reported a method for the decarboxylative fluorination aryl carboxylic acids using stoichiometric copper and fluoride salts (Scheme 7).[60] The irreversible decarboxylation of the aroyloxyl radical ArCOO• (see discussion above, Scheme 3A) generated after Cu-O homolysis is allowed to proceed efficiently due to the reversibility of the photoinduced LMCT step. The resultant aryl radical can be then efficiently trapped by [Cu(II)]-F leading to the desired aryl fluoride

products, taking advantage of the ability of the putative Ar-[Cu(III)]-F intermediates to undergo facile C-F reductive elimination<sup>[84,85]</sup> (Scheme 7, pathway a). Even though the reaction can proceed using only Cu(II), the authors observed a beneficial effect of additional Cu(I) salts. This outcome is rationalized by the higher tendency of Cu(I) to capture aryl radicals in comparison to Cu(II) complexes, that further contributes to reduce competitive HAT pathways which lead to undesired protodecarboxylation products (Scheme 7, pathway b). Overall, this work eloquently exemplifies some of the benefits of LMCT reactivity, with a single metal participating in two crucial steps: a challenging C-radical generation and its subsequent functionalization, enabling an unprecedent synthetic transformation. Mechanistic studies include the formation of a LMCT band on Cu(II) carboxylates and the photoinduced reduction to Cu(I) observed by UV-vis absorption spectroscopy, or the detection of aroyloxyl radicals trapped by chemical probes. This methodology represents a mild avenue towards structurally diverse aryl fluorides, with a scope featuring electron-poor and electron-rich substrates and the presence of halides, aldehydes, or enolizable ketones, among other functionalities. A limitation of this methodology is the lower efficiency of substrates bearing highly coordinating or easily oxidizable amines. However, substrates with  $\alpha$ -heteroatom, benzylic or tertiary C-H bonds that are typically reactive towards HAT are well tolerated, which is another evidence of the short lifetime of aroyloxyl radicals under these reaction conditions.



Scheme 7. Decarboxylative fluorination of aryl carboxylic acids.

Shortly after, the same group extended this mode of activation towards the formation of Csp<sup>2</sup>–OH bonds (Scheme 8).<sup>[61]</sup> The designed strategy consisted in forming an ester Ar–O<sub>2</sub>CAr', followed by hydrolysis with LiOH to yield Ar–OH. Since one of the aryl carboxylic acids is used to produce aryl radicals, the key aspect was to select a different "sacrificial" carboxylic acid (Ar'CO<sub>2</sub>H) to act as the source of OH after hydrolysis without

competing for LMCT decarboxylation with the desired substrate. The authors identified thiophene-2-carboxylate (TC) as the most effective compound for this task, which was rationalized on the basis of its enhanced stability toward decarboxylation as a result of the conjugation of the C–COO• bond with the S lone pair, in line with the hypothesis proposed by Ingold.<sup>[57]</sup> Similarly to their previous methodology, stoichiometric Cu(II) and Cu(I) are required to obtain high yields, and the protocol described is a one-pot photochemical C–O formation starting from a lithium carboxylate, followed by a hydrolysis step. Regarding the scope, electron-rich, -neutral and -poor benzoic acids containing versatile functional groups and some late-stage functionalization of complex molecules are demonstrated.



Scheme 8. One-pot decarboxylative hydroxylation of aryl carboxylic acids.

Concurrently, MacMillan and coworkers independently developed a similar platform for the decarboxylative functionalization of aryl carboxylic acids via LMCT reactivity mediated by copper (Scheme 9). The main difference with Ritter's approach is the use of copper in catalytic amounts, thus requiring the use of an additional oxidant to enable turnover. A variety of oxidants are suitable to obtain productive reactions, although the use of N-fluoro-2,4,6trimethylpyridine consistently leads to more efficient reactions. In their work on decarboxylative halogenation of aryl carboxylic acids<sup>[63]</sup> the group reported iodination, bromination, chlorination and fluorination methods, which are achieved through two distinct mechanisms: via direct XAT from N-X-type reagents such as Niodosuccinimide or N,N'-dibromo-dimethylhydantoin to aryl radicals (X = I, Br) or via aryl-X reductive elimination at putative Cu(III) intermediates (X = CI, F). With those methods in hand, the authors demonstrated the effective access to aryl halides with a broad scope, extending the scope of previously attainable substrates under thermal decarboxylative conditions, in particular towards the use of heterocyclic substrates. As such, a wide variety of heteroaryl carboxylic acids including pyridines, pyrazoles, pyrazines or thiazoles, among others, are successfully engaged. To achieve efficient fluorinations the use of stoichiometric copper salts (3 equiv.) was required, since catalytic amounts of Cu resulted in low yields due to competitive C-O2CAr bond formation (see analogous reactivity described by Ritter and coworkers on Scheme 8). The preparation of 2- or 4fluoropyridines and related compounds, which are notoriously reactive towards S<sub>N</sub>Ar, allowed the sequential nucleophilic substitution of fluorides by different nucleophiles, such as amines,

alkoxides or thiolates after aqueous workup, providing a straightforward route to obtain these compounds from abundant carboxylic acids. Interestingly, the reaction only performed well in MeCN as the solvent; an effect also observed by Ritter<sup>[60]</sup> suggesting a possible role of this coordinative solvent as supporting ligand bounded to copper. Mechanistic studies are also presented, including the trap of aryl radicals with a Giese acceptor olefin, benzene and deuterium (from CD<sub>3</sub>CN), UV-vis absorption studies and, crucially, the detection of aroyloxy radicals under reaction conditions by transient absorption spectroscopy.



Scheme 9. Catalytic decarboxylative halogenation of aryl carboxylic acids.

The MacMillan group also extended their approach towards decarboxylative borylation (Scheme 10).<sup>[62]</sup> Given the relevance of aryl organoboron compounds as nucleophiles in transitionmetal catalyzed cross-couplings, this method constitutes an appealing avenue to access this key building blocks from abundant and structurally-diverse aryl carboxylic acids. In this case. the authors identified the use of Nfluorobenzenesulfonimide (NFSI) as a terminal oxidant, bis(picolinato)diboron (B2pin2) as a borylating reagent and fluoride salts as activator in the presence of [Cu(NCMe)<sub>4</sub>]BF<sub>4</sub> as optimal for this transformation. The use of high-intensity light sources was found beneficial to achieve high conversions. Although the participation of Cu-Bpin species cannot be completely ruled out, the authors proposed a radical addition of Ar• produced after LMCT decarboxylation to [B2pin2F]-,[86] leading to the final aryl-Bpin product. The reported scope is guite general, tolerating synthetic handles such as nitriles, halides or ester in substrates with different substitution patterns (ortho-, meta-, para-) as well as many heteroarenes and drug derivatizations. Recognizing the

synthetic power of the boronic ester products, subsequent onepot palladium-catalyzed cross-couplings were also demonstrated to proceed in good yields by simply adding the required reagents after the photochemical reaction, highlighting the practicality of this strategy to perform this type of couplings bypassing the need for isolation of organoboron intermediates. Moreover, they performed Suzuki-type aryl-aryl coupling using both coupling partners (aryl halide and aryl boronic ester) obtained in a telescoped process from Cu-catalyzed LMCT decarboxylative functionalization, showcasing the enabling power of this strategy to use aryl carboxylic acids as potential downstream nucleophilic/electrophilic fragments.



Scheme 10. Catalytic decarboxylative borylation of aryl carboxylic acids.

Around the same time, the Yoon group also paid attention to the decarboxylation of alkyl carboxylic acids mediated by copper and light, and published their approach for the oxidative functionalization at Csp<sup>3</sup> centers with different nucleophiles (Scheme 11).<sup>[87]</sup> This approach is based on the oxidation of the alkyl radical resultant from LMCT decarboxylation to a carbocation, which is then rapidly trapped by a nucleophile forging a new Csp<sup>3</sup>-Nu bond. The role of Cu(II) in this methodology not only is restricted to photoinduced decarboxylation, but also serving as terminal oxidant to form carbocation intermediates, in line with previous research interest of the same group,<sup>[88-90]</sup> justifying its use in stoichiometric amounts. The scope of carboxylic acids is broad in terms of functional group compatibility and include several drugs, however is restricted to substrates that can form stabilized carbocations after decarboxylation such as benzylic or  $\alpha$ -heteroatom. On the other hand, a large variety of N-,O- and C-nucleophiles can be employed, including sulfonamides, nitriles, carbamates, alcohols or indoles. All together, these aspects make of this approach a truly general strategy for the functionalization of this type of compounds with possible applications in the rapid access to large libraries of pharmaceutically-relevant substances. Mechanistically, the role of nitriles as ligands is also discussed, and a study of the impact of the ratio Cu(II)/alkyl carboxylate on the efficiency of the reaction revealed that an excess of Cu(II) is beneficial, which is proposed to avoid the formation of Cu(II) dimers<sup>[91]</sup> that are photochemically inactive under visible light irradiation and unable to form carbocations effectively.



Scheme 11. Decarboxylative nucleophilic functionalization of alkyl carboxylic acids.

2022 Reiser, Rehbein and Castellano reported the In decarboxylative synthesis of ketones and aldehydes (Scheme 12).<sup>[92]</sup> In this catalytic method oxygen is used as terminal oxidant, which traps carbon radical intermediates and allows turnover via the formation of Cu-alkylperoxo species. The substrates employed are mainly benzylic, although they report two examples of cyclic secondary alkyl showing that this protocol can be extended to this class of inactivated substrates. Notably, the authors isolated and characterized Cu-carboxylate complexes and elegantly demonstrated how the specific coordination mode (chelate vs monodentate) dramatically affects the decarboxylation efficiency. This study combines X-ray diffraction, UV-Vis absorption, FT-IR, EPR, NMR and computational studies to determine Cu speciation and unravel their role on the LMCT decarboxylation process. Since monodentante Cu(II) complexes were found to be much more efficient than paddlewheel-type dimers, the authors managed to favor the formation of the former type by using a bulky neocuproine ligand, which disfavors the formation of dimers and, in turn, results in efficient photocatalytic decarboxylations.



Scheme 12. Cu-catalyzed decarboxylative synthesis of ketones and aldehydes.

Beyond halogen and carboxyl, other radical species have been generated via LMCT in Cu(II) complexes. In 2018 Rhebein and Reiser demonstrated the formation of N<sub>3</sub>• using this strategy, which was successfully applied to the azido-oxygenation of olefins,<sup>[93]</sup> which are valuable intermediates used in the preparation of several bioactive compounds (Scheme 13). This Nradical, generated after Cu-N3 homolysis adds to styrenes resulting in a benzylic radical, which is further oxidized in the presence of O<sub>2</sub> and Cu via alkylperoxide-Cu species delivering the final ketoazide product and enabling turnover. Internal and terminal alkenyl arenes with para- and meta- substituents worked well, while ortho-substituents generally resulted in decreased yields. Styrenes containing different groups such as free amino, nitrile, halides or heteroatom scaffolds were shown, while nonconjugated alkenes remained unreactive. The identification of some key intermediates was performed by independent synthesis confirmed by X-ray crystallography, NMR and EPR spectroscopy, suggesting the formation of a Cu(II) complex under these reaction conditions that rapidly reacts with TMSN<sub>3</sub> (TMS: trimethylsilyl) to give a Cu(II)-azide dimer that is absorbing green light and it is believed to be the LMCT-photoactive species. Several reactivitybased pieces of evidence are also provided, such as the trapping of benzylic radicals by TEMPO or the lack of reactivity under inert atmosphere, which are in line with the proposed mechanism.





Scheme 13. Photocatalytic azido-oxygenation of olefins.

In the same year, Gong and co-workers proposed LMCTtriggered Cu-C homolysis as a key step in the enantioselective alkylation of imines with benzyl trifluoroborate salts (Scheme 14).<sup>[66]</sup> In this methodology alkyl radicals are generated from their trifluoroborate salts which, given their oxidation potential ( $E_{ox}$  = +1.34 V vs SCE), should not be oxidized by Cu(II) complexes via outer-sphere SET. Thus, the formation of C-radicals without the need for an additional photosensitizer is rationalized on the basis of a photochemical homolysis of Cu(II)-alkyl complexes that would occur after transmetalation. Accordingly, copper catalysts are performing a dual role in this reactions: produce benzylic radicals via LMCT excitation and govern the subsequent stereoselective transformation by providing a chiral environment induced by the use of bisoxazoline-type (BOX) chiral ligands. Several mechanistic insights are presented, including EPR and UV-vis absorption spectroscopy or cyclic voltammetry studies. Critically, the presence of the putative Cu(II)-alkyl complex was detected by HRMS and the radical-radical coupling of benzylic radicals was also achieved upon blue light irradiation, supporting this mechanistic proposal. With respect to the scope, organoboron substrates are mainly primary benzylic of diverse electronic character, presenting high yields and good enantioselectivities. One example of a secondary and another of a tertiary are also working well in terms of yield, although presenting modest values of enantiomeric excess. On the imine side, this method requires the presence of a carbonyl in  $\alpha$ -position that works as directing group to effectively coordinate to Cu and achieve effective stereoinduction.



benzylic C–H bonds en route to ketones<sup>[108]</sup> and finding good yields in the cases bicyclic substrates like tetralin or indan (Scheme 15D).



Scheme 14. Enantioselective alkylation of imines.

## 3.2 Reactions mediated by Fe(III) complexes

The first reports on the use of photoreduction of FeCl<sub>3</sub> to oxidize organic molecules appeared in the late 1960s, when Imoto and co-workers reported a series of works dealing with these reactions on the presence of 1,2-glycols, their ethers and toluene (Scheme 15A).<sup>[94-97]</sup> Although much details on the exact operating mechanism were not provided at that stage, these reports probably constitute the first use of photogenerated CI• mediated by iron salts in organic chemistry, although the generation of alkoxy radicals RO• (see below) in the case of diols seems also apparent. Interestingly, in their work on toluene oxidation the authors notice a dramatic effect of the water content on the distribution of products derived from benzyl radical, favoring the C–H chlorination product upon addition of aprox. 4 equiv of H<sub>2</sub>O. Years later Shul'pin carried out a more systematic study on the catalytic C-H photooxidation of alkanes to alcohols and ketones, proposing the decomposition  $FeCl_3 \rightarrow FeCl_2 + Cl_2$  as the main photoinduced process, being responsible for the C-H activation via HAT (Scheme 15B).[98-100] Street lamps were used as light sources, although daylight was also reported to promote these reactions, which were extensively studied with special emphasis on their kinetic profile. Despite of the relatively low yields, it is remarkable the possibility of performing C-H functionalization on inactivated substrates with just 1 mol% of FeCl<sub>3</sub> as catalyst, using sunlight as the light source and oxygen as the terminal oxidant. More recently, this approach was further studied and revisited by Tataki and Fu.<sup>[101-104]</sup> The group of Sato also applied the photoreactivity of FeCl<sub>3</sub> towards the oxidative functionalization of olefins (Scheme 15C).[105-107] Mechanistically, these works are also based on the photogeneration of Cl•, which in this case undergoes addition to cyclic olefins in the presence of oxygen, leading to  $\alpha$ -chloroketones or ring-opening oxidation products. Barbier in 1984 further contributed to demonstrate the synthetic utility of this approach, applying this concept to the oxidation of

Scheme 15. Seminal reports on LMCT reactivity on  $\mathsf{FeCl}_3$  applied to  $\mathsf{C-H}$  functionalization.

These seminal works paved the way for the posterior appearance of modern methodologies exploiting LMCT reactivity on Fe(III) to achieve different synthetic targets. In 2021 the groups of Duan,[51]  $\mathsf{Rovis}^{[109]}$  and  $\mathsf{Jin}^{[110]}$  independently reported photocatalytic C–H alkylation and amination of inactivated alkanes with electrondeficient olefins or azocarboxylates, respectively (Scheme 16). Under similar reaction conditions, the three works invoke LMCT homolysis of Fe-Cl bonds in FeCl3 to release Cl•, which undergoes HAT with the targeted C-H bond. The resultant alkyl radical participates in a polarity-matched addition to a suitable edeficient olefin in a Giese-type reaction and, analogously with the mechanism discussed previously for  $CuCl_2$  and depicted in Scheme 6, this electrophilic radical is able to oxidize Fe(II) to Fe(III), enabling catalytic turnover and delivering the final product after protonation. Notably, these reports display different nuances on their approach. Duan showed an environmental-friendly system for the amination of alkane feedstock via CI-mediated HAT, using the most abundant metal in Earth's crust as catalyst and 365 nm LEDs as the light source. The removal of iron salt, chloride source or light all resulted in no reaction, in line with the proposed hypothesis. Other metal sources, including CuCl<sub>2</sub>, displayed worse performance. Moreover, ICP mass spectrometry was carried out to rule out the presence of any other metal at ppm levels, confirming the key role of Fe in this transformation. Remarkably, this reaction proceeds efficiently with extremely low loadings of FeCl<sub>3</sub>·6H<sub>2</sub>O, resulting in 80% yield at 0.01% Fe, which represents a TON = 8000, and the protocol was also scaled up to 50 mmol. The scope of alkanes included some gaseous, liquid and solid alkanes with functional groups such as ether, thioether, ketone or halogens in combination with azodicarboxylates or Giese acceptors to give C-N or C-C bond formation products. The authors also performed several mechanistic experiments, including the detection of chlorine and carbon radicals in EPR as 5,5-dimethyl-1- pyrroline N-oxide (DMPO) adducts or KIE experiments, revealing that C-H cleavage is the productdetermining but not the rate-determining step. On the other hand, Jin and coworkers were motivated on activating the four most simple gaseous alkenes (methane, ethane, propane and nbutane) in Giese-type reactions under similar reaction conditions as a platform for upgrading gaseous feedstocks. Among all alkenes, methane is perhaps the most challenging to engage in view of the high BDE of its C-H bonds (~105 kcal/mol) and its low solubility, which makes it difficult to handle from a practical point of view. Notably, methane was efficiently engaged in alkylation reactions at room temperature at 50 atm, while the use of atmospheric pressure still afforded product, although in low yields. Due to their higher boiling point and solubility in acetonitrile, ethane, propane and butane could be successfully used at atmospheric pressure in combination with many different electron-deficient olefins such as malononitrile, maleimide or acrylate derivatives. Kinetic and computational studies complement the synthetic work and offered further insights into the mechanism; pointing towards FeCl<sub>3</sub>(NCMe)<sub>3</sub> as the main photoactive species in solution showing a reactive low-lying LMCT state. Finally, the Rovis group directed their attention to the regioselective C-H alkylation reaction influenced by the presence of electron-withdrawing groups. As previously discussed, due to the strong influence of polar effects in HAT, [75,76] the abstraction of stronger, inactivated C-H bonds is preferred over the more thermodynamically favored, but polarity-unmatched acidic C-H bonds that are in  $\alpha$  to EWG such as ketones, esters, nitriles or sulfones. Overall, this strategy allows functionalization in  $\beta$ positions to carbonyl groups, which is complementary to the wellstablished  $\alpha$ -functionalization via enolate of enamine chemistry. The authors demonstrated the utility of this approach on different substrates, which was particularly effective when short alkyl chains or 5-member rings were employed, since only one isomer was obtained. The olefin radical acceptors included acrylate, acrylonitrile derivatives, vinyl sulfone or maleic anhydride, among others. The proposed mechanism is analogous to the one previously described for CuCl<sub>2</sub> (see Scheme 6), suggesting the intermediacy of a Fe(III) enolate and identifying FeCl4- as the main photoactive species.





Scheme 16. C-H alkylation and amination photocatalyzed by FeCl<sub>3</sub>.

Also in 2021 the same group reported an interesting twist in Giese-type reactions via C-H functionalization, which occur after rearrangement of the initial alkyl radical in a process that resembles to the Dowd-Beckwith ring expansion (Scheme 17).<sup>[111]</sup> When using ketones containing tertiary substituents as substrates CI• undergoes HAT to give a primary β-keto-alkyl radical, which rapidly rearranges to a more stable tertiary radical via addition to the carbonyl and subsequent  $\beta$ -scission of the intermediate cyclopropyloxy radical. The resulting C-radical is then participating in a Giese-type addition to olefins, in line with previous reports. Substitution of the carbonyl in  $\beta$ -position to the primary radical by other  $\pi$ -systems such as (hetero)arenes is also effective, expanding the scope of application of this methodology to tert-butyl-substituted electron-deficient arenes. Ring-expansion of cyclopentanones is also achieved, in analogy to the classical Dowd-Beckwith process. Interestingly, this skeletal rearrangement can be modulated adjusting the reaction conditions (temperature, concentration) so that the primary (innate) or tertiary (rearranged) radical addition to the olefin is obtained selectively. Since the rate constants of this type of rearrangement are known and considered as radical clocks, these reactions were also used to evaluate the rates of radical addition to a diverse set of olefin acceptors.



Scheme 17. C-H alkylation via skeletal radical rearrangement.

Subsequently, other reports appeared extending the repertoire of FeCl<sub>3</sub>-catalyzed Csp<sup>3</sup>-H functionalizations beyond alkylation that can be carried out under light irradiation. In 2021 Duan and Jin expanded this concept to the C-H alkynylation of alkanes with alkynyl sulfones (Scheme 18A).[112] The mechanistic basis of this transformation is the addition of the alkyl radical obtained by HAT with CI• to a phenyl arylethynylsulfone which, followed by the elimination of PhSO2•, reforms the triple bond and renders the alkynylation product. The resultant sulfonyl radical PhSO2• is proposed to act as an oxidant to perform the  $Fe(II) \rightarrow Fe(III)$ oxidation that enables catalytic turnover in iron. Several liquid and gaseous alkanes were used as substrates in combination with several aromatic ethynyl sulfones to give internal alkynes as products. Interestingly, steric hindrance seems to affect more to this reaction in comparison with the previously discussed Giese resulting in lower propensity to undergo additions. functionalization in C-H tertiary centers. Very recently, Laulhé and co-workers also used this activation mode for the formation of C-S and C-Se bonds (Scheme 18B).[113] Upon light irradiation in presence of catalytic FeCl<sub>3</sub>, C-H chalcogenation of linear and cyclic amides was reported exclusively at the position in  $\alpha$  to nitrogen, enabling access to amido-N.S-acetals mojeties that are found in several natural products and antibacterials. The α-N-alkvl radical accessed via HAT with CI• attacks to a disulfide/diselenide compound, leading to the desired product and a chalcogen radical (e.g. PhS•) that undergoes SET oxidation of Fe(II) completing the catalytic cycle. When two different alkyl substituents are present in the amino group of the amide, a marked selectivity on methyl over other alkyl moieties was found. Bevond amides. sulfonamides. Boc-protected amines or ethers were also suitable substrates. With respect to the scope on disulfides, mainly aromatic compounds with different substitution patterns and electronic character were engaged, while benzyl and tert-butyl disulfides were presented as examples of alkyl counterparts. Finally, Gong and Wang reported their studies on an optimized system in combination with HCI that allowed to reduce significantly the loading of iron salts (Scheme 18C).[114] While most of the work is devoted to Giese-type alkylations, some examples on divergent C-H functionalizations including oxidation, chlorination, fluorination, amination, alkynylation and sulfonylation are also provided. TONs up to 9900 were enabled by the use of HCl as co-catalyst, which enhances the catalytic activity improving the TON by one order of magnitude. UV-vis absorption spectroscopy studies were presented to investigate the role of HCl, which was found to promote the formation of FeCl<sub>4</sub><sup>-</sup> as the key photoactive species participating in LMCT reactivity. Additionally, it was observed that the addition of H<sub>2</sub>O entails a deleterious effect on the formation of these species. With this data on hand, the authors optimized reaction conditions using just 0.05 mol% of FeCl<sub>3</sub> and 1 mol% of HCl in acetonitrile as the catalytic system, although higher loadings were required for other functionalizations different from Giese-type alkylation.



Scheme 18. Fe-catalyzed C-H functionalizations.

One of the main drawbacks of C–H functionalization mediated by CI• is the poor site selectivity when unbiased alkanes containing non-equivalent C–H bonds are employed as substrates. In 2022 Nocera and coworkers tackled this challenge in an attempt to gain control on the site-selectivity of C–H chlorination reactions (Scheme 19).<sup>[115]</sup> Following the insights obtained during their previous work on photoinduced homolysis of Ni(III)–CI bonds (see section on Ni below),<sup>[116,117]</sup> the authors based their strategy on the confinement of CI• generated after LMCT into the secondary coordination sphere around iron complexes to exert steric control over its reactivity. The interaction between CI• and a pendant arene moiety of a series of pyridine diimine (PDI)-type ligands coordinated to Fe "tames" the reactivity of the otherwise unselective CI• towards HAT. The resultant alkyl radical would then abstract a halogen atom from Fe(III)–CI, CCI<sub>4</sub> or BrCCI<sub>3</sub> to give chlorinated or brominated products. Thus, following this strategy the photochemical halogenation of less congested primary and secondary C-H bonds over the more thermodynamically favorable tertiary or even benzylic positions can be achieved. A comparison on the performance of simple FeCl<sub>3</sub> salts and (PDI)Fe-CI complexes manifest the different regioselectivity on the chlorination products as a direct consequence of the more hindered environment for CI• offered by the latter compounds. Studies based on transient absorption spectroscopy and photocrystallography, together with previous observations by the same group in the solid state,[118] confirmed the formation and confinement of CI• on the coordination sphere of the iron complex via [•Cl---arene] interactions, which also influences its reactivity profile. Even though this study is mainly based on stoichiometric reactions with Fe(III) complexes, this works paves the way for the development of regioselective C-H functionalizations via HAT with CI• mediated by transition metal catalysts.



Scheme 19. Selectivity enhancement of C–H functionalization via steric control of chlorine radical.

Beyond their use for the functionalization of feedstocks to access synthetically valuable intermediates in organic chemistry, this photocatalytic activation mode has also been applied to upgrade or recycle chemically inert polymers. In particular, the degradation of polystyrene waste in presence of oxygen and catalytic amounts of FeCl<sub>3</sub> under light irradiation has recently been reported independently by Zheng,<sup>[119]</sup> Stach<sup>[120]</sup> and Hu<sup>[121]</sup> (Scheme 20). Polystyrene is one of the largest-volume plastics used worldwide, but its chemical inertness complicates its degradation. Moreover, its transformation into products that can be then further utilized on chemical synthesis is also highly desirable. Using similar approaches, iron-catalyzed photochemical degradation of polystyrene has proved to offer a sustainable and cost-effective pathway for the obtention of benzoic acid at room temperature directly from real-life plastics such as packaging foams or plastic cups using O<sub>2</sub> (1 atm) or simply air as a terminal oxidant. Furthermore, the process can also be applied at gram-scale in flow, setting promising basis for possible future industrial applicability. Mechanistically speaking, this transformation involves the irradiation of FeCl<sub>3</sub> at LMCT bands resulting on the production of Cl•, which undergo HAT at benzylic positions of polystyrene. The resultant C-radical reacts with molecular oxygen to form a peroxy radical that oxidizes Fe(II) to Fe(III) allowing catalytic turnover. The resultant alkoxy radical is the key intermediate in the process, since undergoes facile  $\beta$ -scission cleaving a skeletal Csp<sup>3</sup>–Csp<sup>3</sup> bond of the polymer backbone. The resultant fragments of low molecular weight are further degraded to benzaldehyde and, under these oxidative conditions, ultimately to benzoic acid.



Scheme 20. Fe-catalyzed degradation of polystyrene in presence of light and oxygen.

Analogously to Fe-Cl homolysis, photoinduced LMCT reactivity is also known in Fe(III)-O bonds. Nonetheless, the photoinduced homolytic cleavage of Fe(III)-OH to give HO• is the basis of the reactivity known as "photo-Fenton", which is widely used in water detoxification treatments.<sup>[122,123]</sup> In 1986 Sugimori reported a seminal work on the utilization of this elementary step on the decarboxylative C-H alkylation of guinolines with alkyl carboxylic acids (Scheme 21A).[124] Upon light irradiation, homolysis of the Fe-O2CR bond followed by CO2 extrusion results in an alkyl radical, which undergoes a polarity-matched addition to protonated heteroarenes in a Minisci-type<sup>[125]</sup> reactivity. In this process stoichiometric Fe(III) salts were used and the alkyl carboxylic acid was used in large excess, as a co-solvent. Nonetheless, this work represented the first synthetic application of LMCT decarboxylation promoted by iron salts. Building up on these precedents, Jin and coworkers reported in 2019 the catalytic version of this transformation into a more practical and synthetically appealing method, using blue light irradiation in presence of 10 equiv. of carboxylic acid (Scheme 21B).[82] Since an oxidant is needed to re-oxidize Fe(II) to Fe(III) and allow catalysis, the authors screened different reagents and identified the use of inexpensive inorganic salts such as NaBrO3 or NaClO4 as optimal terminal oxidants under these reaction conditions. Interestingly, a key finding was the need for picolinic acid as a ligand, which affects dramatically to the performance of this reaction resulting in 0%, 60% and 94% yield when a loading of 0%, 5% or 10% of ligand was used, respectively. The generality of the reaction is showcased by the use of primary, secondary and tertiary carboxylic acids bearing several functional groups such as alkenes, ketones, halides, alcohols or arenes. A broad scope is also shown on the heteroarene side, comprising structurally diverse scaffolds including quinolines, pyridines, pyrazines, benzothiazoles or purines, among others, representing a robust and general method in which the only drawback is possibly the large excess of carboxylic acid required.



Scheme 21. Decarboxylative Minisci-type alkylation of heteroarenes mediated by iron(III). (A) Stoichiometric reactions. (B) Catalytic method.

Shortly after, the same group reported the iron-catalyzed decarboxylative alkylation and amination of carboxylic acids (Scheme 22).<sup>[126]</sup> According to the proposed mechanism, after LMCT-promoted decarboxylation of a suitable alkyl carboxylic acid the resultant alkyl radical adds to an electron-deficient  $\pi$ -system (*i.e.* Giese-type olefin acceptor or azodicarboxylate). Analogously to the mechanism described above for Cu-mediated C–H alkylation and amination (see Scheme 6), the resultant intermediate electrophilic radicals act as oxidants to promote the SET oxidation Fe(II)  $\rightarrow$  Fe(III) that enables turnover in iron catalysis without the need of an external oxidant and delivers the

product after protonation. Once again, the role of the ligand was markedly important, with 2,2'-picolylamine offering the best results. Interestingly, the authors also showed that other metals salts such as Mn(II), Ni(II), Co(III) or Cu(II) were incapable of promoting this transformation under the same reaction conditions. Although the scope on the olefin is mainly reduced to ethylene malononitrile derivatives, it is contrarily broad in terms of the alkyl carboxylic acid partner and include examples of primary, secondary, tertiary, benzylic and  $\alpha$ -heteroatom derivatives. In the amination protocol, the azodicarboxylate partner is used as limiting reagent requiring an increased amount (4 fold-excess) of the carboxylic acid in this case but also with similarly broad scope in terms of structural diversity and functional group compatibility to access different substituted hydrazines. Only one application of LMCT photocatalysis on aryl carboxylic acids using Fe(III) has been reported so far on the intramolecular C-H acyloxylation described by Jin and Lei.[127] In this case, the slower decarboxylation rate in ArCOO• radicals (see discussion above) combined with the presence of a pendant arene results in the more favorable intramolecular C-O bond formation to access benzocoumarin derivatives, which occurs without CO2 extrusion.



Scheme 22. Fe-catalyzed decarboxylative alkylation and amination.

The photochemical reactivity of alcohols in presence of Fe(III) salts has been known for decades. For example, during their seminal works on the degradation of 1,2-glycols,<sup>[94,95]</sup> the group of Imoto described in 1968 the reaction of FeCl<sub>3</sub> with ethylene glycol to give acetaldehyde and proposed the formation of alkoxy radicals (RO•) as intermediates.<sup>[96]</sup> In 1977 Rose and coworkers also reported the oxidation of methanol to formaldehyde in presence of Fe(III) imino-complexes under sunlight and air atmosphere.<sup>[128]</sup> In this case the authors proposed a homolytic cleavage of the Fe–OMe bond after population of LMCT states as

the primary photoprocess. But this mode for alkoxy radical generation was not employed in modern synthetic methodologies until late 2021, when Hu and Zeng independently reported C-C bond cleavage reactions in alcohols under iron photocatalysis (Scheme 23).[129,130] Both works could capitalize on the LMCT homolysis of Fe(III)-OR bonds to generate alkoxy radicals under mild conditions, which undergo facile  $\beta$ -scission driven by the formation of a C=O bond at expenses of the homolytic cleavage of a Csp<sup>3</sup>–Csp<sup>3</sup> bond on the backbone of the alcohol substrate. The resultant C-radical can then undergo HAT from a thiol cocatalyst or attack to diazocarboxylates resulting in C-H or C-N bond formation and generating a thiyl radical (RS•) or a N-radical, respectively, both of which can re-oxidize Fe(II) allowing catalytic turnover. When cyclic alcohols are used as substrates, this approach represents an effective tactic for the deconstruction of non-strained rings using a catalytic system that can operate in the absence of additional sacrificial oxidants. Interestingly, Hu observed that the presence of chlorides was beneficial for the reactivity and rationalized it in terms of the participation of CI• in the reaction. However, in their work on aminative ring-opening of cyclic alcohols Zeng and coworkers used a mixture of 2 mol% Fe(acac)<sub>3</sub> / 6 mol% *t*-BuOK or Fe(O*t*-Bu)<sub>3</sub> as catalytic system, showing that the generation of alkoxy radicals can be possible in absence of chlorides. Moreover, alkoxy radicals could be captured in situ by reaction with styrene, further supporting photoinduced Fe-O homolysis as the main pathway to access these reactive species under these reaction conditions. In terms of scope, ring-opening of cycloalkanols from ring sizes ranging from 4 to 12 could be achieved, with or without exocyclic substituents in  $\alpha$  to the OH group, leading to linear aldehydes or ketones functionalized in a remote position. Different substituted (hetero)arenes and functional groups were also tolerated in these methodologies, which were also applied to the deconstruction of sugars, steroids and lignin models. In addition, several examples on the C-C bond cleavage of non-cyclic substrates were reported by Hu, representing a tool for the de-hydroxymethylation of alcohols.



Scheme 23. Fe-catalyzed C–C bond cleavage of alcohols.

Along the same lines, Zeng and Li used a similar approach for the  $\delta$ -functionalization of alcohols with azodicarboxylates (Scheme 24). This reactivity is based on the exploitation of a different, but also well-established ability of alkoxy radicals: the intramolecular 1,5-HAT with inactivated C-H bonds, generating C-radicals in remote positions in a regioselective manner.[131] This catalytic method allows the functionalization of linear and cyclic alcohols containing silyl-protected alcohols, ether or ester functionalities. Notably, the amination occurs exclusively at the  $\delta$ -C–H position even in the presence of weaker C-H bonds such as benzylic or those in alpha to heteroatoms showcasing the directed, intramolecular character of HAT step. Primary, secondary and tertiary positions were suitable for the C-N bond formation. Gramscale synthesis was also possible, using loadings as low as 0.1 mol% FeCl<sub>3</sub>. Overall the above-described reactivity profile, which mimics that reported previously for cerium salts by Zuo,[132-134] demonstrates that the formation of alkoxy radicals from alcohols via LMCT excitation is also a valid strategy under iron catalysis, probably aided by the higher oxophylicity of Fe(III) in comparison with other 3d metals.



Scheme 24. Remote amination of alcohols via iron photocatalysis.

#### 3.3 Reactions mediated by Ni(III) complexes

Due to the inherent instability of Ni(III) species, the number of reported compounds is markedly more scarce than Cu(II) and Fe(III) complexes and, in consequence, their LMCT reactivity has been significantly less explored. In fact, it was not until 2015 when the photoinduced homolysis of Ni(III)-CI bonds to produce CIwas demonstrated. With the aim of developing systems based on Earth-abundant metals for energy storage, Nocera and coworkers reported a family of well-defined Ni(III) trichloro-complexes that are capable of producing Cl<sub>2</sub> upon light irradiation (Scheme 25A).<sup>[116,117]</sup> The UV-vis absorption spectra of these complexes in solution present LMCT bands in the visible range, which are responsible for the observed photoreactivity. Computational, photocrystallographic and transient-absorption spectroscopy studies demonstrated that population of LMCT excited states induces the reduction to Ni(II) with concomitant formation of CI+, which is stabilized by interactions with a pendant phenyl ring of the diphenylphosphinoethane (dppe) ligand forming a chargetransfer complex before dimerize to give Cl<sub>2</sub> or undergo HAT with the solvent. The effective stabilization of CI• by charge-transfer to an aryl ring of the second coordination sphere was proposed to play a key role to obtain efficient photoelimination. More recently, the group of Mirica carried out a study focused on a tetradentate N-donor ligand system, supported by different spectroscopic techniques (Scheme 25B).<sup>[135]</sup> Similarly, photoinduced homolysis of the Ni(III)-CI bond was proposed to proceed via population of LMCT states upon visible-light irradiation. In both cases, the parent Ni(III) complexes could be regenerated by treatment with PhICl<sub>2</sub>.



Scheme 25. Photoelimination of chlorine radical from Ni(III)-Cl complexes.

The frequent participation of Ni(III) species in nickel-catalyzed cross-couplings has directed more attention towards the reactivity of these intermediates. In particular, given the broad success of the merge between photoredox and nickel catalysis, significant interest has been attracted to the study of Ni(II) and Ni(III) complexes under photochemical conditions.[31,136-139] In this context, during their studies on metallaphotoredox reactions the Doyle group unveiled in 2016 a method for the cross-coupling of aryl chlorides with ethereal solvents at C-H bonds under blue light irradiation,<sup>[140]</sup> proceeding via the proposed mechanistic depicted in Scheme 26.<sup>[141]</sup> A given [Ni(0)] catalyst undergoes oxidative addition of aryl chloride to form [Ni(II)]ArCl, which is then oxidized by excited-state iridium photocatalyst [Ir(III)]\* to access the key [Ni(III)]ArCI intermediate. Under these photochemical conditions LMCT homolysis of the Ni(III)-CI bond occurs, affording CI• that activates selectively C-H bonds in alpha to the oxygen atom of the solvent via HAT. The resultant C-radical rebounds to [Ni(II)]Ar species and subsequently undergo reductive elimination to give the C-H arylation product and [Ni(I)], which is reduced to [Ni(0)] by [Ir(II)] closing simultaneously both nickel and photoredox catalytic cycles. Thereby, in this reaction the aryl chloride serves not only as coupling partner, but also as the source of chloride ligands that would be transformed into CI• via LMCT at Ni(III). Differently from the methods described above for Cu(II) and Fe(III), photoactive Ni(III) species are not present at the beginning of the reaction but are postulated intermediates generated in situ. For this reason, methodologies based on LMCT reactivity on Ni(III) complexes generally require the participation of an additional photoredox catalyst that carry out the Ni(II)  $\rightarrow$  Ni(III) oxidation, also playing additional roles on other SET steps. A broad scope on the aryl chloride side was reported, enabling access to structurally diverse benzylic ethers. Examples of electron-rich and -poor substrates containing alkenes, aldehydes or nitriles groups and different heterocyclic structures could be engaged in good to excellent yields. The scope of ethers is more limited, but displaying good reactivity in cyclic and acyclic structures. The use of the C-H coupling partner as a solvent is probably the main drawback of this methodology, but the authors demonstrated that a reduction to 10 equivalents is possible by using benzene as cosolvent. In addition, a similar protocol could also be extended to non-ethereal compounds such as toluene and even inactivated cyclohexane as alkyl radical precursors, laying the foundation for future applications. It is worth noting that a similar transformation

using aryl bromides was reported simultaneously by Molander and coworkers.<sup>[142]</sup> In this case Br• generation is proposed to be generated from excited-state Ni(II) complexes, although the photoinduced homolysis of Ni(III)–Br bonds was not fully ruled out.

$$\label{eq:likelihood} \begin{split} & [Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6~(2~mol\%)\\ & \textbf{Ni(cod)_2}~(10~mol\%),~dtbbpy~(15~mol\%) \end{split}$$
Ó K<sub>3</sub>PO<sub>4</sub> (2 equiv.), N<sub>2.</sub> rt, blue LEDs (solvent) 0: 73% 78% 91% 47% C [lr(ll)] [lr(III)]' ſNi A [lr(lll)] HC Ar OR [Ni<sup>0</sup>] [lr(ll)] 6 [lr(III)] A

Scheme 26. Ni-catalyzed C–H arylation of ethers.

Exploiting this idea, the Doyle group next applied this reactivity to target two specific ethereal coupling partners with distinct reactivity profile (Scheme 27). First, the authors explored the use of 1,3-dioxolane as C-H coupling partner through the selective HAT on the C-2 position, enabling a methodology for the masked formylation of aryl halides (Scheme 27A).<sup>[143]</sup> In such a way, the benzylidene acetal derivates obtained under metallaphotoredox catalysis could be deprotected by simple acidic workup giving the corresponding benzaldehyde derivatives, representing a convenient one-pot method for the CO-free formylation of aryl chlorides. The scope of the method proved to be very general, including examples of high complexity such as sugars, drugs, agrochemicals or glycosides, containing many polar and coordinating functional groups in a method that was shown to be effective also in gram scale. Recently, the same group reported the use of trimethyl orthoformate for the methylation of aryl halides (Scheme 27B).<sup>[144]</sup> Starting from a serendipitous discovery, this reactivity is based on the ability of (MeO)<sub>3</sub>C• to undergo β-scission producing dimethylcarbonate and Me•, which is the C-radical species participating in Ni-mediated cross-coupling. Computational calculations predict a favorable energy profile for the formation of Me• following this pathway, which complements the experimental detection of this reactive species, all together providing feasibility to the proposed mechanism. Since methylation protocols frequently use highly reactive electrophilic or nucleophilic Me-sources, this method offers a complementary approach that can be used at late-stages in view of their broad scope and functional group compatibility.



Scheme 27. Ni-catalyzed C–H arylation on functional ethers. (A) one-pot formylation of aryl halides with 1,3-dioxolane. (B) Methylation of aryl halides with trimethyl orthoformate.

This strategy for C-H arylation based on metallaphotoredox catalysis was very recently applied to the enantioselective  $\alpha$ arylation of protected amines (Scheme 28).[145] Based on the above-described reactivity mode, Huo and coworkers not only enabled the use of slight excess (3.0-4.0 equiv.) of the C-H coupling partner with respect to the aryl chloride, but also succeeded in the asymmetric induction through the use of chiral bis(imidazoline) ligands to access valuable enantioenriched aaryl N-heterocycles. A diverse set of aryl chlorides can be employed with good yields and enantioselectivities, including heteroaryl substrates with different functionalities. 5 to 8-member cyclic amides, carbamates and lactams along with several examples of linear substrates are engaged as well, representing a cost-effective method to access valuable building blocks. The utility of the method was further demonstrated by the late-stage diversification of derivatives of pharmaceuticals and natural products and the good performance at gram-scale.



Scheme 28. Enantioselective C-H arylation of protected amines.

Beyond the reaction with aryl halides, Csp<sup>3</sup>–H bonds can also be functionalized with other coupling partners under Ni-catalyzed cross-coupling reactions producing halogen radicals via LMCT processes. In 2018 Doyle and coworkers described a method for C-C bond formation with chloroformate derivatives (Scheme 29A).<sup>[146]</sup> Contrarily to that observed in arylation methods, the deactivated character of the C-H bonds in alpha to the carbonyl group in the product now allows the significant extension of the scope of C-radical precursors beyond ethers to many other compounds bearing inactivated C-H bonds that can be used in much reduced amounts (3 equiv.). Mechanistically, the process is analogous to that reported for aryl chlorides, involving now oxidative addition into R(O)C-CI bonds. Hence, this method provide access to structurally diverse ketones, esters and amides in modest to good yields. The scope on the alkyl fragment side is broad including linear and cyclic alkanes, containing ketones, protected amines, alkyl chlorides or nitriles, among other functional groups. The selectivity amongst different, inactivated C-H bonds matches well the observed for CI in other methodologies. Two years later, the groups of Paixão and König extended the pool of funtionalizations on ethers towards the C-H alkylation with alkyl bromides by means of photoredox-nickel dual catalysis (Scheme 29B).[147] In this case Br•, generated by LMCT homolysis on Ni(III)Br complexes is mediating the HAT to produce C-radicals, which undergo a Csp<sup>3</sup>–Csp<sup>3</sup> reductive elimination to afford the desired product. The scope of alkyl bromides includes primary and secondary substrates bearing different functional groups in combination with tetrahydrofuran (THF), which was used as a solvent. Different ethereal solvents other than THF were attempted, but generally resulting in low yields or no product formation.





Scheme 29. Ni-catalyzed C–H functionalization with chloroformates (A) and alkyl bromides (B).

This strategy was adapted by Wu and coworkers for the hydroalkylation of disubstituted alkynes (Scheme 30).<sup>[148]</sup> Mechanistic studies suggested a more complex scenario, where a key role for chloride salts and a regioselectivity inverse to that expected for radical addition were found. With this data in hand, the authors proposed a mechanism involving LMCT generation of CI• at Ni(III) to activate C–H bonds on a suitable substrate to form an alkyl radical. These species would then enter in conjunction with the reactivity of Ni-H species towards alkynes, ultimately leading to the alkene product with generally good *E/Z* selectivity. A scope consisting in different internal alkynes in combination with ethereal or amide-based C-radical precursors used as (co)solvents was described. Later on, the group of Hong reported a related transformation involving ynones as the alkyne acceptors, yielding alkylated enones under similar reaction conditions.<sup>[149]</sup>



#### 3.4 Reactions mediated by Co(III) complexes

Although other related photoinduced reactions such as decarboxvlation<sup>[150,151]</sup> have been know at a fundamental level for decades, the synthetic applications of photochemical processes in Co(III) have been largely dominated by the facile C-Co homolysis upon LMCT excited-states population<sup>[152-154]</sup> at vitamin B12-derivatives and bis(dimethylglyoximato) complexes, also known as cobaloximes (Scheme 31A). In this section there are summarized some of the most representative examples to provide a general vision of the field, however for a more comprehensive analysis the reader is referred to any of the excellent reviews on these types of catalysts that are reported elsewhere.[155-159] The general reactivity profile of these compounds under photocatalytic conditions is depicted in Scheme 31B.[153] Co(III)-alkyl complexes can be generated following two major pathways: (i) polar S<sub>N</sub>2-type reaction of Co(I) precursors with alkyl electrophiles and other related systems (e.g. epoxides) or (ii) C-radical capture by stable, long-lived Co(II) metalloradicals. Upon visible-light irradiation, the resultant alkylcobalt(III) complexes undergo LMCT homolysis to give Co(II) and an alkyl radical, which in turn can (i) recombine with Co(II) to reform Co(III)-alkyl, (ii) escape from the radical pair solvent cage and participate in free-radical reactions or (iii) react with Co(II) metalloradical via HAT, leading to Co(III)-H and the corresponding alkene through a formal, radical-type  $\beta$ -hydride elimination. These features have been exploited over the years in many applications in the field of organic synthesis.



Scheme 31. (A) Cobaloxime and Vitamin B12 general structures, Co–C photoinduced homolysis. (B) Reactivity modes under light irradiation.

During their studies on radical addition to olefins, Giese and coworkers reported in 1988 the use of alkyl cobaloximes as convenient, stoichiometric C-radical precursors upon light irradiation (Scheme 32).<sup>[160,161]</sup> Unlike other radical initiators at that time, this strategy did not require high temperatures or the use of explosive reagents to generate alkyl radicals, which were

detected by ESR and could be trapped by NO to yield oximes. Upon reaction with olefins two extreme situations where identified. The use of styrene allowed the re-generation of the double bond via  $\beta$ -hydride elimination, affording C–H substitution products. Contrarily, the use of acrylonitrile generate intermediates with polarized Co(III)–C bonds that are heterolytically cleaved to give stabilized carbanions which, after protonation, provide hydroalkylation products.



Scheme 32. Generation of alkyl radicals by irradiation of alkyl Co(III) complexes.

In 2011 the group of Carreira capitalized on the combined polar and photochemical reactivity of cobaloximes to design an elegant method for the catalytic intramolecular Heck-type coupling of alkyl iodides (Scheme 33).[65] The proposed mechanism involves the alkylation of reduced cobaloximes via S<sub>N</sub>2 with alkyl iodides forming a Co(III)-alkyl intermediate which, upon blue light irradiation, experiences homolysis followed by fast 5- or 6-exo-trig radical cyclization into the olefin and rebound to cobaloxime again. The resultant, new Co(III)-alkyl intermediate then undergoes photochemical desaturation via Co-C homolysis+HAT, yielding the final Heck-type alkene product and Co(III)-H. The key aspect to enable turnover and go catalytic in cobalt was the regeneration of active Co(I) by simple deprotonation of the putative Co(III)-H intermediate using iPr2NEt as a base. A stannyl cobaloxime Ph<sub>3</sub>Sn-Co(dmgH)<sub>2</sub>py was used as precatalyst, but the reaction could be initiated as well using alkyl cobaloximes with comparable efficiency. With respect to the scope, different 5-membered rings could be assembled through this C-C bond forming process, resulting from the radical addition to terminal, di- or tri-substituted olefins. 6-membered cycles could also be obtained only in the presence of electron-deficient olefin acceptors. While in most of the cases primary alkyl iodides were utilized, an example of a secondary substrate is also provided, and several functional groups such as aryl iodides, aldehydes or alcohols are tolerated. Finally, the utility of this method was showcased on the concise synthesis of the natural product (±)-samin. Two years later the same group applied this reactivity on the intermolecular reaction between 2,2,2-trifluoroethyl iodide and styrenes, showing as well its scalability in flow.[162]



Scheme 33. Co-catalyzed intramolecular Heck-type reaction of alkyl iodides.

In 2016 the group of Morandi followed a similar strategy for the intramolecular coupling of epoxides or aziridines with alkenes under cobaloxime photocatalysis (Scheme 34).<sup>[163]</sup> Upon S<sub>N</sub>2-type nucleophilic ring opening of the 3-member-heterocylic ring by Co(I), a Co(III)-alkyl intermediate bearing a pendant alkene is obtained, which participate in a similar radical Heck-type process to the one described above. In this case, the use of tertiary amines as bases proved ineffective, but the authors reported the successful use of t-BuOK in catalytic amounts, since an equivalent of strong base is generated after each ring-opening and therefore available to deprotonate Co(III)-H species allowing turnover. A variety of epoxides and aziridines, which were regioselectively opened at the least substituted position, participate in this reactivity to afford 5- and 6-member cyclic homoallylic alcohols and amines as E/Z mixtures, when applicable. Preliminary results on the more challenging intermolecular version of this reaction were provided using of the highly activated diphenylethylene as olefin acceptor. The polar, stereospecific nature of the ring opening by Co(I) was demonstrated by the lack of erosion on enantiomeric excess when a chiral epoxide was utilized. Further mechanistic experiments were performed, confirming the radical nature of the process after ring-opening.



Scheme 34. Intramolecular Heck-type reactivity via ring-opening of epoxides.

This mode of catalytic polar-radical hybrid reactivity has also been demonstrated with vitamin B12 derivatives.<sup>[155,156]</sup> For example, the groups of Gryko and Komeyama have independently reported intermolecular reactions between alkyl tosylates or S-acyl thiopyridines with electron deficient olefins to give Giese-type products under blue LEDs irradiation (Scheme 35).<sup>[164,165]</sup> Those reactions are based on the faculty of these Co(I) "supernucleophiles" to participate in S<sub>N</sub>2-type reactions and subsequent photoinduced LMCT homolysis. In this case the radical intermediate obtained after addition to the olefin is reduced and, since Co(III)-H is generated, the catalytic turnover is not mediated by deprotonation but achieved by direct  $Co(II) \rightarrow Co(I)$ reduction in presence of stoichiometric Zn or Mn reductants. The use of ammonium salts as proton donors was also proven advantageous to obtain high yields. The alkyl and acyl radicals generated via B12 photocatalysis were smoothly added to a wide variety of Michael acceptors such as acrylates, acrylonitriles, vinyl sulfones, vinyl boronates, vinyl pyridine or cyclopentatone, performing also well at gram scale. Structurally diverse alkyl- and arylacyl fragments can be coupled under Gryko's conditions, including heterocyclic groups and tolerating many functionalities. Regarding the scope on alkyl tosylates shown by Komeyama and coworkers, it includes many examples of primary substrates and one example of secondary, possessing good functional group tolerance. As can be expected from the S<sub>N</sub>2-type nature of this reactivity, sterically congested electrophiles react with much reduced yields constituting the main limitation of this strategy. Several mechanistic experiments, including trapping of C-radicals with TEMPO, detection of Co-based intermediates by MS or deuteration labelling were performed, all in agreement with the mechanistic proposal detailed above.



Scheme 35. Giese-type reaction of alkyl tosylates and S-acyl thiopyridines catalyzed by vitamin B12 derivatives.

Recently, the Gryko group explored the catalytic use of vitamin B12 derivatives to undergo tandem ring-opening cross-coupling sequences (Scheme 36). Following this approach, B12-catalysis would be used to generate C-radicals that would then participate in Ni-catalyzed cross-couplings with aryl halides through an interesting Co/Ni dual photocatalytic system, in presence of Zn as terminal stoichiometric reductant. In a first contribution in 2020 the authors worked on the strain-release-driven reactions with bicyclo[1.1.0]butanes to access valuable 1,3-disubstituted cyclobutanes.[166] The proposed mechanism involves the nucleophilic ring opening of these strained rings by attack of Co(I) to form, after protonation, cyclobutyl Co(III) species. Visible-light induced LMCT homolysis of this intermediate provides cyclobutyl radicals that can be intercepted by Ni catalysts to participate in C-C reductive elimination in presence of aryl halides to yield the final arylcyclobutane products. Notably, the cyclobutyl Co(III) intermediate could be isolated and characterized by X-ray crystallography, and their photochemical performance towards LMCT homolysis of the Co(III)-C bond was unambiguously established by trapping the resultant cyclobutyl radical with TEMPO. Other mechanistic experiments by means of deuteration labelling, cyclic voltammetry or UV-vis absorption spectroscopy were in agreement with the proposed mechanism. A wide variety of aryl iodides containing multiple functional groups like nitriles, ketones, alcohols or alkynes were successfully engaged, including examples with heteroarenes and drug derivatives. The presence of an EWG at 1-position of the bicyclobutane was required, allowing the obtention of sulfonyl-, cyano-, carboxyl- or

amido-cyclobutanes with this method that could also be extended to bicyclopentanes. Next, they applied a similar strategy for the cross-coupling of epoxides with aryl iodides.[167] This methodology, which was applicable to aryl and alkyl epoxides, features a highly regioselective ring opening on the least substituted position, providing access to β-arylated linear alcohols. Both cyclic and acyclic, mono- and disubstituted epoxides proved to be suitable substrates for this transformation. Finally, the same group very recently extended this reactivity to oxetanes.<sup>[168]</sup> Due to the higher barrier associated to the nucleophilic ring opening, no direct reaction was observed between Co(I) and oxetanes. For this reason, oxetanes were opened in situ with TMSBr to form bromohydrins that are suitable alkylating substrates for Co(I) via  $S_N2$ . Hence, using this blueprint  $\gamma$ -arylated alcohols were obtained as products, with a scope on aryl iodides comparable to their previous works. It is worth noting that, in addition to the Nimediated arylations, free-radical Giese-type addition to different electron-deficient olefins to yield alkylation products was also described in these publications for bicyclobutanes and oxetanes.



Scheme 36. Tandem ring-opening cross-coupling via dual Co/Ni catalysis.

Cobaloxime catalysis has also found important applications on the desaturation of alkyl radicals. This mode of reaction is based on the ability of Co(II) to trap alkyl radicals to form Co(III)-C bonds, which can then be homolyzed via LMCT excitation and undergo HAT to give an alkene and Co(III)-H. Methodologies involving this type of processes typically require another photocatalyst to generate C-radicals, and a number of methodologies have appeared on the last decade exploiting dual photoredox/cobaloxime catalytic systems.[157,169] Photocatalytic radical desaturations have been performed from different alkyl radical precursors, involving HAT, SET or XAT as activation modes (Scheme 37). In 2015 Sorensen and coworkers demonstrated the possibility of using a redox-neutral, fully catalytic system for the dehydrogenation of alkanes combining tetrabutylammonium decatungstate as HAT catalyst with cobaloxime catalysis.<sup>[170]</sup> Although yields were generally modest, this report constituted a landmark on the field, showcasing the potential of radical desaturation in organic synthesis. More recently, this dehydrogenative synthesis of alkenes was further improved by Huang and Xu with the use of 2-chloroanthraquino as HAT catalyst.<sup>[171]</sup> While this strategy possesses a perfect atom economy, the presence of many undistinguishable C-H bonds in many cases results in mixtures of alkenes and, in this regard, the controlled and site-specific generation of C-radicals offers complementary synthetic advantages. With this idea in mind, the groups of Ritter, Tunge and shortly after Larionov independently developed the photochemical decarboxylative synthesis of olefins, using a photoredox catalyst to undergo SET oxidation of alkyl carboxylates that, after CO<sub>2</sub> extrusion, would lead to alkyl radicals.<sup>[172-174]</sup> This strategy enables access to olefins in structurally complex environments from abundant carboxylic acids under mild conditions, and it is particularly useful when using primary or symmetrical carboxylic acids and aminoacids, where only one alkene regioisomer is obtained. The wide variety of sensitive functional groups tolerated under these conditions makes of these methods a robust and useful synthetic tool that can be applied for late-stage functionalization. Finally, Leonori co-workers recently described the photoinduced and dehydrohalogenation of inactivated alkyl halides by means of photoredox/cobaloxime dual catalysis.<sup>[64]</sup> As a milder and more efficient alternative to classical E2 thermal eliminations, this reaction is based on the generation of C-radicals by XAT with  $\alpha$ aminoalkyl radicals,<sup>[175]</sup> generated in situ via photoredox catalysis, and their subsequent desaturation via cobaloxime catalysis. Primary, secondary and tertiary iodides and bromides smoothly react under these conditions to give alkenes in good to excellent yields in the presence of a variety of functional groups. Notably, the authors demonstrated how modification of the electronic and steric properties of the cobaloxime catalysts allows to modulate the reactivity of the Co(II) intermediate towards HAT and, therefore, control the site-selectivity on the alkene formation. This blueprint was applied to the synthesis of contra-thermodynamic olefins that cannot be accessed by thermal E2 elimination and, in several cases, the regioselectivity of the reaction could be inverted under the same reaction conditions upon careful selection of a suitable cobaloxime catalyst.



Scheme 37. Synthesis of alkenes via catalytic radical desaturation with cobaloximes.

#### 3.5 Reactions mediated by Ti(IV) complexes

Due to its high-valent character and the high electrophilicity of the metal center, most Ti(IV) complexes possess low-lying LMCT states and are thus particularly well-suited to participate in photoinduced LMCT processes.<sup>[176-181]</sup> However, the use of this light-induced reactivity has not been extensively applied to organic synthesis. In the late 1970s Sato and coworkers reported a series of seminal studies on photochemical reactions mediated by Ti(IV) in methanol (Scheme 38).[182-184] In these works. methanol was described to form new C-C bonds with the carbonyl group of ketones and enones in a reactivity that could also be extended to imines and nitriles. The formation of hydroxymethyl radical (•CH<sub>2</sub>OH) from methanol via rearrangement of methoxy radical (CH<sub>3</sub>O•) was rationalized to explain this reactivity, which was applied to the one-step synthesis of frontalin from 2,6heptanedione. Although the specific mechanism was not clear at that stage, in view of the known fast reactivity of TiCl4 with alcohols towards the formation of Ti(IV) alkoxides,[185] these might represent the first seminal uses of LMCT reactivity of Ti(IV)-O bonds in organic synthesis. This reactivity mode has been later applied by Sato and other researchers in related transformations.[186-189]



 $\label{eq:Scheme 38. Seminal reports on the photochemical reactivity of Ti(IV) with alcohols.$ 

More recently the groups of Flowers and Gansäuer<sup>[190]</sup> and shortly after Iwasawa<sup>[191]</sup> used light irradiation to access reactive Ti(III) species from Ti(IV) precursors via LMCT excitation, bypassing the common need for metal reductants<sup>[192,193]</sup> (Scheme 39). Differently from other approaches discussed along this review, in these works the main interest is focused not in the species derived from the ligand, but on the metal-based species generated after Ti(IV)-L homolysis and their innate reactivity towards C-O bond cleavage. In this manner, the radical-type reactivity of Ti(III) towards oxygen atoms was exploited by Flowers and Gansäuer for the reductive ring-opening of epoxides, which can be carried out under green-light irradiation with catalytic amounts of Cp2TiCl2 in the presence of stoichiometric amines and a thiol as a HAT catalyst. The authors proposed the use of amines to enable turnover and also playing a role as reductant to efficiently form Ti(III) after LMCT excitation. The scope of this reaction included mono- and di-substituted alkylic epoxides in a variety of structures, although the functional group compatibility was not explored in detail. The application of radical ring-opening coupled with a subsequent radical cyclization with a pendant alkene or alkyne in a tandem cascade process was also demonstrated, providing access to more structurally complex scaffolds. On the other hand, Iwasawa and coworkers focused their attention on the radical deoxygenative dimerization of benzylic alcohols. Using Ti(Oi-Pr)4 as photocatalyst, upon UV light irradiation Ti(IV)-O homolysis is expected to proceed via LMCT population, and the resultant Ti(III) species can undergo de-hydroxylation on benzylic alcohols enabled by the formation of a stable benzylic radical, which dimerizes to give the final product. The stability of the benzylic radical seems to have a strong influence, since the scope of the methodology is mainly restricted to highly activated bis-benzylic alcohols, although two examples of monosubstituted benzylic alcohols are also shown to proceed in low yields.



Scheme 39. Radical C–O activation by photogenerated Ti(III).

Very recently, Mitsunuma and Kanai<sup>[194]</sup> and the groups of Walsh and Schelter<sup>[195]</sup> simultaneously reported the Csp<sup>3</sup>–H alkylation of hydrocarbons catalyzed by Ti(IV) chlorides (Scheme 40). Analogously to the reactivity observed for Cu(II) or Fe(III) chlorides, this reactivity arises from the generation of CI- via LMCT homolysis of Ti(IV)-CI bonds. Hence, CI. can activate C-H bonds in alkanes by HAT, generating alkyl radicals that then participate in Giese-type additions to electron-deficient olefins. Schelter and Walsh used the air-stable salt [Ph<sub>4</sub>Ph]<sub>2</sub>TiCl<sub>6</sub> as photocatalyst and provided detailed mechanistic studies based on UV-vis absorption measurements and computational calculations. Notably, the in situ-produced Ti(III) intermediates could also be isolated and characterized. Several hydrocarbons, including gaseous methane and ethane, were reacted in combination different Michael acceptors in good yields. Under similar conditions, Mitsunuma and Kanai reported analogous findings on the formation of Ti(III) species after irradiation of TiCl<sub>4</sub> with 370 nm LEDs. Their Giese-type alkylation included monosubstituted alkene acceptors and different substrates used for C-H functionalization such as alkyl ketones, amides or ethers. Interestingly, the authors also reported the addition of alkyl radicals to aromatic ketones, which is considerably more challenging owing to the instability of the resultant alkoxy radical intermediates. The fact that replacement of TiCl<sub>4</sub> other metal salts able to produce CI• photochemically such as CuCl<sub>2</sub>, FeCl<sub>3</sub> or CeCl<sub>6</sub><sup>3-</sup> resulted in no reaction suggest that Ti(III) species are also involved in the stabilization of the O-radical intermediate, enabling radical addition to carbonyls. In this case, the use of stoichiometric



TMSCI was also required to re-generate Ti(IV)–CI from Ti(IV)–OR species, allowing catalytic turnover.

 $\label{eq:scheme 40.} Scheme \ 40. \ \mbox{Ti}(IV) \ \mbox{catalyzed C-H} \ \mbox{alkylation of alkanes}.$ 

#### 3.6 Reactions mediated by V(V) complexes

Although the use of vanadium in organic synthesis is largely dominated by epoxidation and related oxidations via vanadium oxo-complexes,<sup>[196]</sup> some examples on their photochemical behavior arising from LMCT excited states have also been described. In 1975 Bamford and coworkers first reported the photoinduced production of methoxy radicals from V(V)-OMe complexes with 8-hydroxyquinolinate ligands upon irradiation at 365 nm (Scheme 41A).<sup>[197,198]</sup> The formation of V(IV) complexes and MeO• after irradiation was confirmed by IR, UV-vis absorption and ESR spectroscopy, and this reactivity was used for the photoinitiation of methyl methacrylate polymerization. The authors also showed how this reactivity could also be extended to other V(V) alkoxides, representing a general route to produce alkoxy radicals. These studies were further extended to other V(V) complexes by the group of Aliwi.[199-202] More recently, Soo and coworkers exploited LMCT reactivity of V(V) complexes for the degradation of lignin models (Scheme 41B).[203-205] This strategy is based on the formation of O-radicals via LMCT on the hydroxy aroups of lignin, subsequently undergoing B-scission to enable Csp<sup>3</sup>–C sp<sup>3</sup> cleavage on the backbone of this polymeric material under mild conditions, without requiring pre-oxidation processes. The presence of atmospheric oxygen is allowing the re-oxidation  $V(IV) \rightarrow V(V)$ , enabling catalytic turnover of this method, which could be efficiently carried out using visible light with a suitable, redox-noninocent ancillary ligand for vanadium. The mechanism of this transformation was interrogated by kinetic, spectroscopic and electrochemical measurements and was also supported by DFT calculations. Moreover, the authors also employed this blueprint for C–C bond cleavage on diverse small-molecule alcohols as substrates and on the degradation of hydroxylated plastics such as polyethylene glycol. In 2020, the group of Wang reported a related work using commercially available vanadium complexes such as  $VO(i-Pr)_3$  as photocatalysts, showing activity on the degradation of dioxasolv ligning extracts.<sup>[206]</sup>



**Scheme 41.** LMCT photochemistry on V(V). (A) Seminal reports on the generation of alkoxy radicals. (B) Application on lignin models degradation.

### 4. Conclusion and Future Perspectives

Ligand-to-metal charge-transfer excited states are widely present in many first-row metal complexes and can be conveniently accessed via visible or near-UV light irradiation. One of the key characteristic features of LMCT which differentiates it from other classes of excited states is their innate tendency to undergo chemical reactivity without the need for long-lived species. LMCT reactivity retains a historically unrealized synthetic potential, but is nowadays emerging as an unparalleled platform for the generation of highly reactive radical species without involving strong oxidants or reductants at room temperature, enabling synthetic methods to proceed under remarkably mild conditions with broad substrate scope. Moreover, LMCT reactivity allows the use of Earth-abundant metal catalysts under visible-light irradiation, in some cases also under redox-neutral conditions, representing a truly sustainable approach towards chemical synthesis.

In this review there are summarized some of the most relevant accomplishments of this strategy in organic synthesis, including both seminal contributions and state-of-art methodologies. While the most common synthetic applications are based on the generation of halogen radicals to undergo HAT in C–H functionalization methods, it has been proved that the homolysis of other M–L bonds can result in highly appealing reactivity (e.g. decarboxylation of benzoic acids, controlled release of C-radicals

or generation of alkoxy radicals from alcohols). In some methodologies the use of stoichiometric metal complexes is required. However, the use of inexpensive simple salts of Earthabundant metals in these cases alleviates the concerns in terms of cost, justifying the lack of catalytic settings when providing remarkable new reactivity pathways, something that would be difficult to implement in the case of precious metals. Even though they have common features, it is worth noting the versatility in reactivity brough by 3d metals offering uniquely different reactivity profiles, such as the decarboxylation of aryl carboxylic acids in Cu, the formation of alkoxy radicals by Fe and Ti, the desaturation channel offered by Co or the ability to readily participate in subsequent C-C cross-couplings offered by Ni complexes. In this manner, from stable precursors (Cull, Felli) to intermediates generated in situ (Ni<sup>III</sup>), with a key reactive species based on the oxidized ligand (CI+, RO+) or the reduced metal (Till), LMCT activation mode open numerous different reactivity modes by using a clean and selective source of energy.

Unveiled opportunities can be opened through further exploration of future directions on the field. For example, in contrast to works on Cu, Co or Fe systems, LMCT reactivity in other 3d metals such as Cr, Mn or Ti is comparatively underdeveloped, and could enable interesting methodologies in the near future. On the other hand, in comparison with halogen- or O-radicals, the generation of other open-shell heteroatom species such as N-radicals via LMCT is significantly less explored, despite their synthetic relevance. Likewise, given the ability of 3d-metal complexes to catalyze cross-coupling reactions, further integration of LMCT activation and organometallic reactivity in a single catalyst would offer new horizons on sustainable catalysis. Finally, further indepth mechanistic studies on this activation mode based on combined photophysical, computational and other techniques are required to provide a better understanding on the factors that govern each type of transformation. In particular, this may lead to the discovery of novel systems through the exploration of the influence of ancillary ligands that could modulate or enable catalytic activity and offer new opportunities, for example, in asymmetric synthesis. Looked in perspective, the broad application of LMCT reactivity as a general tool for synthesis is relatively recent, and was first applied in modern methodologies in 2016 for cerium<sup>[132]</sup> and nickel,<sup>[140]</sup> in 2019 for iron<sup>[82]</sup> and in 2020 for copper.<sup>[73]</sup> Considering this, the examples provided here certainly represent only the beginning of what we can foresee, and it is reasonable to anticipate a rapid further development of this field, and its broader adoption in both Academia and industry. I hope this review serves to provide a better understanding on LMCT and stimulate the curiosity of researchers towards the use of this photoinduced reactivity as enabling tool to design future chemoselective transformations in a sustainable manner.

### Acknowledgements

F.J. thanks "La Caixa" Foundation (ID 100010434) and the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 847648 for their financial support (LCF/BQ/PI21/11830026).

**Keywords:** LMCT • photocatalysis • sustainability • radical chemistry • transition-metal catalysis

- C. L. McIntosh, R. E. Blankenship, in *Encycl. Inorg. Bioinorg. Chem.* (Ed.: R.A. Scott), John Wiley & Sons, Ltd, Chichester, UK, **2014**, pp. 1–27.
- [2] J. Barber, *Chem Soc Rev* **2009**, *38*, 185–196.
- [3] J. F. Endicott, Isr. J. Chem. 1970, 8, 209–226.
- [4] V. Balzani, L. Moggi, *Coord. Chem. Rev.* **1990**, 97, 313–326.
- [5] L. E. Orgel, Q. Rev. Chem. Soc. 1954, 8, 422.
- [6] Proc. R. Soc. Lond. Ser. Math. Phys. Sci. 1956, 235, 518–536.
- [7] H. L. Schläfer, Ed. , Z. Für Phys. Chem. 1957, 11, 65–77.
- [8] H. D. Roth, Angew. Chem. Int. Ed. Engl. 1989, 28, 1193–1207.
- [9] G. Ciamician, Science 1912, 36, 385–394.
- [10] C. K. Prier, D. A. Rankic, D. W. C. MacMillan, Chem. Rev. 2013, 113, 5322–5363.
- [11] J. Twilton, C. Le, P. Zhang, M. H. Shaw, R. W. Evans, D. W. C. MacMillan, *Nat. Rev. Chem.* 2017, 1, 0052.
- [12] D. Ravelli, S. Protti, M. Fagnoni, Chem. Rev. 2016, 116, 9850–9913.
- [13] L. Marzo, S. K. Pagire, O. Reiser, B. König, Angew. Chem. Int. Ed. 2018, 57, 10034–10072.
- [14] R. C. McAtee, E. J. McClain, C. R. J. Stephenson, *Trends Chem.* 2019, 1, 111–125.
- [15] P. Li, J. A. Terrett, J. R. Zbieg, ACS Med. Chem. Lett. 2020, 11, 2120– 2130.
- [16] L. Candish, K. D. Collins, G. C. Cook, J. J. Douglas, A. Gómez-Suárez, A. Jolit, S. Keess, *Chem. Rev.* 2022, *122*, 2907–2980.
- [17] S. P. Pitre, L. E. Overman, Chem. Rev. 2022, 122, 1717–1751.
- [18] L. Buglioni, F. Raymenants, A. Slattery, S. D. A. Zondag, T. Noël, *Chem. Rev.* 2022, 122, 2752–2906.
- [19] C. B. Larsen, O. S. Wenger, Chem. Eur. J. 2018, 24, 2039–2058.
- [20] O. S. Wenger, J. Am. Chem. Soc. 2018, 140, 13522–13533.
- [21] C. Förster, K. Heinze, Chem. Soc. Rev. 2020, 49, 1057–1070.
- [22] N. A. Romero, D. A. Nicewicz, Chem. Rev. 2016, 116, 10075–10166.
- [23] A. Vega-Peñaloza, J. Mateos, X. Companyó, M. Escudero-Casao, L. Dell'Amico, Angew. Chem. Int. Ed. 2021, 60, 1082–1097.
- [24] T. Bortolato, S. Cuadros, G. Simionato, L. Dell'Amico, Chem. Commun. 2022, 58, 1263–1283.
- [25] J. D. Hayler, D. K. Leahy, E. M. Simmons, Organometallics 2019, 38, 36–46.
- [26] R. M. Bullock, J. G. Chen, L. Gagliardi, P. J. Chirik, O. K. Farha, C. H. Hendon, C. W. Jones, J. A. Keith, J. Klosin, S. D. Minteer, R. H. Morris, A. T. Radosevich, T. B. Rauchfuss, N. A. Strotman, A. Vojvodic, T. R. Ward, J. Y. Yang, Y. Surendranath, *Science* **2020**, *369*, eabc3183.
- [27] J. R. Ludwig, C. S. Schindler, Chem 2017, 2, 313–316.
- [28] P. Chirik, R. Morris, Acc. Chem. Res. 2015, 48, 2495–2495.
- [29] K. P. S. Cheung, S. Sarkar, V. Gevorgyan, Chem. Rev. 2022, 122, 1543– 1625.
- [30] W.-M. Cheng, R. Shang, ACS Catal. 2020, 10, 9170–9196.
- [31] C. Zhu, H. Yue, J. Jia, M. Rueping, Angew. Chem. Int. Ed. 2021, 60, 17810–17831.
- [32] R. Jamatia, A. Mondal, D. Srimani, Adv. Synth. Catal. 2021, 363, 2969– 2995.
- [33] Y. Xiong, S. Li, H. Xiao, G. Zhang, Synthesis 2021, 53, 4327–4340.
- [34] Y. Abderrazak, A. Bhattacharyya, O. Reiser, Angew. Chem. Int. Ed. 2021, 60, 21100–21115.
- [35] H. Tsurugi, K. Mashima, J. Am. Chem. Soc. 2021, 143, 7879–7890.
- [36] R. Zhao, L. Shi, Org. Chem. Front. 2018, 5, 3018–3021.
- [37] L. Chang, Q. An, L. Duan, K. Feng, Z. Zuo, Chem. Rev. 2022, 122, 2429– 2486.
- [38] V. Balzani, S. Campagna, Eds., Photochemistry and Photophysics of Coordination Compounds I, Springer Berlin Heidelberg, Berlin, Heidelberg, 2007.
- [39] A. Vogler, H. Kunkely, in *Photosensit. Photocatal. Using Inorg. Organomet. Compd.* (Eds.: K. Kalyanasundaram, M. Grätzel), Springer Netherlands, Dordrecht, **1993**, pp. 71–111.
- [40] V. Balzani, V. Carassiti, Photochemistry of Coordination Compounds, Academic Press, London, New York, 1970.
- [41] O. Horvat, O. Horváth, K. L. Stevenson, Charge Transfer Photochemistry of Coordination Compounds, VCH, New York Weinheim, 1993.
- [42] V. Balzani, P. Ceroni, A. Juris, *Photochemistry and Photophysics:* Concepts, Research, Applications, Wiley-VCH, Weinheim, 2014.
- [43] K. Ando, J. Phys. Chem. B **2004**, 108, 3940–3946.

- A S Mereshchenko P K Olshin A M Karimov M Yu Skripkin K A [44] Burkov, Y. S. Tveryanovich, A. N. Tarnovsky, Chem. Phys. Lett. 2014, 615. 105-110.
- [45] D. A. Cagan, D. Bím, B. Silva, N. P. Kazmierczak, B. J. McNicholas, R. G. Hadt, J. Am. Chem. Soc. 2022, 144, 6516-6531.
- K. S. Kiær, N. Kaul, O. Prakash, P. Chábera, N. W. Rosemann, A. [46] Honarfar, O. Gordivska, L. A. Fredin, K.-E. Bergquist, L. Häggström, T. Ericsson, L. Lindh, A. Yartsev, S. Styring, P. Huang, J. Uhlig, J. Bendix, D. Strand, V. Sundström, P. Persson, R. Lomoth, K. Wärnmark, Science 2019. 363. 249-253.
- [47] A. K. Pal, C. Li, G. S. Hanan, E. Zysman-Colman, Angew. Chem. Int. Ed. **2018**, *57*, 8027–8031.
- [48] S. Otto, M. Grabolle, C. Förster, C. Kreitner, U. Resch-Genger, K. Heinze, Angew. Chem. Int. Ed. 2015, 54, 11572-11576.
- D. M. Arias-Rotondo, J. K. McCusker, Chem. Soc. Rev. 2016, 45, 5803-[49] 5820
- S. M. Treacy, T. Rovis, J. Am. Chem. Soc. 2021, 143, 2729–2735. [50]
- Y. Jin, Q. Zhang, L. Wang, X. Wang, C. Meng, C. Duan, Green Chem. [51] 2021, 23, 6984-6989.
- J. Xuan, Z. Zhang, W. Xiao, Angew. Chem. Int. Ed. 2015, 54, 15632-[52] 15641.
- J. Schwarz, B. König, Green Chem. 2018, 20, 323-361. [53]
- [54] D. M. Kitcatt, S. Nicolle, A.-L. Lee, Chem. Soc. Rev. 2022, 51, 1415-1453
- L. McMurray, T. M. McGuire, R. L. Howells, Synthesis 2020, 52, 1719-[55] 1737
- J. W. Hilborn, J. A. Pincock, J. Am. Chem. Soc. 1991, 113, 2683–2686. [56]
- J. Chateauneuf, J. Lusztyk, K. U. Ingold, J. Am. Chem. Soc. 1988, 110, [57] 2886-2893
- J. Chateauneuf, J. Lusztyk, K. U. Ingold, J. Am. Chem. Soc. 1988, 110, [58] 2877-2885
- [59] H. Misawa, K. Sawabe, S. Takahara, H. Sakuragi, K. Tokumaru, Chem. Lett. 1988. 17. 357-360.
- P. Xu, P. López-Rojas, T. Ritter, J. Am. Chem. Soc. 2021, 143, 5349-[60] 5354
- [61] W. Su, P. Xu, T. Ritter, Angew. Chem. Int. Ed. 2021, 60, 24012–24017.
- N. W. Dow, P. S. Pedersen, T. Q. Chen, D. C. Blakemore, A.-M. Dechert-[62] Schmitt, T. Knauber, D. W. C. MacMillan, J. Am. Chem. Soc. 2022, 144, 6163-6172
- T. Q. Chen, P. S. Pedersen, N. W. Dow, R. Fayad, C. E. Hauke, M. C. [63] Rosko, E. O. Danilov, D. C. Blakemore, A.-M. Dechert-Schmitt, T. Knauber, F. N. Castellano, D. W. C. MacMillan, J. Am. Chem. Soc. 2022, 144, 8296-8305.
- [64] H. Zhao, A. J. McMillan, T. Constantin, R. C. Mykura, F. Juliá, D. Leonori, J. Am. Chem. Soc. 2021. 143. 14806-14813.
- M. E. Weiss, L. M. Kreis, A. Lauber, E. M. Carreira, Angew. Chem. Int. [65] Ed. 2011, 50, 11125-11128.
- Y. Li, K. Zhou, Z. Wen, S. Cao, X. Shen, M. Lei, L. Gong, J. Am. Chem. [66] Soc. 2018, 140, 15850-15858.
- [67] A. Y. Chan, I. B. Perry, N. B. Bissonnette, B. F. Buksh, G. A. Edwards, L. I. Frye, O. L. Garry, M. N. Lavagnino, B. X. Li, Y. Liang, E. Mao, A. Millet, J. V. Oakley, N. L. Reed, H. A. Sakai, C. P. Seath, D. W. C. MacMillan, Chem. Rev. 2022, 122, 1485-1542.
- [68] A. D. Kirk, Chem. Rev. 1999, 99, 1607–1640.
- G. Ferraudi, J. Granifo, J. Phys. Chem. 1985, 89, 1206-1210. [69]
- [70] S. B. Kumar, S. Bhattacharyya, S. K. Dutta, E. R. T. Tiekink, M. Chaudhury, J. Chem. Soc. Dalton Trans. 1995, 2619.
- [71] D. G. Lee, C. R. Moylan, T. Hayashi, J. I. Brauman, J. Am. Chem. Soc. 1987, 109, 3003-3010.
- [72] J. K. Kochi, J. Am. Chem. Soc. 1962, 84, 2121–2127.
- P. Lian, W. Long, J. Li, Y. Zheng, X. Wan, Angew. Chem. Int. Ed. 2020, [73] 59, 23603-23608.
- [74] Z. Tian, A. Fattahi, L. Lis, S. R. Kass, J. Am. Chem. Soc. 2006, 128, 17087-17092.
- [75] B. P. Roberts, Chem. Soc. Rev. 1999, 28, 25-35.
- [76] M. Bietti, Angew. Chem. Int. Ed. 2018, 57, 16618-16637.
- J. Y. Morimoto, B. A. DeGraff, J. Phys. Chem. 1972, 76, 1387–1388. [77]
- J. Y. Morimoto, B. A. DeGraff, J. Phys. Chem. 1975, 79, 326-331. [78]
- [79] P. Natarajan, G. Ferraudi, *Inorg. Chem.* **1981**, *20*, 3708–3712.

- [80] G Ferraudi S Muralidharan Coord Chem Rev 1981 36 45-88
- [81] R. Matsushima, Y. Ichikawa, K. Kuwabara, Bull. Chem. Soc. Jpn. 1980, 53. 1902-1907.
- [82] Z. Li, X. Wang, S. Xia, J. Jin, Org. Lett. 2019, 21, 4259-4265.
- V. R. Yatham, P. Bellotti, B. König, Chem. Commun. 2019, 55, 3489-[83] 3492.
- [84] A. Casitas, M. Canta, M. Solà, M. Costas, X. Ribas, J. Am. Chem. Soc. 2011. 133. 19386-19392.
- [85] P. S. Fier, J. F. Hartwig, J. Am. Chem. Soc. 2012, 134, 10795–10798.
- [86] Y.-M. Tian, X.-N. Guo, H. Braunschweig, U. Radius, T. B. Marder, Chem. Rev. 2021, 121, 3561-3597.
- [87] Q. Y. Li, S. N. Gockel, G. A. Lutovsky, K. S. DeGlopper, N. J. Baldwin, M. W. Bundesmann, J. W. Tucker, S. W. Bagley, T. P. Yoon, Nat. Chem. 2022, 14, 94-99.
- N. L. Reed, T. P. Yoon, Chem. Soc. Rev. 2021, 50, 2954-2967. [88]
- [89] N. L. Reed, M. I. Herman, V. P. Miltchev, T. P. Yoon, Org. Lett. 2018, 20, 7345-7350.
- B. J. Lee, K. S. DeGlopper, T. P. Yoon, Angew. Chem. Int. Ed. 2020, 59, [90] 197-202.
- A. Tsybizova, B. L. Ryland, N. Tsierkezos, S. S. Stahl, J. Roithová, D. [91] Schröder, Eur. J. Inorg. Chem. 2014, 2014, 1407-1412.
- A. Reichle, H. Sterzel, P. Kreitmeier, R. Fayad, F. N. Castellano, J. [92] Rehbein, O. Reiser, Chem. Commun. 2022, 58, 4456-4459.
- A. Hossain, A. Vidyasagar, C. Eichinger, C. Lankes, J. Phan, J. Rehbein, [93] O. Reiser, Angew. Chem. Int. Ed. 2018, 57, 8288-8292.
- [94] H. Inoue, K. Tamaki, N. Komakine, E. Imoto, Bull. Chem. Soc. Jpn. 1966, 39, 1577-1582.
- H. Inoue, K. Tamaki, N. Komakine, E. Imoto, Bull. Chem. Soc. Jpn. 1967, [95] 40.875-880.
- H. Inoue, N. Komakine, E. Imoto, Bull. Chem. Soc. Jpn. 1968, 41, 2726-[96] 2733.
- [97] H. Inoue, M. Izumi, E. Imoto, Chem. Lett. 1973, 2, 571-572.
- [98] G. B. Shulpin, M. M. Kats. React. Kinet. Catal. Lett. 1990, 41, 239–243.
- G. B. Shul'pin, G. V. Nizova, Y. N. Kozlov, New J. Chem. 1996, 20, 1243-[99] 1256
- [100] G. B. Shul'pin, M. M. Kats, Pet Chem 1991, 31, 647-656.
- [101] K. Takaki, J. Yamamoto, Y. Matsushita, H. Morii, T. Shishido, K. Takehira, Bull. Chem. Soc. Jpn. 2003, 76, 393-398.
- [102] K. Takaki, J. Yamamoto, K. Komeyama, T. Kawabata, K. Takehira, Bull. Chem. Soc. Jpn. 2004, 77, 2251-2255.
- [103] W. Wu, Z. Fu, X. Wen, Y. Wang, S. Zou, Y. Meng, Y. Liu, S. R. Kirk, D. Yin, Appl. Catal. Gen. 2014, 469, 483-489.
- [104] W. Wu, X. He, Z. Fu, Y. Liu, Y. Wang, X. Gong, X. Deng, H. Wu, Y. Zou, N. Yu, D. Yin, J. Catal. 2012, 286, 6-12.
- [105] E. Muravama, A. Kohda, T. Sato, Chem. Lett. 1978, 7, 161–164.
- [106] A. Kohda, K. Ueda, T. Sato, J. Org. Chem. 1981, 46, 509-515.
- [107] T. Sato, T. Oikawa, K. Kobayashi, J. Org. Chem. 1985, 50, 1646–1651.
- [108] M. Barbier, Helv. Chim. Acta 1984, 67, 866-869.
- [109] Y. C. Kang, S. M. Treacy, T. Rovis, Synlett 2021, 32, 1767–1771.
- [110] Q. Zhang, S. Liu, J. Lei, Y. Zhang, C. Meng, C. Duan, Y. Jin, Org. Lett. **2022**, 24, 1901–1906.
- [111] Y. C. Kang, S. M. Treacy, T. Rovis, ACS Catal. 2021, 11, 7442–7449.
- [112] Y. Jin, L. Wang, Q. Zhang, Y. Zhang, Q. Liao, C. Duan, Green Chem. 2021. 23. 9406-9411.
- [113] B. Niu, K. Sachidanandan, M. V. Cooke, T. E. Casey, S. Laulhé, Org. Lett. 2022. 24. 4524-4529.
- [114] Z.-Y. Dai, S.-Q. Zhang, X. Hong, P.-S. Wang, L.-Z. Gong, Chem Catal. 2022, 2, 1211-1222.
- [115] M. I. Gonzalez, D. Gygi, Y. Qin, Q. Zhu, E. J. Johnson, Y.-S. Chen, D. G. Nocera, J. Am. Chem. Soc. 2022, 144, 1464–1472.
- [116] S. J. Hwang, D. C. Powers, A. G. Maher, B. L. Anderson, R. G. Hadt, S.-L. Zheng, Y.-S. Chen, D. G. Nocera, J. Am. Chem. Soc. 2015, 137, 6472-6475.
- [117] S. J. Hwang, B. L. Anderson, D. C. Powers, A. G. Maher, R. G. Hadt, D. G. Nocera, Organometallics 2015, 34, 4766-4774.
- [118] D. Gygi, M. I. Gonzalez, S. J. Hwang, K. T. Xia, Y. Qin, E. J. Johnson, F. Gygi, Y.-S. Chen, D. G. Nocera, J. Am. Chem. Soc. 2021, 143, 6060-6064
- [119] G. Zhang, Z. Zhang, R. Zeng, Chin. J. Chem. 2021, 39, 3225–3230.

- [120] S. Oh, E. E. Stache, J. Am. Chem. Soc. 2022, 144, 5745–5749.
- [121] M. Wang, J. Wen, Y. Huang, P. Hu, ChemSusChem 2021, 14, 5049– 5056.
- [122] S.-M. Kim, A. Vogelpohl, Chem. Eng. Technol. 1998, 21, 187–191.
- [123] S. Malato, P. Fernández-Ibáñez, M. I. Maldonado, J. Blanco, W. Gernjak, Catal. Today 2009, 147, 1–59.
- [124] A. Sugimori, T. Yamada, Bull. Chem. Soc. Jpn. 1986, 59, 3911–3915.
- [125] R. S. J. Proctor, R. J. Phipps, Angew. Chem. Int. Ed. 2019, 58, 13666– 13699.
- [126] G. Feng, X. Wang, J. Jin, Eur. J. Org. Chem. 2019, 2019, 6728–6732.
- [127] S. Xia, K. Hu, C. Lei, J. Jin, Org. Lett. 2020, 22, 1385–1389.
- [128] D. W. Reichgott, N. J. Rose, J. Am. Chem. Soc. 1977, 99, 1813–1818.
- [129] T. Xue, Z. Zhang, R. Zeng, Org. Lett. 2022, 24, 977–982.
- [130] W. Liu, Q. Wu, M. Wang, Y. Huang, P. Hu, Org. Lett. 2021, 23, 8413– 8418.
- [131] N. Xiong, Y. Li, R. Zeng, Org. Lett. 2021, 23, 8968–8972.
- [132] J.-J. Guo, A. Hu, Y. Chen, J. Sun, H. Tang, Z. Zuo, Angew. Chem. Int. Ed. 2016, 55, 15319–15322.
- [133] A. Hu, J.-J. Guo, H. Pan, H. Tang, Z. Gao, Z. Zuo, J. Am. Chem. Soc. 2018, 140, 1612–1616.
- [134] K. Zhang, L. Chang, Q. An, X. Wang, Z. Zuo, J. Am. Chem. Soc. 2019, 141, 10556–10564.
- [135] H. Na, M. B. Watson, F. Tang, N. P. Rath, L. M. Mirica, *Chem. Commun.* 2021, 57, 7264–7267.
- [136] B. J. Shields, B. Kudisch, G. D. Scholes, A. G. Doyle, J. Am. Chem. Soc. 2018, 140, 3035–3039.
- [137] S. I. Ting, S. Garakyaraghi, C. M. Taliaferro, B. J. Shields, G. D. Scholes,
  F. N. Castellano, A. G. Doyle, *J. Am. Chem. Soc.* 2020, *142*, 5800–5810.
- [138] L. Tian, N. A. Till, B. Kudisch, D. W. C. MacMillan, G. D. Scholes, J. Am. Chem. Soc. 2020, 142, 4555–4559.
- [139] N. A. Till, L. Tian, Z. Dong, G. D. Scholes, D. W. C. MacMillan, J. Am. Chem. Soc. 2020, 142, 15830–15841.
- [140] B. J. Shields, A. G. Doyle, J. Am. Chem. Soc. 2016, 138, 12719–12722.
- [141] S. K. Kariofillis, A. G. Doyle, Acc. Chem. Res. 2021, 54, 988–1000.
- [142] D. R. Heitz, J. C. Tellis, G. A. Molander, J. Am. Chem. Soc. 2016, 138, 12715–12718.
- [143] M. K. Nielsen, B. J. Shields, J. Liu, M. J. Williams, M. J. Zacuto, A. G. Doyle, Angew. Chem. Int. Ed. 2017, 56, 7191–7194.
- [144] S. K. Kariofillis, B. J. Shields, M. A. Tekle-Smith, M. J. Zacuto, A. G. Doyle, J. Am. Chem. Soc. 2020, 142, 7683–7689.
- [145] X. Shu, D. Zhong, Y. Lin, X. Qin, H. Huo, J. Am. Chem. Soc. 2022, 144, 8797–8806.
- [146] L. K. G. Ackerman, J. I. Martinez Alvarado, A. G. Doyle, J. Am. Chem. Soc. 2018, 140, 14059–14063.
- [147] M. S. Santos, A. G. Corrêa, M. W. Paixão, B. König, Adv. Synth. Catal. 2020, 362, 2367–2372.
- [148] H.-P. Deng, X.-Z. Fan, Z.-H. Chen, Q.-H. Xu, J. Wu, J. Am. Chem. Soc. 2017, 139, 13579–13584.
- [149] S. Y. Go, G. S. Lee, S. H. Hong, Org. Lett. 2018, 20, 4691-4694.
- [150] T. S. Roche, J. F. Endicott, Inorg. Chem. 1974, 13, 1575–1580.
- [151] M. Z. Hoffman, E. R. Kantrowitz, J. F. Endicott, J. Phys. Chem. 1971, 75, 1914–1920.
- [152] G. N. Schrauzer, L.-P. Lee, J. W. Sibert, J. Am. Chem. Soc. 1970, 92, 2997–3005.
- [153] P. J. Toscano, L. G. Marzilli, in *Prog. Inorg. Chem.* (Ed.: S.J. Lippard), John Wiley & Sons, Inc., Hoboken, NJ, USA, **2007**, pp. 105–204.
- [154] A. R. Jones, Photochem. Photobiol. Sci. 2017, 16, 820–834.
- [155] M. Giedyk, K. Goliszewska, D. Gryko, Chem. Soc. Rev. 2015, 44, 3391– 3404.
- [156] T. Wdowik, D. Gryko, ACS Catal. 2022, 12, 6517–6531.
- [157] K. C. Cartwright, A. M. Davies, J. A. Tunge, Eur. J. Org. Chem. 2020, 2020, 1245–1258.
- [158] P. V. Kattamuri, J. G. West, Synlett 2021, 32, 1179–1186.
- [159] K. Ram Bajya, S. Selvakumar, Eur. J. Org. Chem. 2022, 2022, DOI 10.1002/ejoc.202200229.
- [160] B. Giese, J. Hartung, J. He, O. Hüter, A. Koch, Angew. Chem. Int. Ed. Engl. 1989, 28, 325–327.
- [161] A. Ghosez, T. Göbel, B. Giese, Chem. Ber. 1988, 121, 1807–1811.

- [162] L. M. Kreis, S. Krautwald, N. Pfeiffer, R. E. Martin, E. M. Carreira, Org. Lett. 2013, 15, 1634–1637.
- [163] G. Prina Cerai, B. Morandi, Chem. Commun. 2016, 52, 9769–9772.
- [164] M. Ociepa, O. Baka, J. Narodowiec, D. Gryko, Adv. Synth. Catal. 2017, 359, 3560–3565.
- [165] K. Komeyama, T. Michiyuki, Y. Teshima, I. Osaka, RSC Adv. 2021, 11, 3539–3546.
- [166] M. Ociepa, A. J. Wierzba, J. Turkowska, D. Gryko, J. Am. Chem. Soc. 2020, 142, 5355–5361.
- [167] A. Potrząsaj, M. Musiejuk, W. Chaładaj, M. Giedyk, D. Gryko, J. Am. Chem. Soc. 2021, 143, 9368–9376.
- [168] A. Potrząsaj, M. Ociepa, W. Chaładaj, D. Gryko, Org. Lett. 2022, 24, 2469–2473.
- [169] M. Kojima, S. Matsunaga, *Trends Chem.* **2020**, *2*, 410–426.
- [170] J. G. West, D. Huang, E. J. Sorensen, Nat. Commun. 2015, 6, 10093.
- [171] M.-J. Zhou, L. Zhang, G. Liu, C. Xu, Z. Huang, J. Am. Chem. Soc. 2021, 143, 16470–16485.
- [172] X. Sun, J. Chen, T. Ritter, Nat. Chem. 2018, 10, 1229–1233.
- [173] K. C. Cartwright, J. A. Tunge, ACS Catal. 2018, 8, 11801–11806.
- [174] V. T. Nguyen, V. D. Nguyen, G. C. Haug, H. T. Dang, S. Jin, Z. Li, C. Flores-Hansen, B. S. Benavides, H. D. Arman, O. V. Larionov, ACS Catal. 2019, 9, 9485–9498.
- [175] T. Constantin, M. Zanini, A. Regni, N. S. Sheikh, F. Juliá, D. Leonori, *Science* 2020, 367, 1021–1026.
- [176] Z.-T. Tsai, C. H. Brubaker, J. Organomet. Chem. 1979, 166, 199–210.
- [177] J. W. Kenney, D. R. Boone, D. R. Striplin, Y. H. Chen, K. B. Hamar, Organometallics 1993, 12, 3671–3676.
- [178] C. Godemann, D. Hollmann, M. Kessler, H. Jiao, A. Spannenberg, A. Brückner, T. Beweries, J. Am. Chem. Soc. 2015, 137, 16187–16195.
- [179] C. Godemann, L. Dura, D. Hollmann, K. Grabow, U. Bentrup, H. Jiao, A. Schulz, A. Brückner, T. Beweries, *Chem. Commun.* 2015, *51*, 3065–3068.
- [180] H. Kunkely, A. Vogler, Z. Für Naturforschung B 1998, 53, 224–226.
- [181] M.-A. Tehfe, J. Lalevée, F. Morlet-Savary, B. Graff, J.-P. Fouassier, Macromolecules 2012, 45, 356–361.
- [182] T. Sato, S. Yoshiie, T. Imamura, K. Hasegawa, M. Miyahara, S. Yamamura, O. Ito, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2714–2730.
- [183] T. Sato, S. Yamaguchi, H. Kaneko, *Tetrahedron Lett.* **1979**, 20, 1863– 1864.
- [184] T. Sato, H. Kaneko, T. Takahashi, *Chem. Lett.* **1981**, *10*, 1469–1472.
- [185] D. A. Wright, D. A. Williams, Acta Crystallogr. B 1968, 24, 1107–1114.
- [186] A. G. Griesbeck, S. Buhr, J. Lex, Tetrahedron Lett. 1998, 39, 2535–2536.
- [187] S. Ichikawa, K. Takahashi, M. Tanaka, T. Sato, Bull. Chem. Soc. Jpn. 1988, 61, 505–512.
- [188] A. G. Griesbeck, M. Reckenthäler, Beilstein J. Org. Chem. 2014, 10, 1143–1150.
- [189] M. Reckenthäler, J.-M. Neudörfl, E. Zorlu, A. G. Griesbeck, J. Org. Chem. 2016, 81, 7211–7216.
- [190] Z. Zhang, T. Hilche, D. Slak, N. R. Rietdijk, U. N. Oloyede, R. A. Flowers, A. Gansäuer, *Angew. Chem. Int. Ed.* **2020**, *59*, 9355–9359.
- [191] K. Sumiyama, N. Toriumi, N. Iwasawa, Eur. J. Org. Chem. 2021, 2021, 2474–2478.
- [192] A. Gansäuer, H. Bluhm, M. Pierobon, J. Am. Chem. Soc. 1998, 120, 12849–12859.
- [193] M. Manßen, L. L. Schafer, Chem. Soc. Rev. 2020, 49, 6947–6994.
- [194] M. Yamane, Y. Kanzaki, H. Mitsunuma, M. Kanai, Org. Lett. 2022, 24, 1486–1490.
- [195] G. B. Panetti, Q. Yang, M. R. Gau, P. J. Carroll, P. J. Walsh, E. J. Schelter, *Chem Catal.* **2022**, *2*, 853–866.
- [196] T. Hirao, Chem. Rev. 1997, 97, 2707–2724.
- [197] S. M. Aliwi, C. H. Bamford, J. Chem. Soc. Faraday Trans. 1 Phys. Chem. Condens. Phases 1975, 71, 1733.
- [198] S. M. Aliwi, C. H. Bamford, J. Chem. Soc. Faraday Trans. 1 Phys. Chem. Condens. Phases 1977, 73, 776.
- [199] S. M. Aliwi, J. Photochem. Photobiol. Chem. 1988, 44, 179-186.
- [200] S. M. Aliwi, A. W. Al-Shorachi, B. Y. Al-Banna, J. Photochem. Photobiol. Chem. 1994, 81, 31–36.
- [201] S. M. Aliwi, S. M. Abdullah, Polym. Int. 1994, 35, 309-314.

m. Chem. Soc. **2020**, 142, 7683–7689. Zhong, Y. Lin, X. Qin, H. Huo, *J. Am. Chem. Soc.* **2022**, 144,

- [202] S. M. Aliwi, A. W. Al-Shorachi, B. Y. Al-Banna, J. Photochem. Photobiol. Chem. 1994, 83, 171–175.
- [203] S. Gazi, W. K. Hung Ng, R. Ganguly, A. M. Putra Moeljadi, H. Hirao, H. S. Soo, *Chem. Sci.* **2015**, 6, 7130–7142.
- [204] S. Gazi, M. Đokić, A. M. P. Moeljadi, R. Ganguly, H. Hirao, H. S. Soo, ACS Catal. 2017, 7, 4682–4691.
- [205] S. Gazi, M. Đokić, K. F. Chin, P. R. Ng, H. S. Soo, Adv. Sci. 2019, 6, 1902020.
- [206] H. Liu, H. Li, N. Luo, F. Wang, ACS Catal. 2020, 10, 632–643.

## Entry for the Table of Contents

LMCT

radical generation via *ligand-to-metal charge-transfer* in 3d-metal complexes

The population of ligand-to-metal charge-transfer (LMCT) excited states upon light irradiation of abundant and inexpensive 3d-metal complexes represents an effective platform to access open-shell intermediates of high synthetic value. This review provides guidelines for the utilization of this inner-sphere reactivity, a comparison of its distinct profile in comparison with photoredox catalysis, and a collection of the most relevant achievements applied to organic synthesis.

Institute and/or researcher Twitter usernames: @FabioJulia7, @ICIQchem