ABSTRACT: Alkyl radicals are key intermediates in organic synthesis. Their classic generation from alkyl halides has a severe drawback due to the employment of toxic tin hydrides to the point that “flight from the tyranny of tin” in radical processes was considered for a long time an unavoidable issue. This review summarizes the main alternative approaches for the generation of unstabilized alkyl radicals, using photons as traceless promoters. The recent development in photochemical and photocatalyzed processes enabled the discovery of a plethora of new alkyl radical precursors, opening the world of radical chemistry to a broader community, thus allowing a new era of photon democracy.

1. INTRODUCTION

Among all the open-shell species, carbon-centered radicals are intriguing neutral intermediates that find extensive use in organic synthesis, despite the initial distrust about their possible application.1−5 In particular, the generation of unstabilized alkyl radicals under mild conditions granting the controlled and selective outcome of the ensuing reactions has been a challenge for many years. The first and more obvious way to form such species is the homolytic cleavage of a labile C−X bond; alkyl halides appeared as the ideal choice in this respect. The real breakthrough in radical chemistry was the discovery of Bu3SnH to promote radical chain reactions as reported about 60 years ago in the reduction of bromocyclohexane.6 Reduction of an organotin halide by lithium aluminum hydride formed the reactive tin hydride in solution. In subsequent modifications of the protocol, both sodium borohydride7 and sodium cyanoborohydride8 acted as effective reducing agents. Alkyl radicals generated via tin chemistry were then used for C−C bond formation mainly via the addition to (electron-poor) olefins, the well-known Giese reaction,9−12 an

Notes
Biographies
Acknowledgments
Abbreviations
References

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As illustrated in Figure 1a, tributyltin hydride has the double role of allowing the formation of Bu₃Sn⁺ as the radical chain carrier and as a hydrogen donor to close the catalytic cycle. The unique features of this catalytic cycle are attributed to the forging of stronger Sn–X and C–H bonds at the expense of the cleavage of the more labile Sn–H and C–X ones. A more quantitative aspect of this reaction can be appreciated comparing the different bond dissociation energies (BDE) associated with the steps mentioned above (see Figure 1a). More recent applications showcase the crucial role of tin intermediates in controlling the outcome of different reactions. Sn–O interactions direct the regioselective addition of the radical in the radical stannylation of the triple bond in propargyloxy derivatives, whereas tin radicals induced the synthesis of stannylated polyarenes via double radical perinnulations, increasing the solubility of the products.

The performance of Bu₃SnH was so competitive that more than 20 years ago it was claimed that it was improbable to have “flight from the tyranny of tin” in radical processes. A hard statement that subtly introduces the problem of the substantial toxicity and high biological activity of triorganotin compounds. The LD₅₀ of 0.7 mmol/kg in murine species combined with the long half-lives in aquatic environment represent the biggest concerns for the application of these otherwise extremely versatile species, especially in the absence of viable alternatives. Indeed, O-thiocarbonyl derivatives like xanthates (I, obtained from alcohols) were considered an alternative to the alkyl halides, albeit the radical generation required in most cases the use of tin hydrides (Figure 1c). Efforts in substituting toxic tin derivatives with other hydrides such as (TMS)_3SiH or lauroyl peroxides and xanthates met some success, however, only in limited cases. Other initiators to promote tin-free radical chain reactions were organoboranes, thiols, P–H-based reagents, and 1-functionalized cyclohexa-2,5-dienes but nowadays they are not commonly used in synthetic planning.

Figure 1. (A) Thermal generation of radicals from alkyl halides in the Giese reaction. (B) LD₅₀ values for selected organotin compounds. (C) Thermal generation of radicals from alcohols via xanthates (I). (D) Thermal and photochemical generation of radicals from carboxylic acids via Barton esters (II).
the development of suitable alkyl substituents able to facilitate redox reactions making the derivatives more oxidizable or reducible. The strategy that is followed in Figure 2B consists in the conversion of a common functional group (e.g., OH or COOH), which in most cases is tethered to the alkyl group, into a different electroauxiliary group88 (Figure 2B). As a result, the interaction of the activated species with an excited photoredox catalyst (PCSET) able to induce a single electron transfer (SET) process generates the corresponding radical ions, either by an oxidative pathway or a reductive pathway. The desired alkyl radical is then formed by fragmentation of these radical ion intermediates. The oxidative pathway is efficient when the radical precursor is negatively charged (see further Figure 3) as in the case of alkyl carboxylates and alkyl sulfonates causing the CO2 or SO2 loss, respectively, despite the fact that the exothermicity of the process is verified only in the C–C cleavage rather than the C–S cleavage.69 On the contrary, positively charged Katritzky salts were ideal candidates for the releasing of radicals via the reductive pathway (Figure 3).70

A viable alternative is the photogeneration (often from a photoredox process) of a reactive radical on a heteroatom like a silyl radical, which can exploit a halogen atom transfer reaction to afford an alkyl radical through the smooth Si–X bond formation (XAT, Figure 2C).71,72 This strategy provides an elegant way to overcome the Giese conditions in the tin mediated activation of alkyl halides. Recently, an α-amino radical was used in the same strategy, promoting the formation of alkyl radicals via C–X bond cleavage.73

A more challenging approach requires the photocatalyzed selective cleavage of a strong alkyl–H bond, via a direct hydrogen atom transfer reaction (d-HAT, Figure 2D) operated by an excited photocatalyst (PCHAT).72,74–76 The indirect version of the latter path exploits the photogeneration of a stable heteroatom based radical (i-HAT, Figure 2D) that will become the competent intermediate in the abstraction of the H atom from the alkyl moiety.76 An indirect HAT (i-HAT) may also take place by intramolecular hydrogen transfer thus releasing an alkyl radical (Figure 2E).76–81 As an alternative, the photochemical radical generation may induce a ring-opening in strained structures like cyclobutanes, to form a substituted alkyl radical (Figure 2F).82

Figure 3 showcases a collection of the main alkyl radical precursors devised for the generation under photochemical conditions of unstabilized alkyl radicals. In this figure, the radical precursors were collected depending on the C(sp3)–Y bond cleaved during the radical release. As apparent, the photochemically triggered cleavage of several C-heteroatom bonds like C–X,71,83–88 C–O,89–98 C–B,99–102 C–S,103–106 or C–N70 (Figure 3) affords carbon-centered radicals. The alkyl radical generation is granted by the very versatile photochemical tool. This feature includes particular cases such as C–Se (in alkyl selenides),107,108 C–Te (in (aryltelluro)formates,109,110 for a previous thermal generation of alkyl radicals from diorganyl tellurides, see ref 111), and C–Si (in tetra alkyl silanes and bis-chatecolates)112–114 to be added to C–Sn (in alkyl stannanes).112,113 Interestingly, even the more resilient C–H5,76 or C–C15,85,86,94,116–130 bonds may be cleaved for alkyl radical generation, opening up new exciting possibilities for the synthetic (photo)chemist (Figure 3). For the clarity of the reader, each radical precursor is accompanied by its oxidation potential (Eox, in orange) or its reduction potential (Ered, in green) to guide the feasibility on

Figure 2 collects the main paradigmatic approaches to the photogeneration of alkyl radicals (either photochemically or photocatalyzed). The more classical, although the less employed, path to generate alkyl radicals consists of the introduction of a photoauxiliary group which renders a bond labile to a direct photochemical cleavage (Figure 2A).67 The Barton esters are the archetypal moiety belonging to this class.59 A conspicuous body of literature have been focusing on

the generation of the radical via the oxidative or reductive pathway (type B, Figure 2B), respectively. Since the redox potentials may vary with the nature of the alkyl group, the values reported are referred to known structures. In alternative, the BDE values of the bond that is broken by direct photocleavage (type A, Figure 2A) or by photocatalyzed hydrogen abstraction (type D, Figure 2D) are reported. Figure 3 (right part) likewise collects the redox properties of commonly used photoredox catalysts including metal-free photoorganocatalysts (POC) to be used in the oxidative/reductive pathways.

The reactions collected and commented on in this review are primarily divided according to the type of the bond formed, namely the forging of C−C or C−heteroatom bonds, along with the construction of rings of different sizes. When possible, in each section, we will further categorize the reactions depending on the mechanism of the radical generation, ascribing them to the six types (A−F) described in Figure 2.

2. FORMATION OF A C(SP³)-C BOND

Photochemically generated alkyl radicals have been employed to forge C(sp³)-C(sp³) bonds (n = 1−3) in an intermolecular fashion following different strategies. In most cases, a conjugate addition onto a Michael acceptor or a Minisci-like reaction occurred, albeit alkenylations, acylations, or oxaalkylations are likewise used.

2.1. Formation of a C(sp³)-C(sp³) Bond

2.1.1. Addition to C−C Double Bonds: Hydroalkylations. Many reactions belonging to this class involve the nucleophile alkyl radical addition onto an electrophilic Michael acceptor, resulting in a formal hydroalkylation of the double bond viz. the incorporation of an alkyl group (in position β with respect to the EWG group in the starting unsaturated compound) and a hydrogen atom (in position α). This reaction is usually one of the first that many authors would test during the discovery process of a new radical precursor, as testified by the plethora of reagents that are used in this transformation. Photoredox catalysis is by far the preferred approach here, especially by using the oxidation of a negatively charged precursor (oxidative pathway in Figure 2B).

A typical example is the oxidation of carboxylates [138,139] that releases an alkyl radical via CO₂ loss from the carboxyl radical intermediate (Scheme 1). Adamantylation of both acrylonitrile (Scheme 1a) [140] and dimethyl 2-ethylidene malonate starting from adamantane carboxylic acid 1-1 (Scheme 1b) [141] were carried out following this strategy. In the former case, the...
authors employed 1,4-dicyanonaphthalene (DCN) as the POC under UV light irradiation, while visible light and an Ir<sup>III</sup> complex in the latter case. The approach used in Scheme 1b was also useful for the three steps preparation of the medicinal agent (±)-pregabalin. Also, the Fukuzumi catalyst (9-mesitylene-10-methylacridinium perchlorate, [Ac<sup>−</sup>Mes]<sup>+</sup>ClO<sub>4</sub>¯) can promote this Giese-type reaction, allowing the alkylation of α-aryl ethenylphosphonates for the synthesis of fosmidomycin analogues.

A variation of this procedure is the decarboxylative-decarbonylation process occurring on an α-keto acid 2-1 under sunlight-driven photoredox catalyzed reaction conditions (Scheme 2).

**Scheme 2. Decarboxylative-Decarbonylation of an α-Keto Acid**

Oxalates are another class of electron-donors having two carboxylic moieties that can be lost upon photocatalyzed oxidation. These species may be introduced in situ by reaction of the alcohol with oxalyl chloride. The process induced the cleavage of a C–O bond, and the resulting radical could be trapped by butenolide 3–1 to form the menthyl derivative 3–2 used for the enantioselective preparation of cheloviolene A (3–3, Scheme 3). An Ir<sup>III</sup>-based photocatalyst efficiently promoted the reaction also in this case, allowing the synthesis of quaternary centers and the total synthesis of trans-clerodane diterpenoids.

Alkyl trifluoroborates stand out as another important class of easily oxidizable moieties. The photocatalyzed oxidation of these salts (e.g., 4–1) causes the smooth release of BF₃ and the formation of the reactive alkyl radical. Such a reaction was employed to functionalize Michael acceptors under sunlight irradiation (Scheme 4a) exploiting Ac⁺Mes as the POC. Complexation of 4–4 by a chiral rhodium complex (Λ-RhS, Scheme 4b) delivered 4–5 in good yields with 97% ee.

This synthetic strategy can be extended to neutral boronic acids or esters, upon in situ activation by a Lewis base (LB). The so formed negatively charged species is consequently more prone to oxidation, which eventually will provide the formation of the alkyl radicals. A typical example is illustrated in Scheme 5 where the boronic acid 5–1 was activated by 4-dimethylaminopyridine (DMAP) and then oxidized by an Ir<sup>III</sup> complex. The resulting cyclobutyl radical was trapped by methyl vinyl ketone to access the substituted ketone 5–2 in a good yield.

Interesting results were also obtained using the Photosyn reactor. In such a way, the authors could synthesize gram amounts per hour of the analogues of some drugs belonging to the GABA family.

Following the examples of the carboxylate derivatives, the electron-donating species may be generated in situ by deprotonation, as in the case of sulfonamides, employed in the desulfitative conjugate addition of alkyl radicals onto Michael acceptors (Scheme 6). Again, the process is based on a photocatalyzed oxidation pathway. The starting sulfonamide 6–1 was first deprotonated by a mild base (K₂HPO₄), and the resulting anion was easily oxidized to a N-centered radical. Loss of N-sulfinylbenzamide generates the desired radical that gave the adduct 6–3 upon reaction with 6–2 in 75% yield.

In some instances, the radical precursor is a neutral compound. This situation is possible only when the derivative contains a highly oxidizable or reducible moiety. 4-Alkyl-1,4-dihydropyrimidines (alkyl-DHPs) under PC-free conditions act as radical precursors when combined with photoexcited iminium ion catalysis (Scheme 7). Here, enal 7–1 formed a chiral iminium ion 7–4⁺ by reaction with amine 7–3. Cation 7–4⁺ upon visible light excitation oxidized the alkyl-DHP 7–2 that in turn released the radical 7–5⁺ upon fragmentation, along with radical 7–4⁺. Radical recombination followed by hydrolysis gave the desired alkylated dihydrocinnamaldehyde 7–6 in a satisfactory yield with a good enantioselective excess (Scheme 7). A similar Giese reaction was later proposed, where the alkyl-DHP was excited and a SET reaction with Ni(bpy)₄<sup>2⁺</sup> as an electron mediator, took place. The alkyl radical derived from the radical cation of alkyl-DHP readily attacked a series of Michael acceptors.

Looking at the other edge of the redox spectrum, easily reducible compounds were devised as radical precursors via a photocatalyzed process. As an example, the incorporation of a N-phthalimidoyl moiety in an organic compound helps its photocatalyzed reduction, ultimately leading to the release of the alkyl radical. A typical case is represented by N-(acyloxy)phthalimides. A stereoselective variant of this reaction was applied to the synthesis of (−)-solidagolactone (8–4, Scheme 8). Thus, the photocatalyzed reduction of phthalimide 8–1 by a Ru<sup>0</sup> complex released a tertiary carbon radical. Attack to the terminal carbon of the unsaturated core present in β-vinylbutenolide 8–2 yields 8–3 with a very high diastereomeric excess. Further elaboration of compound 8–3 gave 8–4 in a single step. This reaction emerges as a very interesting tool to construct quaternary carbons and to synthesize biologically active derivatives, e.g., (−)-aplyviolene.

Interesting results were also obtained using N-phthalimidoyl oxalates such as 9–1 in place of the N-(acyloxy)phthalimides.
for the generation of alkyl radicals starting from tertiary alcohols (Scheme 9). The similarity of this reaction to the one presented in Scheme 8 is striking, despite a less atom economical radical generation.

Reduction of an organic compound may be carried out even on organic iodides by using cyanoborohydride anion as the reducing agent. The reaction is chemoselective, since no alkyl bromides or chlorides could be activated following this way. Giese adducts were formed by irradiation with a Xe lamp of the reaction mixture in good yields as illustrated by the formation of 10−2 from 10−1 in Scheme 10. This is another interesting example to circumvent the use of tin hydrides in the activation of alkyl halides.

Alkyl chlorides can be activated using Ir(dtbby)(ppy)2PF6 in the presence of micelles. The micellar environment stabilizes the photogenerated [Ir(dtbby)2]−(ppy)2 species (−1.51 V vs SCE), unable to directly reduce the alkyl chlorides (ca. −2.8 V vs SCE). A second excitation of this long-lived intermediate allows the electron transfer to the halide, which could react with different electron-poor olefins, forging a novel C−C bond.

The micellar system allowed intramolecular cyclizations to form five-membered cycles. Reduction of the alkyl halide 11−1 could be avoided applying a halogen transfer reaction. In fact, due to the strong BDE of the Si-halogen bond, an alkyl radical is formed thanks to the action of a purposely generated silyl radical (from (Me3Si)3SiH, TTMSS) by a photoredox catalytic step. Radical addition onto an unsaturated amide (11−2) gave the 1,8-difunctionalized derivative 11−3, a key compound in the preparation of Vorinostat 11−4, a histone deacetylase (HDAC) inhibitor active against HIV and cancer (Scheme 11). This is the typical case where the radical is formed by...
the cleavage of an Alk-Br bond without the assistance of tin derivatives. It is interesting that the reaction requires a substoichiometric amount of silane to proceed. Indeed, with higher loadings the product yield decreases, possibly due to the presence of competing nonproductive pathways. A chain reaction mechanism could be envisaged; however, the quantum yield for this reaction ($\Phi = 0.45$) does not fully clarify the mechanistic details of the transformation.

In many instances the formation of the alkyl radical arose from a direct or indirect photocatalyzed C−H homolytic cleavage. The excited state of the decatungstate anion in its tetrabutylammonium salt form (TBADT) promoted in several cases the direct chemoselective cleavage of a C−H bond. Scheme 12 depicts two examples involving the hydroalkylation of acrylonitrile. Unsubstituted cycloalkanes were suitable hydrogen donors under flow conditions (yielding 12−1 Scheme 12a). Moreover, the chemoselective cleavage of the methine hydrogen in isovaleronitrile allowed the preparation of dinitrile 12−2 in 73% yield (Scheme 12b). Similarly, the presence of a tertiary hydrogen was the driving force of the chemoselective TBADT-photocatalyzed C−H cleavage in several derivatives, as depicted in Scheme 13. As an example, alkylpyridine 13−1 was selectively functionalized and gave derivative 13−2 as the exclusive product in the reaction with a vinyl sulfone (Scheme 13a). Interestingly, the labile benzylic hydrogens present in 13−1 remained untouched under these reaction conditions. Noteworthy, steric and polar effects cooperatively operated in the derivatization of lactone 13−3. As a result only the methine hydrogen of the isopropyl group was selectively abstracted and afforded 13−4 in very high yields by reaction with fumaronitrile (Scheme 13b), albeit the seven different types of hydrogens present in 13−3. The C−H cleavage may also take place in branched alkanes as witnessed by the derivatization of 13−5 to form the succinate derivative 13−6 (Scheme 13c).
In rare instances, the hydroalkylation reaction may be applied to olefins different to the usual Michael acceptors. Thus, substituted vinylpyridines were functionalized by TBADT-photocatalyzed addition of cycloalkanes. Scheme 14

Scheme 14. Functionalization of a Vinylpyridine with a Cycloalkane

showed the smooth synthesis of 14−2 starting from 14−1 simply by irradiation of the reaction mixture containing a slight excess of cyclohexane in the presence of a catalytic amount of the decatungstate salt.164

Recently, alternative PCs have been developed for the direct photocatalyzed activation of C−H bonds in cycloalkanes, namely uranyl cation163 and Eosin Y,165 both having the advantage of absorbing in the visible light region. The alkyl radical formation may be induced by a photogenerated stable radical which acts as a radical mediator. An IrIII based photoredox catalyst oxidized the chloride anion (being the radical which acts as a radical mediator). An IrIII based radical formation may be induced by a photogenerated stable radical which acts as a radical mediator. An IrIII based radical formation may be induced by a photogenerated stable radical which acts as a radical mediator.

Scheme 15. Indirect HAT Mediated by a Cl Atom

When the reaction was applied to compound 16−1, an oxidative PCET generated a neutral amide radical that promotes the 1,5-hydrogen atom abstraction forming a tertiary radical which is able to functionalize olefin 16−2 in a complete regioselective fashion affording 16−3 (Scheme 16a).171 The reaction was also applied to medicinally relevant molecules such as the steroid-derived trifluoroacetamide 16−4 (Scheme 16b). Despite the fact that this compound has several labile C−H bonds including tertiary C−H bonds and C−H bonds adjacent to heteroatoms, the intramolecular hydrogen abstraction followed by conjugate addition onto 16−5 gave 16−6 as the sole product.172

The remote activation of the C−H bond in the δ-position following this approach is a general reaction as demonstrated in related systems applied to amides protected with a carbamate group173 or in simple benzamide derivatives.174 In the latter case, the reaction was carried out in the presence of a chiral Rh-based Lewis acid catalyst that allowed the asymmetric alkylation of α,β-unaturated 2-acyl imidazoles.174

The abstracting species could be likewise a photogenerated iminyl radical as illustrated in Scheme 17. Here a carboxyl radical is converted in an oxime derivative (e.g., 17−1) by reaction with an α-amino acid. Photocatalyzed oxidation followed by fragmentation of the resulting carboxyloxy radical gave an iminyl radical prone to a 1,5-HAT to a tertiary radical that upon addition to acrylate 17−2 gave compound 17−3 in 77% yield.175

2.1.2. Heteroalkylation of C−C Double Bonds. An interesting variation of the functionalization of a double bond is the formation of a C−C bond (upon an alkylation step) followed by the formation of another C−Y bond (Y ≠ H) on the adjacent carbon. As an example, alkyl diacyl peroxides were reduced photocatalytically and the fragmentation released an alkyl radical and a carboxylate anion both incorporated in the structure of the product. Thus, 2-vinylnaphthalene 18−2 was converted into compound 18−4 in a very good yield upon reaction with lauroyl peroxide 18−1 upon an oxidative quenching process by consecutive C−C and C−O formation (Scheme 18).176 The reaction was made possible by the oxidation of the resulting radical adduct 18−3′ (by RuIII, the oxidized form of the PC) that generated the cation 18−3′ that was easily trapped by the carboxylate anion previously released.

N-(acyloxy)phthalimide 19−1 as radical precursor found use in a similar multicomponent oxyalkylation of styrenes. The addition of the alkyl radical onto the vinylarene followed by the incorporation of water present in the reaction mixture afforded derivative 19−2 in 72% yield (Scheme 19).177 Noteworthy, the labile C−Br bond in 19−1 remained untouched in the process.

The use of water as the oxygen source was likewise used in the disfunctionalization of aryl akenes where the carbon-centered radical was formed by an intramolecular 1,5-HAT of a photogenerated iminyl radical.178

Performing the reaction in DMSO allows for the use of the solvent as an oxygen donor adopting the Kornblum oxidation. The intermediate benzyl radical formed after the alkylation step reacts with the solvent and eventually forming a carbonyl group in place of a simple C−O bond. An elegant example is shown in (Scheme 20) for the synthesis of ketonitrile 20−4.179 A cycloketone oxime ester (20−1) was photocatalytically reduced, inducing a ring opening on the resulting iminyl...
radical. The resulting cyano-substituted alkyl radical reacted with styrene $20^-2$, and the addition with DMSO formed the intermediate $20^-3$, that, upon Me$_2$S loss, afforded the product. A related oxyalkylation of styrenes made again the use of the Kornblum oxidation as the last step in the synthesis of substituted acetophenones. Indeed, N-hydroxyphthalimides (e.g., $21^-1$) were employed as the radical source, and an Ir$^{	ext{III}}$ complex was used as the PC, obtaining good yields even

Scheme 16. Intramolecular 1,5-HAT Forming Tertiary Alkyl Radicals

Scheme 17. 1,5-HAT Promoted by an Iminyl Radical

Scheme 18. Oxyalkylation via Alkyl Diacyl Peroxides

Scheme 19. Multicomponent Oxyalkylation of Styrenes

Scheme 20. Photocatalyzed Oxyalkylation of Styrenes Based on the Kornblum Oxidation
Scheme 21. Oxyalkylation by Using N-(Acloyx)phthalimide Derivatives as Radicals Source

ketone 21–5 in 61% yield (Scheme 21b). In this case, however, the decarboxylative alkylation was applied to silyl enol ethers having the carbonyl oxygen already incorporated in the initial structure such as 21–4. The same process described in Scheme 21b can be carried out under uncatalyzed conditions under blue LED irradiation in the presence of an excess of NaI (150 mol %) and PPh₃ (20 mol %). The reaction was based on the photoactivation of a complex formed by N-(acloyx)phthalimide with NaI and PPh₃ through Coulombic and cation-π interactions. In this case, the excitation caused the reduction of the phthalimide by a SET reaction within the complex.

Alkylated ketones 22–3a–d were likewise obtained by the IrIII photocatalyzed reaction between a 2-mercaptopthiazolium salt (22–1, as alkyl radical precursor) and silyl enol ethers 22–2a–d (Scheme 22).

Lauryl peroxide (LPO, see Scheme 18) was adopted for the Ru-catalyzed three-component carbofluorination of styrenes as illustrated in Scheme 23a. The vinylic double bond of compound 23–1 derived from estrene was functionalized twice by using triethylamine trihydrofluoride Et₃N·HF as the fluoride anion source to deliver the desired alkyl-fluorinated olefin 23–2 in 61% yield. The reduction of LPO is mediated by the presence of a copper salt in the role of a cocatalyst in a dual catalytic process. The carbofluorination was later applied to dehydroalanine derivative 23–4 by using alkyltrifluoroborates and an excess of Selectfluor as an electrophilic fluorine source (Scheme 23b).

Scheme 22. Synthesis of Alkylated Ketones from Mercaptothiazolinium Salts

Alkylated ketones 22–3–5 were obtained from mercaptothiazolinium salts 22–1 by using triethylamine trihydrofluoride Et₃N·HF as the fluoride source. The reaction can be carried out under uncatalyzed conditions under blue LED irradiation in the presence of an excess of NaI (150 mol %) and PPh₃ (20 mol %). The reaction was based on the photoactivation of a complex formed by N-(acyloxy)phthalimide with NaI and PPh₃ through Coulombic and cation-π interactions. In this case, the excitation caused the reduction of the phthalimide by a SET reaction within the complex. Alkylated ketones 22–3–5 were obtained from mercaptothiazolinium salts 22–1 by using triethylamine trihydrofluoride Et₃N·HF as the fluoride source. The reaction can be carried out under uncatalyzed conditions under blue LED irradiation in the presence of an excess of NaI (150 mol %) and PPh₃ (20 mol %). The reaction was based on the photoactivation of a complex formed by N-(acyloxy)phthalimide with NaI and PPh₃ through Coulombic and cation-π interactions. In this case, the excitation caused the reduction of the phthalimide by a SET reaction within the complex.

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with 26−2, to obtain product 26−3 in 60% yield (Scheme 26).127

Photocatalyzed reduction of Katritzky salts 27−1a−c obtained from the corresponding amines (Scheme 27) gave access to the allylated compounds 27−3a−c. Thus, the mono-electronic reduction of pyridinium salts 27−1a−c caused the release of the corresponding pyridines along with the substituted cyclohexyl radicals than upon trapping by 27−2 efficiently afforded acrylates 27−3a−c.190

A remote allylation under visible light irradiation was devised starting from amide 28−1 making use of eosin Y (EY) as the PC (Scheme 28). The excited EY is able to reduce 28−1 thanks to the electron-withdrawing capability of the substituted phenoxy group on the nitrogen of the amide. The amidal radical formed upon fragmentation of 28−2•\textsuperscript{−} efficiently afforded acrylates 27−3a−c.191

A different approach involved the use of trifluoromethyl-substituted alkenes (e.g., 29−1) that upon addition of the alkyl radical gave access to valuable gem-difluoroalkenes such as 29−2a−b (Scheme 29). The oxidation of alkyltrifluoroborates was here assured by the organic photocatalyst 4CzIPN, leading to nonstabilized primary, secondary, and tertiary radicals. The defluorinative alkylation resulted from the reduction of the radical adduct, followed by an E1cB-like fluoride elimination.192

A dual catalytic approach was designed for valuable allylation using vinyl epoxides as allylation agents (Scheme 30). The mechanism was investigated by quantum mechanical calculations [by DFT and DLPNO−CCSD(T)] and supported an initial complexation of Ni0 to 30−2 that quickly underwent a SN2-like ring opening, followed by the incorporation of the alkyl radical formed by DHP-derived compounds 30−1a,b into the metal complex. Allyl alcohols 30−3a,b were then formed by inner sphere C(sp\textsuperscript{2})-C(sp\textsuperscript{3}) bond formation from the resulting Ni\textsuperscript{III} complex.193

2.1.4. sp\textsuperscript{3}−sp\textsuperscript{3} Cross-coupling. Another intriguing possibility offered by the photochemical approach to alkyl radicals is the formation of a C−C bond by a sp\textsuperscript{3}−sp\textsuperscript{3} cross-coupling reaction. The transformation could lead to novel pathways to interesting targets, as represented by the synthesis of the drug tirofiban in only four steps, starting from easily available compounds. The protocol made use of two consecutive photocatalyzed reactions applying a metallaphotoredox strategy (Scheme 31). The key step is the coupling between carboxylic acid 31−1 and alkyl halide 31−2. The halide is first complexed by a Ni\textsuperscript{0} catalyst and the resulting Ni\textsuperscript{I} complex trapped the alkyl radical (obtained by photocatalyzed decarboxylation) to yield a Ni\textsuperscript{III} complex that in turn released the sp\textsuperscript{3}−sp\textsuperscript{3} coupled product 31−3 after desilylation with TBAF. The desired tirofiban was then obtained by elaboration of 31−3 in two subsequent steps.194

Another example of a C(sp\textsuperscript{3})−C(sp\textsuperscript{3}) cross-coupling process is the reaction between alkylsilicates and alkyl halides. As in the previous case, a dual catalytic Ir/Ni system was required.195
The alkyl radical may be likewise generated from an alkyl halide by a halogen atom transfer with a photogenerated silyl radical (from a silanol). The radical that is hence formed could be coupled with another alkyl bromide, e.g., methyl bromide, using a Ni₀ catalyst to perform valuable methylation reactions. Aliphatic carboxylic acids were used to form alkyl-CF₃ bonds via a photocatalyzed reaction making use of Togni’s reagent as the trifluoromethylating agent. The reaction was promoted under visible light irradiation employing an Ir³⁺ photocatalyst coupled with a CuI salt. This process tolerates various functionalities including olefins, alcohols, heterocycles, and even strained ring systems.

The alkylation of a benzylic position in N-aryl tetrahydroisoquinolines 32−1 was reported following two different approaches (Scheme 32). The first allowed the reaction of an unactivated alkyl bromide (32−2) by the excitation of a Pd⁰ catalyst. The second involved the use of a Metallaphotoredox strategy.
complex. Compound 32−1 was oxidized in the catalytic cycle, and the resulting α-amino radical coupled with the isopropyl radical to form 32−4 in 81% yield (Scheme 32a). An alternative heavy-metal-free route catalyzed by a dye-sensitized semiconductor is depicted in Scheme 32b. Excitation of an inexpensive dye (erythrosine B) caused the reduction of titanium dioxide that in turn was able to reduce phthalimide in 84% yield (Scheme 34b).

### 2.1.5. Other Reactions

In particular cases, a C=−N bond can be made sufficiently electrophilic to undergo alkyl radical addition as in the case of N-sulfinimines, exploited for the preparation of protected amines. A high degree of diasteroselectivity can be obtained when starting from chiral precursors under metal-free conditions adopting 4CzIPN as a high potential in the excited state considerably lower for the reaction to occur (ca. −1.63 V vs SCE). This can be explained by the formation of an inner sphere exciplex between the excited dimeric catalyst and 34−1 that promotes the otherwise thermodynamically unfavorable redox process, generating an Au−Au dimer and 34−4. The combination of the latter species formed an AuIII complex that induces a semipinacol rearrangement coupled with C(sp3)−C(sp3) reductive elimination, which furnished 34−3 in 84% yield (Scheme 34b).

A similar reaction was later developed starting from cycloalkanol-substituted styrenes and N-acyclophthalimides under IrIII photocatalysis.

### 2.2. Formation of a C(sp3)−C(sp3) Bond

#### 2.2.1. Alkenylation

The reaction between an alkyl radical with a cinnamic acid followed by loss of the COOH group is one of the more common approaches to promote an alkenylation reaction. Thus, the radical formed from salt 35−3 attacked the benziodoxole adduct 35−2, synthesized from acrylic acid 35−1. The reaction yielded 83% of the diphenylethylene derivative 35−4 upon a deboronization/decarbonylation sequence (Scheme 35). The benziodoxole moiety gave efficient results in promoting the radical elimination step, while other noncyclic III reagents were ineffective.

#### Scheme 35. Alkenylations Mediated by Benziodoxole

![Scheme 35. Alkenylations Mediated by Benziodoxole](image)

The alkenylation of related imines can be carried out by using ammonium alkyl bis(catecholato)silicates as the radical precursors under metal-free conditions adopting 4CzIPN as the POC or by using potassium alkyltrifluoroborates in the alkenylation of N-phenylimines.

Another particular case is the alkylative semipinacol rearrangement devised for the synthesis of 2-alkyl-substituted cycloalkanones. The reaction involved the photocatalytic reaction between TMS protected α-styrenyl substituted cyclic alcohol 34−2 and the unactivated bromoalkane 34−1 (Scheme 34a). The reaction was promoted by the dimeric gold complex [Au2(dpmm)2]Cl2. This complex is able to reduce 34−1 (ca. −2.5 V vs SCE) despite having an oxidation potential in the excited state considerably lower for the reaction to occur (ca. −1.63 V vs SCE). This can be explained by the formation of an inner sphere exciplex between the excited dimeric catalyst and 34−1 that promotes the otherwise thermodynamically unfavorable redox process, generating an Au−Au dimer and 34−4. The combination of the latter species formed an AuIII complex that induces a semipinacol rearrangement coupled with C(sp3)−C(sp3) reductive elimination, which furnished 34−3 in 84% yield (Scheme 34b).

A similar reaction was later developed starting from cycloalkanol-substituted styrenes and N-acyclophthalimides under IrIII photocatalysis.

#### Scheme 34. Gold Catalyzed Activation of Bromoalkanes

![Scheme 34. Gold Catalyzed Activation of Bromoalkanes](image)

Different decarbonylative alkenylations have been reported by changing the radical source and the photocatalyst (Scheme 36). The homolytic cleavage of an alkyl-I bond has been promoted by a Cu complex and the resulting cyclohexyl radical afforded styrene 36−3 in 68% yield upon addition onto cinnamic acid 36−1 (path a). The same product may be obtained as well starting from the same substrate by using phthalimide 36−2 under visible light irradiation with the help of an IrIII complex (path b) or a RuII photocatalyst. As an additional bonus, the formation of adduct 36−3 was obtained with a preferred E configuration.

The alkenylation may mimic a Heck reaction as in the visible light-induced Pd-catalyzed reaction between a vinyl (hetero)-arene and an α-heteroatom-substituted alkyl iodide or bromide (see Scheme 37). Here, the generation of the radical is induced by the reduction of the TMS-derivative 37−1 by the excited PdII species. Radical addition onto 37−2 followed by β-H elimination from the adduct radical delivered allyl silane 37−3.
in 81% yield. Noteworthy, the same reaction did not take place under usual thermal Pd-catalysis.

Alkylation of styrenes could be carried out using an inexpensive palladium source (Pd(PPh₃)₄) with no need of any base or classical photocatalyst. The reaction was promoted by visible light, adopting N-hydroxyphthalimides as radical sources. Other visible light Pd promoted alkenylations include the reaction of vinyl arenes with carboxylic acids or tertiary alkyl halides as radical precursors. Other metal catalysts, however, were helpful for the substitution of a vinylic hydrogen atom with an alkyl group. In this respect, a dinuclear gold complex was employed for the activation of an alkyl bromide to promote a photocatalyzed Heck-like reaction. The synergistic combination of a POC and a cobaloxime catalyst promoted the photocatalyzed decarboxylative coupling between 38−1 and styrene 38−2 to give the alkenylated product 38−3 in 82% yield and with a complete E/Z selectivity as illustrated in Scheme 38.

The addition of the alkyl radical may take place even on substituted alkenes via an ipso-substitution reaction. An example is shown in Scheme 39 where a vinyl iodide (39−2) is used for an alkenylation by the reaction with a radical generated from silicate 39−1, obtaining compound 39−3. The RuII photocatalyst in the dual catalytic system has the role of generating the radical, while the Ni0 catalyst activates the C(sp2)-I bond.

2.2.2. Acylation. Acylation owes its importance to the possibility to convert an alkyl radical into a ketone, a reaction that proceeds in most cases with the intermediacy of an acyl radical. A classical approach is based on the homolytic cleavage of an alkyl-I bond followed by carbonylation with CO and reaction with electrophiles of the resulting nucleophilic acyl radical. Scheme 41 illustrates the concept. Irradiation of iodide 41−1 with a Xe lamp in the presence of CO (45 atm) and a Pd0 complex led to an electron transfer reaction which formed an alkyl radical that, upon carbonylation and addition onto phenyl acetylene, gave ynone 41−2 in 63% yield. The reaction is supposed to proceed via a photoinduced electron transfer from the Pd0 catalyst to the iodoalkane, furnishing a PdII species and the alkyl radical. The carbon-centered radical promptly reacts with CO to generate an acyl radical. The PdII catalyst intervenes here again to couple the acyl derivative with another molecule of CO.

2.2.2.2. Other Metal-Catalyzed Alkenylation Reactions. Other metal catalysts have been employed for the alkenylation of alkenes. For instance, a cobaloxime catalyst has been used to promote the photocatalyzed decarboxylative coupling between 38−1 and styrene 38−2 to give the alkenylated product 38−3 in 82% yield and with a complete E/Z selectivity as illustrated in Scheme 38.

The addition of the alkyl radical may take place even on substituted alkenes via an ipso-substitution reaction. An example is shown in Scheme 39 where a vinyl iodide (39−2) is used for an alkenylation by the reaction with a radical generated from silicate 39−1, obtaining compound 39−3. The RuII photocatalyst in the dual catalytic system has the role of generating the radical, while the Ni0 catalyst activates the C(sp2)-I bond.

Alkenylation of alkyl iodide 40−1 can also take place starting from an alkyl sulfone (40−2). Also in this case, an ipso-substitution is central to the novel bond formation and the Pd0 catalyst formed the radical by a SET reaction with 40−1. After the addition of the radical onto 40−2, the sequence is completed by the elimination of a sulfonyl radical affording 53% yield of 40−3 (Scheme 40).

Alkyl bromides were used in alkenylations by reaction with vinyl sulfones made possible by the photocatalytic generation of silicon centered radical that in turn formed the alkyl radical by a halogen atom transfer reaction.
the alkyne, preserving the triple bond in the final product. This reaction was later applied to the acylation of styrenes to give the corresponding enones. The electrophilic nature of the alkyne could be exploited if the moiety is placed in the same reagent bearing the iodide. In this case, the first reaction observed was an intramolecular cyclization forming an alkenyl radical which eventually reacted with CO, furnishing an observed was an intramolecular cyclization forming an alkenyl unsaturated ketone. 

A reductive step induced the generation of the alkyl radical through an IrIII-photocatalyzed C–N bond activation in pyridinium salt (Scheme 42). Trapping of the alkyl radical with CO followed by addition onto 1,1-diphenylethylene gave access to the Heck-type product with no interference by the 2,4-dioxo-3,4-dihydropyrimidin-1-yl ring.

The alkyl radical to be carbonylated was likewise formed starting from a cycloalkane for the preparation of unsymmetrical ketones via radical addition onto Michael acceptors. The reaction proceeded via a photocatalyzed decatungstate hydrogen atom transfer reaction. When cyclopentanones were subjected to the photocatalyzed C–H activation, a regioselective β-functionalization occurred. Thus, 1,4-diketones were smoothly formed by reaction of the photogenerated acyl radical onto Michael acceptors (Scheme 43).

Unsymmetrical ketones have been likewise formed by carboxylation of alkyl radicals generated from organosilicates by using 4CzIPN as POC under visible-light irradiation. Potassium alkyltrifluoroborates were extensively used for acylation reactions having recourse to a dual photocatalytic system. The unstabilized alkyl radical was generated from trifluoroborate via a photoredox/nickel catalytic cross-coupling reaction (Scheme 44). Meanwhile, the acid was converted in situ into a mixed anhydride (by reaction with dimethyl dicarbonate, DMDC) that was activated by a Ni0 complex. Addition of the alkyl radical onto the resulting complex led to the acylated product in 43% yield. In a similar vein, Ir-photoredox/nickel catalytic cross-coupling reactions were devised by using acyl chlorides and N-aclypyrrolidine-2,5-diones as acylating reagents.

A Ni/Ru, dual-catalyzed amidation protocol was possible thanks to the coupling between an alkyllisilicate and an isocyanate. Even in the latter case, the alkyl radical attacked the complex formed between the isocyanate and a Ni0 species and, as a result, the mild formation of substituted amides took place.

The acylation of the radical was also exploited for the synthesis of esters. This elegant approach involves the generation of radicals from unactivated C(sp3)–H bonds (e.g., in cycloalkanes). The hydrogen abstraction on cycloalkanes was induced by a chlorine atom released from the photocleavage of the complex formed between chloroformate and a Ni0 complex, allowing one to synthesize scaffolds with different ring sizes.

2.2.3. Minisci-Like Reactions. A fundamental transformation for the C(sp2)–C(sp3) bond is the Minisci reaction, where the functionalization of heteroaromatics took place by substituting a H atom with an alkyl group. The reaction was widely investigated in the last years and mainly involves the functionalization of a nitrogen-containing heterocycle. An interesting example is the methylation reported in Scheme 45. A methyl radical was formed by using a peracetal such as 46–1. The protonation of 46–1 by acetic acid facilitates a PCET reduction of the peracetate by the IrIII PC. A double fragmentation ensued, and the resulting methyl radical may attack the protonated form of biologically active heterocycles (e.g., fusadil 46–2) in a mild selective manner to afford 46–3 in 43% yield.

Another approach made use of an alkyl boronic acid as the radical precursor. The process is initiated by the Ru41–photocatalyzed reduction of acetoxynbenziodoxole (BI-OAc) that liberated the key species ArCOO+ (Scheme 47). Upon addition onto an alkyl boronic acid, this ortho-iodobenzyloxy radical made available the alkyl radical that in turn functionalized pyridine in position 2 in 52% yield (47–2, Scheme 47).

The generation of the alkyl radical from boron-containing derivatives was made easier starting from alkyltrifluoroborates. A POC (Ac=Mes) is, however, required, but in all cases, the regioselective functionalization of various nitrogen-containing ketones would be achieved.

### Scheme 41. Photocatalyzed Synthesis of Ynones

**Type B: reductive pathway**

**Scheme 42. Synthesis of Enones via Photocatalyzed C–N Bond Activation**

**Scheme 43. Photocatalyzed Synthesis of Unsymmetrical Ketones**

**Scheme 44. Photocatalyzed Synthesis of NFSI**

**Scheme 45. Photocatalyzed Synthesis of NFSI**
heterocycles was achieved. A related chemical oxidant-free approach process was later developed where alkyl radicals were formed by merging electro and photoredox catalysis.

Alkyl halides are versatile substrates for the photoinduced functionalization (e.g., butylation) of lepidine (Scheme 48). An uncatalyzed redox process is a rare occurrence here, since alkyl halides reduction is more demanding. This drawback can be overcome by the adoption of a dimeric AuI complex (see Scheme 34) that upon excitation coordinates an unactivated haloalkane promoting an inner sphere PET. This interaction pushes the activation of R-Br despite its larger E_red with respect to the PC (Scheme 48a). A different approach promoting the homolytic cleavage of the R-I bond is shown in Scheme 48b. Decacarbonyldimanganese Mn_{10}(CO)_{10} was cleaved upon visible light irradiation, and the resulting Mn-based radical was able to abstract the iodine atom from an alkyl iodide thus generating the alkyl radical. The TFA liberated in the process was crucial for the activation of the nitrogen heterocycle and adduct 49–3 was isolated in 95% yield (path b). Very recently, an interesting approach for the generation of alkyl radicals from the C–C cleavage in alcohols was reported making use of a CFL lamp as irradiation source. The combination of 2,2-dimethylpropan-1-ol (50–1) with benzioxazole acetate (BI-OAc) gave adduct 50–3. Photocatalytic reduction of compound 50–3 released an alkoxy radical that upon fragmentation formed a t-butyl radical that reacted with N-heteroarene 50–2 to form 50–4 in 57% yield (Scheme 50).

The use of hypervalent iodine III in promoting the decarboxylation of R-COOH was effective in the derivatization of drugs or drug-like molecules. As a result, the quinine analogue 51–2 was formed in a 76% yield from quinine 51–1, utilizing Acr+Mes as the POC (Scheme 51). Azoles can be adamantylated starting from adamantane carboxylic acid by a dual catalytic approach (Acr+Mes as the POC and [Co(dmgH)(dmgH2)Cl2] as the cocatalyst) or simply C2-alkylated under photoorganocatalyzed conditions. The photocatalyzed reduction of N-(acyloxy)phthalimide 52–1 induced by an IrIII complex is an alternative approach for the functionalization of N-heterocycles such as 2-
chloroquinonxaline $S_2-2$ to form the cyclopentenyl derivative $S_2-3$ (Scheme 52).

The reductive pathway is feasible even when the generation of the alkyl radical was carried out starting from the redox-active pyridinium salt $S_3-1$. In this case, the obtained cycloalkyl radical gave a regioselective addition onto 6-chloroimidazo[1,2-$b$]pyridazine $S_3-2$ to yield $S_3-3$ under mild conditions (Scheme 53).

The alkyl radical could be formed even from simple hydrocarbons via hydrogen atom transfer reaction. A valuable example is reported in Scheme 54. The hypervalent iodine oxidant PFBI$^-$OH is reduced by an excited Ru$^{II}$ complex generating a carbonyloxy radical that acted as hydrogen atom abstracting agent. Functionalization of isoquinoline $S_4-2$ by the resulting radical (derived from $S_4-1$) afforded adduct $S_4-3$ in 65% yield (>15:1 dr). The high selectivity observed in the functionalization of $S_4-1$ was ascribed to the slow addition of the tertiary alkyl radical possibly formed onto $S_4-2$. The direct (rather than indirect) C–H cleavage in cycloalkane was possible by using decatungstate anion as PC. Various nitrogen-containing heterocycles were then easily derivatized even under simulated solar light irradiation.

PFBI–OH was likewise used for the remote C(sp$^3$)–H heteroarylation of alcohols (Scheme 55). As an example, the reaction of pentanol with PFBI–OH gave adduct $S_5-1$ that was reduced by the photocatalyst releasing the alkoxy radical $S_5-2$. 1,5-HAT and addition onto protonated phthalazine $S_5-3$ afforded adduct $S_5-4$ and the functionalized hetero-
As previously stressed, an acid is often required for an efficient Minisci-like reaction. To overcome this problem the alkylation may be carried out on the corresponding N-oxide derivatives as it is the case of pyridine N-oxides (56−2, Scheme 56). The radical is generated from a trifluoroborate salt (56−1) and the alkylation is regioselective in position 2 (forming compound 56−3). The process is efficient thanks to the photocatalytic degradation of BI-OAc that promoted a hydrogen abstraction, operated by the resulting carbonyloxy radical, on the Minisci radical cation adduct.

On the other hand, the pyridine N-oxide 57−1 can be acylated in situ with suitable acyl chlorides to furnish the electron-poor 57−2a−c+ derivatives. Photocatalytic reduction of these intermediates leads to the generation of alkyl radicals prone to attack the pyridine nucleus itself in the ortho position resulting in a decarboxylative alkylation (57−3a−c, Scheme 57).

2.2.4. Ipso-Substitution Reactions. The forging of an alkyl-sp2 bond (e.g., an alkyl-Ar bond) is undoubtedly one of the most crucial goals pursued by a synthetic organic chemist. Alkyl radicals generated via different mild routes can be
Successfully employed for the arene ipso functionalization, given the presence of a suitable group X on the (hetero)aromatic ring that directs the selective formation of a new Ar–C bond at the expense of an Ar-X bond. Dual catalysis (with the help of a Ni-based complex) is one of the preferred approaches.

In a recent example, the hydrogen atom transfer ability of the excited TBADT catalyst (see also Scheme 12) is used to form an alkyl radical starting from different aliphatic moieties (see Scheme 58). \(^{250}\) The combined action of the tungstate anion and the nickel catalyst (Ni(dtbbpy)Br\(_2\)) allowed the coupling of (hetero)aromatic bromides with unactivated alkanes, overcoming their high bond dissociation energies (ca. 90–100 kcal/mol) and low acidities. Both linear (41–56% yield) and cyclic (57–70% yield) alkanes could be functionalized with a vast range of competent partners. Interestingly, the radicals are generated preferentially on the less sterically demanding secondary carbons in alkanes, affording a remarkable selectivity.

The scope of this method could be extended to the functionalization of natural products and drugs, such as in the preparation of the bicyclic derivative 58–3a (61% yield) and the N-Boc protected epibatidine alkaloid 58–3b (28%, Scheme 58). \(^{250}\) A very similar approach was later reported for the dual photocatalytic formation of an Ar–C bond starting from aryl bromides and cycloalkanes. \(^{251}\)

Another dual-catalytic approach allowed the coupling reaction of aryl bromides (59–2, Scheme 59) and alkyl sulfinates (59–1), in the presence of Ni(COD)\(_2\) and tetramethyleneurane (TMHD, Scheme 59a) to give 59–3 in 84% yield under air. \(^{104}\) The photogenerated radical was trapped by the Ni complex that mediated the coupling with the aryl halide 59–2. The method was then applied to the synthesis of 59–5, selective ATP-competitive inhibitors of the casein kinase 1δ, an enzyme related to the regulation of the circadian rhythm (Scheme 59b). \(^{104}\)

A very similar strategy to access C(sp\(^3\)) radicals involves the photoredox induced cleavage of alkyl oxalate 60–1, starting from the corresponding alcohols (see Scheme 60, see also Scheme 3). \(^{252}\) The rapid in situ formation of the oxalate (without purification) was followed by the metallaphotoredox sequence based on Ni catalysis, allowing to obtain the C(sp\(^3\))-C(sp\(^3\)) coupling to give derivatives 60–3a–e in good yields.

The advantage of the use of potassium and ammonium bis-catecholato silicates relies in the smooth generation of unstabilized primary and secondary alkyl radicals to be engaged in dual catalysis. \(^{253,254}\) An example is the consecutive functionalization of bromo(iodo)arene 61–2 (Scheme 61, see

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**Scheme 58. Dual TBADT-Ni Catalysis for the Synthesis of Pyridyl-Functionalized Bicycles**

- R\(_1\) = CH\(_3\) R\(_2\) = CF\(_3\) 61%
- R\(_1\) = NBoc, R\(_2\) = Cl 28%, dr > 20:1

**Scheme 59. Dual Catalytic Cross-Coupling of Aryl Bromides with Alkyl Sulfinates**

**Scheme 60. Coupling of Alkyl Oxalates with Aryl Bromides**

**Scheme 61. Consecutive Functionalization of Bromo-Iodo Arenes with bis-Catecholato Silicates**

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also Scheme 25) for the preparation of 61−4 where the radical (from 61−1) is trapped by Ni0 (stabilized by a phenanthroline ligand). The synthesis of 61−3 can be achieved in high yields on 10 mmol scale with reduced effect on yield (75%) and selectivity (98%). The crude bromide 61−3 can be achieved in high yields on 10 mmol scale with reduced effect on yield (75%) and selectivity (98%). The crude bromide 61−3 was further functionalized by a second Ni/photoredox cross-coupling of the alkylsilicate 61−5, affording product 61−4 in 66% yield.255 The procedure was extended successfully to alkyl triflates, tosylates and mesylates,256 and to brominated borazaronaphthalene cores.257 The latter approach was crucial to access previously unknown isosteres of azaborines.

The action of a silyl radical on an alkyl bromide 62−1 forms an alkyl radical that, again with the help of a Ni based catalyst, reacted with aryl bromides 62−2 (Scheme 62, see also Scheme 11). The scope of products 62−3 that can be obtained is varied and includes both aromatic and heteroaromatic substrates, along with cycloalkanes of different size.71

Scheme 62. Ir/Ni Complex Mediated Coupling Between Alkyl and Aryl Bromides

Dual photoredox/nickel catalysis was successfully applied to couple β-trifluoroboratoketones 64−1 with aryl bromides 64−2a−f (Scheme 64, see also Scheme 4). Arylated compounds 64−3a−f were efficiently prepared with substituents of different electronic nature on the aryl ring.259

Scheme 64. Photoredox/Nickel Dual Catalytic Coupling of β-Trifluoroboratoketones with Aryl Bromides

Potassium tetrafluoroborate salts have been applied to generate secondary alkyl radicals via Ir photocatalysis coupled with Ni.260 However, they were found to be likewise suitable for cross-coupling reactions devoted to the forging of quaternary carbon centers (Scheme 65) without the need of using reactive organometallic species.261 In the amanylation of bromides 65−1a−d better yields were obtained when the aryl ring was substituted with electron-withdrawing groups.

An interesting application of this synthetic strategy is the functionalization of 7-azaindole pharmacophores with cycloalkyl scaffolds to improve the drug likeness of the azaindole core structure. Different potential drug candidates (66−3a−c, Scheme 66) were prepared via dual photocatalysis in a flow setup varying the dimension and substitution of the ring.262

In a similar way, a DHP-functionalized cyclohexene 67−1 was used to generate a secondary alkyl radical. In this case, the authors promoted the oxidation of 67−1 by using the strongly oxidizing 4CzIPN photocatalyst. Coupling with bromopyridine 67−2 gave substituted pyridine 67−3 in moderate yields (Scheme 67, see also Scheme 7).118

DHP-derivatives (68−1) may be used in ipso-substitution reaction even in the absence of a photocatalyst (Scheme 68). Violet light LED illumination directly excited didehydropyr-
Scheme 65. Adamantylation of Aryl Bromides

Scheme 66. Functionalization of 7-Azaindole Pharmacophores in Flow

Scheme 67. Coupling of DHP-Cyclohexene with Cyanobromopyridine

Scheme 68. Photocatalyst-Free Activation of DHPs

Scheme 69. CopperI-Mediated Synthesis of Nitriles

Scheme 70. Cyanation of (a) Triﬂuoroborates and (b) Carboxylic Acids

The reduction of an N-alkoxy pyridinium salt generated an allyl radical that upon intramolecular 1,5-HAT formed an alkyl radical that is cyanated with the help of the copper catalyst.  

A typical cyanation procedure, however, makes use of tosyl cyanide as cyanating agent. Thus, the radical obtained by oxidation of triﬂuoroborate 70−1a (by excited Acr+Mes) or acid 70−1b (by riboﬂavin tetraacetate RFTA) was trapped by tosyl cyanide to afford nitrile 70−2 by a substitution reaction (Scheme 70).

Scheme 71. Cyanation of remote C(sp3)−H bonds by a 1,5-HAT followed by cyano migration to form cyanoketones 71−3a−d (Scheme 71).

A related RuII-photocatalyzed cyanation employing Ts-CN starting from alkyl triﬂuoroborates but requiring BI-OAc as a mild oxidant has been likewise reported.  

An elegant way to forge an alkyl-CN bond required the photocatalyzed elaboration of cyanohydrines 71−1a−d. At first, the interaction of the OH group with the sulfate anion (generated by the decomposition of persulfate anion) allowed its oxidation by a proton-coupled electron transfer (PCET) process promoted by an in situ formed IrIV species. Alkoxy radicals 71−2a−d were then formed and promoted a regioselective cyanation of remote C(sp3)−H bonds by a 1,5-HAT followed by cyano migration to form cyanoketones 71−3a−d (Scheme 71).

2.3.2. Alkynylation. Direct alkynylation of photogenerated alkyl radicals could be accomplished utilizing a reagent or catalyst that activates the alkyne moiety, making it more prone to the forging of a novel C(sp3)−C(sp) bond. One of the first
strategies that were employed made use of benziodoxole-functionalized alkynes to promote the reaction with the alkyl radical. A representative case is illustrated in Scheme 72.

[Ru(bpy)$_3$](PF$_6$)$_2$ promoted the alkyl radical formation from trifluoroborate salt 72 that upon addition onto the alkynyl derivatives 72-2a–d induced the alkynylation via the intermediacy of vinyl radicals 72-3a–d. This deboronative alkynylation strategy could be performed in neutral DCM:water (1:1) at room temperature, giving access to the alkynylation of primary, secondary, and tertiary derivatives. To further prove the mildness of the conditions used, the authors carried out the reaction in PBS at pH 7.4 in the presence of biomolecules such as amino acids, but also single-stranded DNA and proteins (e.g., bovine serum albumin), obtaining satisfactory yields ranging from 68 to 86% of selectively alkynylated product.

The nature of the substituents on the alkynylbenziodoxole reagent were proved to determine the outcome of the alkynylation process. The electron-rich compounds performed better in the photocatalyzed transformation, both as radical acceptor and oxidative quencher of the RuII photocatalyst.

A similar strategy to the one mentioned before consists in the IrIII-photoredox-catalyzed alkynylation of carboxylic acids (Scheme 73 a, path a). In this case benziodoxole derivatives 73-1 were again used to activate the sp carbon of the alkyne to the radical attack, affording good yields of products 73–3. Following these results, they developed a reaction to synthesize ynones 73–4 utilizing the same reaction conditions in the presence of gaseous CO (see Scheme 73a, path b and Section 2.2.2). Gram-scale reactions and late-stage functionalization of natural terpenoids such as ursolic acid 73–5, Scheme 73b) were likewise reported.

Alkynyl sulfones were extensively employed as alkynylation reagents, with a mechanism like the one described in Scheme 72. Alkynyl phenyl sulfone was used in combination with N-acyloxyphthalimide derivatives as radical precursors in a RuII-photocatalyzed reaction that gave direct access to TIPS-substituted alkynes. N-Phthalimidoyl oxalates and tolyl alkynyl sulfones were found to be competent for the reaction (even for the preparation of internal alkynes having quaternary carbons), the latter even in combination with pyridinium salts as radical precursors. The consecutive photoredox decarboxylative coupling of doubly functionalized adipic acid derivatives with alkynyl phenyl sulfones induced the cascade formation of interesting cyclic derivatives with an exo double bond (Scheme 74). In this case, compound 74–1 underwent two efficient consecutive photoredox decarboxylative couplings leading first to alkyne 74–3 that it was subjected to radical cyclization to form radical 74–4* and styrene 74–5 from it. The authors reported the formation of five-membered rings via the consecutive formation of two C–C bonds, along with one.
example showing the application to the synthesis of six-membered derivatives (31% yield).278

In rare instances alkynyl bromides could be used as sp counterpart in the radical addition of alkyl derivatives obtained from the oxidative decomposition of various Hantzsch esters under visible light conditions promoted by 4CzIPN.279

The versatility of the photocatalytic method, however, allowed to obtain functionalized alkynes starting from terminal alkynes (Scheme 75). The first approach involves the UV light induced cleavage of the C−I bond in iodide 75−1 (used in large excess) in basic aqueous media. Addition of the cyclohexyl radical onto alkyl 75−2 followed by the incorporation of the iodine atom gave vinyl iodide 75−3. The strong basic conditions used (NaOEtBu) coupled with heating (up to 50 °C) favored an elimination of HI to yield the desired alkyn 75−4 under metal-free conditions (Scheme 75a).280 Visible-light (450 nm) was used in the copper-catalyzed coupling of an alkyl iodide (75−5) and again a terminal alkyn (75−6, Scheme 75b). The success of the reaction was ascribed to the use of terpyridine ligand 75−8 that avoided the photoinduced copper-catalyzed polymerization of the starting substrates. Probably, the reaction started by the excitation of the first formed copper acetylide that upon SET with 75−5 promoted the synthesis of alkyn 75−7 in high yields.281

3. FORMATION OF A C(SP3)-Y BOND

3.1. C−B Bond

Borylation of an alkyl derivative to access differently substituted boron containing compounds can be carried out under mild conditions, employing different photochemical approaches. Thus, the alkyl radical formed from an N-hydroxyphthalimide 76−1 (derived from dehydrocholic acid) may be trapped either by bis(pinacolato)diboron (B2pin2) to give the corresponding alkyl pinacol boronates 76−2 (Scheme 76, path a) or by tetrahydroxydiboron (B2(OH)4) followed by treatment with KHF2 to give alkyl tetrafluoroborates (Scheme 76, path b).282

A variation of the previous methodology involves the irradiation of N-hydroxyphthalimide esters 77−2 in the presence of B2cat2 (77−1) with the help of N,N-dimethylacetamide (DMAc) as the solvent under uncatalyzed conditions (Scheme 77). These components formed a heteroleptic ternary complex able to be excited by blue light and ultimately leading to the corresponding benzo[1,3,2]dioxaborole 77−4 that upon treatment with pinacol and TEA released the desired pinacol boronic ester 77−3. The functionalization of a series of drugs and natural products, such as pinonic acid and fenbufen were likewise effective, underlying the broad scope and functional group tolerance of the method.283

Scheme 74. Cascade Double Alkynylation of Functionalized Adipic Acids

Scheme 75. Alkylation of Terminal Alkynes

Scheme 76. Photocatalyzed Borylation of N-Hydroxyphthalimides

Scheme 77. Photocatalyst-Free Borylation
Two related approaches were later developed and involve the irradiation of the ternary complex formed by differently substituted N-alkyl pyridinium salts, B$_2$cat$_2$ and DMAC. The reaction gave again pinacol boronic esters in what is considered a deaminative protocol for the borylation of aliphatic primary amines since the latter compounds were used for the synthesis of the pyridinium salts.$^{284-286}$

Interestingly, 2-iodophenyl thionocarbonates were later adopted as radical precursor for the preparation of boronic ester via photocatalyzed reaction with B$_3$cat$_2$ (Scheme 78).$^{95}$

Scheme 78. Borylation of 2-Iodophenyl Thionocarbonates

The strategy is based on the photoinduced reduction of compound 78-1 that upon iodide anion elimination formed aryI radical 78-2$^*$ that underwent a 5-endo-trig cyclization causing the release of benzo[d][1,3]oxathiol-2-one 78-3 and alkyl radical 78-4$^*$. Usual borylation gave boronic ester 78-5 in 85% yield.

3.2. C–N Bond

Diverse structural motifs based on the C–N bond such as hydrazine and hydrazide cores were accessed by the photochemical addition of alkyl radicals onto the N=N of azodicarboxylates. TBADT-photocatalyzed HAT was applied to synthesize hydrazines by the coupling of cycloalkyl radicals with diisopropyl azodicarboxylate (DIAD). A synthetically challenging three component reaction can be achieved in the presence of CO, allowing the synthesis of the corresponding hydrazides.$^{287}$

The C–H amination can be smoothly achieved even starting from light hydrocarbons, such as methane (79-1, Scheme 79), with ditert-butylazodicarboxylate (DBAD, 79-2) in the presence of Ce$_{III}$ salts. This inexpensive photocatalyst furnished the desired product 79-3 in 63% yield, with a turnover number up to 2900. The authors proposed a ligand-to-metal charge transfer excitation between the cerium salt and trichloroethanol as the source of alkoxy radicals that acted as hydrogen atom transfer agents.$^{288}$

Aminated alkanes can be obtained by reacting aliphatic carboxylates with DIAD making use of Acr+Mes as a photoredox catalyst.$^{289}$ A cerium catalyst was adopted for the generation of several alkyl radicals starting from carboxylic acids, under basic conditions, allowing for the functionalization of a broad range of substrates, including natural products such as drugs like gemfibrozil (80-2) and tolmetin (80-1, Scheme 80).$^{289}$

Scheme 79. Photocatalyzed Amination of Methane

Scheme 80. Cerium-Catalyzed Decarboxylative Amination

The N=N bond of differently substituted azobenzenes (81-1a–e) can be functionalized on both nitrogens with a tandem N-methylation and N-sulfonylation, by cleavage of DMSO by UV irradiation of the Fenton reagent (FeSO$_4$/H$_2$O$_2$, Scheme 81).$^{105}$

Synthesis of amides can be achieved recurring to copper photocatalysis. Secondary alkyl bromide 82-1 could be efficiently coupled with cyclohexane carboxyamide 82-2 in 90% yield using CuI in catalytic amounts (Scheme 82a). The authors were able to isolate the catalytic species (a copper–

Scheme 81. Tandem N-Methylation and N-Sulfonylation of Azobenzenes
amidate complex), formed by the assembly of four copper ions and four amides.291

Scheme 82. Photocatalyzed Synthesis of (a) Amides and (b) Carbamates

The same group reported the functionalization of carbamates with secondary alkyl bromides by shifting the wavelength of irradiation in the visible region by developing a tridentate carboxazide/bisphosphine ligand 82−4 for the copper catalyst thus able to prepare Boc-pregnenolone 82−5 in 90% yield (Scheme 82b).292 A variation of this protocol was applied to the synthesis of amines, using secondary unactivated alkyl iodides and CuI/BINOL as the catalytic system293 applied to the synthesis of amines, using secondary unactivated alkyl iodides and CuI/BINOL as the catalytic system.

Several reagents can be used as an azide source to synthesize synthetically valuable C−N3 bonds. Tertiary aliphatic C−H bonds can be selectively functionalized via Zhdankin azidoiodane reagent 83−2. Visible light was used to excite Ru(bpy)3Cl2 that cleaves the labile I−N3 bond, triggering the cascade of radical reactions that leads to the product formation (Scheme 83). The selectivity and compatibility of this reaction allows the C−H to C−N3 conversion in menthol benzoate 84−1 to give azide 84−4 in a satisfying yield, with a regioselectivity favoring the more electron-rich tertiary position.296

The synthesis of amines is undoubtedly more challenging to be dealt with, relying on radical chemistry. However, several strategies were developed to effectively forge this fundamental functional group. A classic reaction for the synthesis of amine is the Curtius reaction that has the drawback in handling of potentially dangerous azides. A dual copper/photoredox catalytic approach mimicked this process for the obtainment of N-protected amines from the N-hydroxypthalimide ester of cholic acid triacetate 85−1 (Scheme 85, see also Scheme 86). The alkyl radical was again formed by Cu′-photocatalyzed reduction of 85−1, but this recombine with the CuII-phthalimide complex formed to release 85−2 (52% yield) by a formal decarboxylation process. A great variety of functional groups are compatible with this reaction including steroidal structures.

A very interesting approach to synthesize β-aminoalcohols from the unfunctionalized alcohol 86−1 relies on the introduction of a radical relay chaperone to direct the C−H functionalization of the β position of the OH group (Scheme 86). Imidate radicals can be accessed via the photodecomposition of Phl(OAc)3. A transient sp3 N-centered radical is generated from 86−2, which allows a 1,5-hydrogen atom transfer. A source of iodine promotes the formal transfer of an iodine radical to the β-position to the imidate, followed by cyclization to obtain 86−3 which can be promptly hydrolyzed to 86−4. The nature of the substituents on acetimide 86−2 may affect the overall yield.298

Direct cross-coupling between alkyl carboxylic acids and nitrogen nucleophiles can be achieved by dual copper/photoredox catalysis through iodonium activation. The scope of the transformation is broad and applicable to a diverse array of nitrogen nucleophiles such as heterocycles, amides, sulfonamides, and anilines to give the corresponding C−N coupling product in excellent yields on short time scales (5 min to 1 h). The high regioselectivity obtained in late stage functionalization of complex pharmaceuticals such as Skelaxin 87−2 (to give 87−3 in 90% yield from 87−1, Scheme 87, see also Scheme 48) gave an idea of the importance of the approach.299

Similar strategies were explored for the synthesis of amines via C(sp3)−N cross-coupling combining a copper catalyst and the action of a photoredox catalyst by using anilines or

Scheme 84. Photocatalyzed C−H to C−N3 Conversion

with different groups is underlined by the conversion of the dipeptide 83−1 to 83−3 in 30% yield.294 A related C−H azidation was performed by using tosyl azide as an alternative azide source with the help of 4-benzyopyridine to promote the photocatalytic C−H cleavage in various cycloalkanes.295

Another example of the functionalization of unactivated C−H bonds is depicted in Scheme 84 making use of tosyl azide 84−2. The reaction needs the intermediacy of an oxygen radical center on a phosphate group, previously oxidized by the action of the mesityl acridinium photocatalyst 84−3. This

Scheme 83. Azidation of Tertiary Aliphatic C−H Bonds
3.3. C–O Bond

The C–O bond formation is without doubt a prerogative of polar chemistry. However, there are examples of photochemically driven reactions making use of an alkyl radical for the introduction of different oxygen-containing functional groups. In Scheme 88, the nonenolizable ester 88–1 is transformed into 88–2 via a photochemically promoted decarboxylation of the NPhth-ester (see also Scheme 8) in the presence of Hantzsch ester to yield a tertiary radical. The intermediate is promptly quenched by TEMPO, affording 88–2 in 91% yield, in a multigram scale reaction.303

A similar reaction was employed to synthesize alkyl aryl ethers, given their importance in medicinal and agricultural chemistry. A tandem photoredox and copper catalysis approach allows the decarboxylative coupling of alkyl N-hydroxypythalimide esters (NHPI) with phenols (89–2 Scheme 89). Various NHPI esters of different drugs and natural products easily underwent a late-stage decarboxylative etherification. As an example, the chlorambucil derivative 89–1 was converted into the corresponding 2-MeO phenyl ether 89–3 in 49% yield.304

Following a similar strategy, carboxylates are converted into alcohols via a photocatalytic decarboxylative hydroxylation mediated by the mesityl acridinium salt. In this case, molecular oxygen is used as the oxidant, to promote the formation of the desired C–O bond. Since the reactions gave mainly a mixture of ketones and hydroperoxides, reduction in situ by sodium borohydride allowed the synthesis of alcohols in good yields.305 A decarboxylative hydroxylation may be carried out with the intermediacy of Barton esters that upon irradiation in oxygen-saturated toluene followed by treatment with P(OEt)3 afforded an alcohol intermediate for the total synthesis of Crotophorbolone.306 The more challenging oxidation of unactivated alkanes to alcohols or ketones can be achieved through a photoelectrochemical approach, as testified by the C–H bond activation of cyclohexane to prepare a mixture of cyclohexanone and cyclohexanol (the so-called KA oil) with high partial oxidation selectivity (99%) and high current utilization ratio (76%). The highest current ratio was observed illuminating the solution with 365 nm wavelength.307

Decatungstate photocatalysis was efficiently applied to oxidize activated and unactivated C–H bonds. Taking advantage of a microflow reactor setup, a late stage regioselective CH2/C=O conversion in several natural compounds, such as artemisinin 90–1 to form artemisitone-9 90–2 was readily pursued even in a 5 mmol scale (Scheme 90).308

3.4. C-Halogen Bond

Halogenation of alkanes through a radical reaction under UV irradiation is one of the core pathways to chemically activate a para. Industrially, chlorine gas is used to functionalize methane. A major drawback of the classical chain reaction using either Cl2 or Br2 under direct irradiation is the formation of di or polyhalogenated products. The application of microflow technology in combination with visible light irradiation (with an absorption maximum in the near UV at ca. 350 nm) allowed the monobromination of different alkanes with molecular bromine. High selectivity for the monobrominated compound and excellent overall yields (between 60 and 99%) could be achieved for secondary and tertiary alkanes, along with primary benzylic positions.309

Chlorination with molecular chlorine, on the other hand, suffers from the low yields of the reaction, typically around

Scheme 85. Decarboxylative C–N Coupling in Cholic Acid Triacetate

Scheme 86. Radical Relay Chaperone Strategy Driven by the Photodecomposition of PhI(OAc)2

Scheme 87. Late Stage Functionalization of Skelaxin

Scheme 88. Radical Relay Chaperone Strategy Driven by the Photodecomposition of PhI(OAc)2

Scheme 89. Late Stage Functionalization of Skelaxin

benzophenone imines301 as nitrogen source. Hydroxylamines were instead formed under photoorganocatalytic conditions by reaction of carboxylic acids and nitrosoarenes.302
50%, from the high concentrations of HCl generated in the process and from the toxicity of the chlorine gas itself. However, when Cl₂ was generated by mixing NaClO with HCl and the chlorination took place under flow conditions, efficient Cl⁻ to C⁻Cl conversion resulted. A photochemical alternative using NaCl as chlorine source was developed. In the reaction, Cl₂ was formed in situ by oxidation of the chloride anion with oxone. The monochlorination of cyclohexane to give could be obtained in 93% isolated yield thus overcoming the limitation of the classical chlorination process with chlorine gas (Scheme 91, see also Scheme 15).

Fluorination is essential to modern medicinal chemistry, both as a viable way to insert radiotracers or to deactivate specific degradation pathways in drugs. Photochemistry is a reliable tool to achieve the fluorination of C–H bonds, following different strategies. Excited TBADT may form a radical intermediate (from unactivated alkanes) that abstracts the fluorine atom from the labile N–F bond of the fluorinating agent N-fluorobenzenesulfonimide (NFSI). An N-centered radical resulted which closes the radical cycle oxidizing the reduced photocatalyst. Acetate was fluorinated in 40% yield following this procedure to yield (Scheme 92). The reaction applied to sclareolide, however, was not selective and gave a mixture of fluorinated regioisomers (68% overall yield).

Following a similar reaction scheme, uranyl acetate was employed in combination with NFSI to promote the fluorination of secondary alkanes but poorly on the benzylic positions. Indeed, in the absence of an aromatic scaffold, the excited U=O abstract a hydrogen atom through HAT, while the presence of an aromatic ring deactivated the excited state of the catalyst via exciplex formation preventing the fluorination to occur. Acetophenone in its excited state promoted the hydrogen abstraction of secondary alkanes, with the advantage that a common CFL housebulb can be used to promote an efficient conversion, using Selectfluor as the fluoride source. In this case, the authors irradiated the tail of the n-π* absorption band of the ketone which can be found in the visible region due to the high concentration of the photocatalyst present in solution. N-Alkyl phthalimides having an alkyl chain linked to the nitrogen was fluorinated by using Selectfluor under photocatalyst-free conditions. An exciplex was supposed to be formed between the reagents and it was proposed that the C–F bond formation took place concomitantly with hydrogen atom abstraction with the nitrogen radical of the fluorinating agent.

A considerable regioselectivity in the fluorination reaction can be achieved using carboxylates as alkyl radical precursors and again Selectfluor as a fluorinating reagent. The reaction is
possibly initiated by reduction of Selectfluor 93−2 by means of Ir[dF(CF₃)ppy]₂(dtbppy)PF₆. Fluorination of different carboxylic acids can be achieved in very high yields (between 70 and 99%), and 93−1 was readily converted into 93−3 in 90% yield (Scheme 93). In case of unactivated primary substrates, a prolonged irradiation (12−15 h) was mandatory to achieve a high conversion of the substrate.

Scheme 93. Regioselective Fluorination of Carboxylates

![Scheme 93](image)

An interesting case is the fluorination of compounds having the MOM group to direct the halogenation event. In this case, the PC oxidized an imidine base (DBN) that acted as hydrogen atom abstractor of the dioxolanyl group in compound 94−1 (Scheme 94). The resulting α,α-dioxy radical released an alkyl radical (upon formiate loss) that was fluorinated by Selectfluor. This metal-free approach again used visible light and is particularly successful when applied to tertiary alkyl ethers to give sterically hindered alkyl fluorides (e.g., 94−3).

Scheme 94. DBN-Mediated HAT in C−F Bond Formation

![Scheme 94](image)

94−2 released an alkyl radical (upon formiate loss) that was fluorinated by Selectfluor. This metal-free approach again used visible light and is particularly successful when applied to tertiary alkyl ethers to give sterically hindered alkyl fluorides (e.g., 94−3).

Interestingly, fluorination of carboxylates with Selectfluor was also reported to occur under heterogeneous photocatalytic conditions, using titania as photocatalyst to promote the oxidation of the carboxylate anion. Fluorination and chlorination of nitriles and ketones could be obtained starting from oximes, using Selectfluor and NCS as halogen sources, respectively. With this methodology, γ-functionalization of ketones and a complex photoinduced ring-opening/halogenation of oximes via the intermediacy of an iminyl radical was pursued. Indeed, the excitation with visible light of an N−I imidate group, formed in situ from the reaction of a trichloroacetimidate with PhI(OAc)₂ as an iodine source, allowed the synthesis of a small library of gem-di-I compounds in good yields. As an example, the cholic acid derivative 97−1 has been converted to its corresponding di-iodo derivative 97−2 in 71% yield (Scheme 97). Moreover, the authors could also achieve a dibromination using NaBr and TBABr and visible light, while only monochlorination is reported when NaCl, TBACl, and UV light were adopted.

3.5. C−S or C−Se Bonds

Alkyl radicals were sparsely used for the unusual introduction of a SCF₂X (X = F, H) or an SAR moiety in an organic compound. The introduction of a SCF₂X group has recently sparked attention due to the remarkable hydrogen donor nature of the group when X = H, making it the lipophilic surrogate for OH or NH groups. On the other hand, the trifluoromethylthio group increases the metabolic stability and the lipophilicity of drugs.
One strategy for the introduction of a SCF₂X group is the photocatalyzed (by Ir(III) PC) oxidation of alkyl carboxylates via visible light irradiation in the presence of PhthN-SCF₂H⁻(98−) as the sulfur donor. Indeed, 98−1 was converted into 98−3 in high yields (Scheme 98). The reaction was sustained by the stability of the imidyl radical liberated in the process, that was able to promote a chain reaction oxidizing a further carboxylate group. Indeed, the quantum yield for the reaction was found to be 1.7.325 Bis-methylthiolation was observed in different cases, possibly due to HAT triggered by an intermediate of the reaction, presumably PhthN• and following transfer of SCF₂X from the reactant. To avoid the formation of byproducts either mesitylene or 3-(methyl) toluate were added as sacrificial hydrogen donors.

An interesting follow-up for this methodology from the same group made use of the hydrogen atom transfer process previously reported as detrimental for the reaction yield. In fact, when using an aryl carboxylate instead of an aliphatic one, the carboxyl radical that is formed upon electron transfer with the excited Ir catalyst is now stable enough to act as a hydrogen abstractor, selectively targeting secondary or tertiary H in alkyl chains. Also, in this case, PhthN-SCF₂X acted as the sulfur source. The conversion of ambroxide 99−1 to its trifluoromethylthiol derivative 99−2 proceeded with 95% yield (Scheme 99).326

A photocatalyst-free decarboxylative arylthiation took place by mixing an N-acyloxyphthalimide (e.g., 100−2) in the presence of an aryl thiol (100−1) under basic conditions (by Cs₂CO₃) upon visible light irradiation. In this case, a SET between 100−1 and 100−2 caused the formation of 100−2⁺ along with thyl radical 100−3⁺ (that easily dimerized to disulfide 100−4). Trapping of the resulting cyclohexyl radical (by loss of PhthN⁺ from 100−2⁺) with 100−4 afforded alkylaryl sulfoxide 100−5 in 89% yield (Scheme 100).327

The most widely used reaction for the C−S bond synthesis requires the incorporation of sulfur dioxide by using DABSO (DABCO(SO₂)₂) as its surrogate as depicted in Scheme 101.328 Thus, excited mesityl acridinium salts promoted the oxidation of an alkyl-BF₃K salt that generated a nucleophilic radical able to react with DABSO. The sulfonyl radical intermediate formed has been employed in a three-component reaction with electron poor olefins (e.g., a vinyl pyridine 101−1, Scheme 101a)329 or an alkyne (phenyl acetylene, Scheme 101b),330 affording alkyl sulfoxide (101−2) or (E)-vinyl sulfoxide (101−3), respectively.

Alternatively, alkyl iodides can be used to react with olefins decorated with EWGs and DABSO to generate a broad range of alkyl sulfones.331 A very similar strategy was implemented by the same authors using differently substituted Hantzsch esters as alkyl radical precursors, upon irradiation in the presence of Eosin Y.332 In the latter case, the sulfonyl radical added onto vinyl azides and, after releasing of molecular nitrogen, an imidyl radical resulted which reacted with the reduced photocatalyst, forming an anion that is easily protonated. After a tautomeric equilibrium, (Z)-2-(alkylsulfonyl)-1-aryleth-
en-1-amines were formed, with good regioselectivity and complete control over the configuration of the double bond.\textsuperscript{332}

Cyclobutanone oximes can be reduced via photocatalytic means in the presence of Ir(dtbbpy)(ppy)\(_2\)PF\(_6\) to form \(\gamma\)-cyanoalkyl radicals after radical fragmentation. In this process, a vinyl sulfone was used having the dual role of radical acceptors and SO\(_2\) source, allowing the synthesis of \(\beta\)-ketosulfones or allylsulfones through a radical transfer mechanism.\textsuperscript{333}

3.6. C–H Bond

Classical radical reductive dehalogenation is one of the most successful reactions based on tin chemistry.\textsuperscript{21} Photocatalysis and photochemistry propose a milder and more environmentally friendly alternative to this process, via different strategies. As an example, fac-Ir(ppy)\(_3\) was used to convert alkyl iodides 102–1 into their corresponding alkyl radicals using Hantzsch ester or HCO\(_2\)H as the hydrogen atom source for the HAT process that drives the reaction to the formation of 102–2 (Scheme 102). The authors optimized their procedure by using tributylamine as the sacrificial electron donor to reduce the oxidized form of the catalyst and restore the catalytic cycle.\textsuperscript{334} A variation of this protocol using p-tolueneethiol, DIPEA, and fac-Ir(mppy)\(_3\) was used to synthesize D-albucidin.\textsuperscript{335}

Other catalytic systems were proved to be competent in the reduction of halides. In particular, unactivated aryl and alkyl bromides could be reduced using [Ir(ppy)\(_2\)(dtbbpy)]PF\(_6\) in combination with TTMSS as a reducing agent. The mild conditions typical of the reaction were critical to obtain both the mono and the bis reduction of a gem-dibromocyclopropane in a selective fashion.\textsuperscript{336}

Alkyl iodides and bromides were reduced under metal-free conditions via irradiation of 4-carbazolyl-3-(trifluoromethyl)-benzoic acid as the photocatalyst and 1,4 cyclohexadiene as sacrificial hydrogen donor.\textsuperscript{337} The reduction of C–X bonds to C–H bonds can take place under photocatalyst-free conditions by PET reactions between the halide and an amine as sacrificial reductant. In this way, adamantine was obtained in 95\% yield by photochemical reduction of 1-bromoadamantane.\textsuperscript{338}

Borohydride-mediated radical photoreduction of alkyl halides (iodides, bromides, and chlorides) is another valuable tool for the formation of a C–H bond.\textsuperscript{339}

The C–H bond formation could be achieved via a hydrodecarboxylation of carboxylic acids. In fact, carboxylic acid 103–1 could be reduced in 97\% yield to 103–2 by generating the corresponding carboxyl radical through excitation of an acridinium photocatalyst with 450 nm LEDs, in the presence of 10\% mol of (PhS)\(_2\) (Scheme 103). The authors achieved good yields in the decarboxylation of different carboxylic acids. Most notably they succeeded in the double reduction of doubly substituted malonic acids, although with the necessity of longer irradiation times and higher catalyst loading to compensate for the increased amount of substrate to be reduced.\textsuperscript{340}

The challenging reduction of alcohols to the corresponding alkane can take place via functionalization of the OH group to form an O-thiocarbamate. This compound is the substrate of a photocatalyzed Barton-McCombie deoxygenation in combination with Ir(ppy)\(_3\) and DIPEA under an oxidative quenching. Accordingly, the xylofuranose derivative 104–1 was cleanly reduced to 104–2 in 70\% yield by maintaining the benzoyl group in position 5 (Scheme 104).\textsuperscript{93} The reaction was studied mostly on secondary alcohol derivatives being another interesting alternative to the usual tin-mediated reaction.\textsuperscript{22}

An alternative pathway to reduce the hydroxy function required a more sophisticated functionalization of the OH group making use of two consecutive photochemical reactions. Conducting the reaction in CBr\(_4\) under UVA irradiation, the hydroxy groups of a series of primary alcohols were converted into their bromides and then subjected to a one-pot photoreduction mediated by the dimeric gold complex \([\text{Au}_2(\text{dppm})_2]\)Cl\(_2\) in the presence of DIPEA.\textsuperscript{341}
4. FORMATION OF A RING

4.1. Three/Four-Membered Rings

In this last section, selected examples will be given when a photogenerated alkyl radical is used for the construction of a ring. Scheme 105 shows one example of formation of a three-membered ring. 1,1-Disubstituted cyclopropanes 105−3a−d were obtained through the addition of an alkyl radical (from silicate 105−1) onto homoallylic tosylates 105−2a−d. The trick here is a radical/polar crossover process where the reduction of the benzyl radical adducts to benzyl anions (by SET with the reduced form of the photoorganocatalyst 4-CzIPN) followed by intramolecular substitution gave the three-membered ring (Scheme 105). The versatility of the method was demonstrated by using alkyl trifluoroacetates or 4-alkyldihydropyridines as radical precursors and a good tolerance of various functional groups. A related approach was adopted for the construction of cyclobutanes. Here, the alkyl radical was formed by easily oxidizable electron-rich alkyl arylboronate complexes and added to an iodide-tethered alkene such as methyl 5-iodo-2-phenylpentanoate. However, changing the length of the chain in the haloalkyl alkenes led to the synthesis of three-, five-, six-, and seven-membered rings.

4.2. Five-Membered Rings

Five-membered ring is one of the privileged structures accessible via photogenerated alkyl radicals. A common approach is the cyclization onto an alkyne to form an exocyclic double bond as exemplified in Scheme 106. In most cases, an alkyl halide is reduced by an excited photocatalyst and the resulting radical cyclizes in a S-exo dig fashion to form the desired alkene. When using a dimeric gold complex 106−5 the reaction of alkyl bromide 106−1 generates diester 106−2 in 93% yield (Scheme 106a). Cyclopentanes were likewise formed starting from an unactivated alkyl iodide that underwent an intramolecular radical closure by using a strong reducer in the excited state (Ir(ppy)_2(dtb-bpy)PF_6). The iodine atom, however, was incorporated in the final product forming an alkyl iodide. The same metal-based photocatalyst was effective to induce a visible light-promoted preparation of five-membered heterocycles (Scheme 106b). The cyclization step was applied on a Ueno−Stork reaction starting from 2-iodoethyl propargyl ethers (e.g., 106−3a,b) to construct a tetrahydrofuran ring (in 106−4a,b).

The examples described in Scheme 106 required an amine as a sacrificial donor. However, amines can be used as efficient reducing agents by a PET reaction with excited alkynyl halides. The resulting photocyclization may then be carried out under metal-free conditions and in a flow photomicroreactor providing the preparation of five-membered rings in a 4 g scale.

The dehalogenation/cyclization strategy was explored even under heterogeneous conditions by using platinum nanoparticles on titania (PtNP@TiO_2) as the photocatalyst. The pyrrolidine scaffold was then obtained by reaction of N-(2-idoethyl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide under irradiation (DIEPA as sacrificial donor). As an alternative, a biphasic system may be adopted (Scheme 107). In fact, a polysisobutylene-tagged fac-Ir(ppy)_3 complex (Ir(ppy)_2(dtb-bpy)PF_6) soluble in heptane was prepared. The substrate 107−1 along with the reagents were soluble in a MeCN phase. However, heating at 85 °C allowed the two phases to mix. Preparation of tetrahydrofuran derivative 107−2 was then accomplished in continuous flow in a satisfying yield with an automatic recovery and reuse of the catalyst (Scheme 107).

Alkyl N-hydroxyphthalimide esters were used as alkylation reagents in the functionalization of alkoenoic acid 108−2 (Scheme 108). The alkyl radical added onto the double bond, and the resulting benzyl radical was oxidized to a benzyl cation readily trapped by water and cyclization of the resulting hydroxy acid gave alkyl-substituted lactones 108−3a−e in moderate yields.

Alkyl N-hydroxyphthalimide esters were exploited for the photocatalyzed (by a Ru^{II} complex) alkylation of N-arylacrylamides that caused the cyclization of the adduct...
radical onto the phenyl ring to afford 3,3-dialkyl substituted oxindoles. Moreover, the same radical precursors have been used for the derivatization of alkynylphosphine oxides under metal- and oxidant-free conditions to form benzo[b]-phospholes in very good yields.

A five-membered ring may be accessed via late-stage C(sp3)-H functionalization in N-chlorosulfonamides. The IrIII-photocatalyzed reduction of \( \text{109}^{-1} \) induced the elimination of the chloride anion along the formation of a N-centered radical prone to abstract a hydrogen atom from a remote position to afford an alkyl radical. Oxidation of this radical to the cation followed by incorporation of the chloride anion gave the corresponding chloride \( \text{109}^{-2} \) that upon treatment with solid NaOH formed pyrrolidine \( \text{109}^{-3} \) by an intramolecular nucleophilic substitution.

Even primary nonactivated sp\(^3\)-hybridized positions were functionalized again by a remote intramolecular radical, 1,5-hydrogen abstraction in \( \gamma \)-bromoamides to produce several \( \gamma \)-lactones in a one-pot fashion. Trifluoroethyl amides were found useful as the directing group increasing the efficiency of the hydrogen abstraction process.

It is also possible to incorporate more than one heteroatom in the ring starting from benzyl amine \( \text{110}^{-2} \) and unactivated bromides \( \text{110}^{-1a-e} \) (Scheme 110). Compound \( \text{110}^{-2} \) incorporates CO\(_2\) (with the help of the base TBD), and the resulting carbamate underwent attack by an alkyl radical photogenerated by reaction of \( \text{110}^{-1a-e} \) and an excited Pd\(^0\) photocatalyst (Pd(PPh\(_3\))\(_4\)). Ring closing yielded valuable 2-oxazolidinones \( \text{110}^{-3a-e} \) under very mild conditions and easy scalability.

### 4.3. Six-Membered or Larger Rings

Different approaches were devised to form a six-membered ring even containing heteroatoms. A cyclohexane ring was constructed by ring opening of an iminyl radical by IrIII-photocatalyzed reduction of a 3-phenyl O-acyl oxime (e.g., \( \text{111}^{-1} \)) to give radical \( \text{111}^{-2} \) that upon addition onto unsaturated esters \( \text{111}^{-3a-e} \) and ensuing cyclization led to cyanoalkylated 1,2,3,4-tetrahydrophenanthrenes (\( \text{111}^{-4a-e} \), Scheme 111).

Six-membered rings have been likewise obtained by ring expansion in cycloalkanone derivatives. This expansion was caused by the photocatalyzed decarboxylation of \( \alpha-((\omega\text{-carboxyalkyl})\beta\text{-keto esters, followed by an exo-trig cyclization of the resulting radical onto the carbonyl group that ultimately led to the one-carbon expanded cycloalkanones by } \beta\text{-cleavage.}

Reduction of indoles having an unactivated haloalkane chain is a useful approach to construct a ring. As an example, bromo derivatives \( \text{112}^{-1a,b} \) were reduced by a Au\(^+\) photocatalyst and radical cyclization onto the heteroaromatic ring afforded 6,7,8,9-tetrahydropyrido[1,2-\(a\)jindoles \( \text{112}^{-2a,b} \) in excellent...
Interestingly, changing the reaction conditions and starting from \(\text{N-(2-iodoethyl)indoles} \text{112} - \text{3a,b}\) in place of \(\text{112} - \text{1a,b}\) in the presence of Michael acceptors \(\text{112} - \text{4a} - \text{c}\) caused a dearomatizative tandem \([4 + 2]\) cyclization to deliver tri- and tetracyclic benzindolizidines \(\text{112} - \text{5aa} - \text{bc}\) with high diastereoselectivity and yield (Scheme 112b).359

The phenanthidine core is one of the elective scaffolds to be prepared by using a cyclization step induced by photo-generated alkyl radicals. Scheme 113 illustrated a representative case where an alkyl radical added onto a vinyl azide \(\text{113} - \text{2}\), and after nitrogen loss the resulting iminyl radicals \(\text{113} - \text{3a-c}\) yielded phenanthridines \(\text{113} - \text{4a-c}\) by ring closure.360 The method has several advantages including metal-free conditions (a dye as a POC) an excellent functional group tolerance and a broad substrate scope.

An alternative way to prepare phenanthridines is by having recourse to photoredox gold catalysis employing bromoalkanes as alkyl radical source. In this case, radicals attack a biaryl isonitrile thus forming a sp\(^2\)-hybridized radical that readily cyclizes upon the pendant arene.361 Aryl isocyanides (e.g., \(\text{114} - \text{2a-d}\)) were largely used for the construction of heterocycles such as pyrrolo[1,2-\(a\)]quinoxalines \(\text{114} - \text{4a-d}\). Phenylindoline\(^{111}\) dicarboxylate \(\text{114} - \text{1}\) was used for the incorporation of the cyclohexyl group both in batch and flow under \(I^3\)-photocatalyzed conditions (Scheme 114, see also Scheme 49).362

The photocatalyzed insertion of \(\text{SO}_2\) into an unactivated \(\text{C(sp}\(^2\))\)-H bond was designed to prepare 1,2-thiazine 1,1-dioxide derivatives under uncatalyzed conditions. In fact, visible light irradiation of the complex between an electron-poor O-aryl oxime and \(\text{DABCO-SO}_2\) releases an iminyl radical that upon 1,5-HAT, \(\text{SO}_2\) incorporation and cyclization gave the hoped-for heterocycle in a satisfying yield.363

In rare instances a ring larger than six may be constructed. By using the approach depicted in Scheme 115, it was possible to pursue a late stage functionalization on ursolic acid (a compound having excellent pharmaceutical activity). Accordingly, the NHPI ester of ursolic acid acetate (\(\text{115} - \text{2}\)) underwent a radical addition cascade by a photocatalyzed reaction with acrylamide-tethered styrene (\(\text{115} - \text{1}\)) with the intermediacy of radical \(\text{115} - \text{3}\)•. As a result, the benzazepine unit was incorporated in the end compound \(\text{115} - \text{4}\) combining two privileged bioactive scaffolds.364

**5. CONCLUSIONS AND OUTLOOK**

This review provides a concise and up-to-date selection of modern methods to generate alkyl radicals via photochemistry and photocatalysis. The effort and interest of the chemical community in developing and applying these new methods is witnessed by the rapid increase in the number of articles devoted to this topic that appeared in the literature in the last two decades. Indeed, the rediscovery of photocatalysis and the renaissance of visible light-driven processes have contributed to elevate radical chemistry from the isolated (yet efficient) niche of the tyrannical organotin compounds to a vast plethora of methodologies that relies on more environmental benign compounds. The facile synthesis of the precursors necessary for these transformations, along with the readily available setups (a vast number of reactions can occur by simple
irradiation with visible LEDs), made radical chemistry approachable, appointing the photon as the agent of this revolutionary democracy.

Photocatalysis has reached the stage of maturity; however, we are still far from the statement of Ciamician envisioning “industrial colonies without smoke […] forests of glass tubes […]”; inside of these will take place the photochemical processes that hitherto have been the guarded secret of the plants, but that will have been mastered by human industry which will know how to make them bear even more abundant fruit than nature, for nature is not in a hurry and mankind is. New practical methods and theoretical assumptions are needed to foster the revolution that has just started. A promising approach makes use of the upconversion of reductants to generate strongly reductive species, but the method was not applied so far to alky radicals. This phenomenon can be exploited, for example, if the reaction of a radical anion R"" to give P"" is less exergonic (see the ΔG"" value in Figure 4A) than its neutral counterpart (ΔG, referred to R → P conversion). The difference between these two free energies defines the upconversion energy (ΔGup = ΔG"" − ΔG). The high quantum yields associated with the transformation of R into P in Figure 4A (Φ = 44) were attributed to the presence of electrocatalytic cycles propagated by P"", which is able to transfer an electron to the reactant, closing the catalytic cycle. This phenomenon is attributed to P"" being a better reductant than R"", due to the diminished conjugation (Figure 4A).

The novel approach granted by the merging of homogeneous photocatalysis with electrocatalysis (see Figure 4B) is surfacing as the new challenge in this constantly evolving topic.

![Figure 4](https://dx.doi.org/10.1021/acs.chemrev.0c00278)

**Figure 4.** (A) Upconversion of the reducing power of the intermediates in a photocatalytic/photoinitiated cyclization. (B) Two pathways to employ the photoelectrocatalytic strategy: either promoting a single electron transfer with photocatalysis first and a second one with electrocatalysis or vice versa.

Joining the almost unlimited potential of these two interchangeable fields of research would open unprecedented scenarios in chemical synthesis, allowing one to tweak the reactivity of intermediates and excited state species at will, walking on the path carved by the institution of the photon democracy.

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**Author Contributions**

S.C. and M.F. discussed and contributed to the final manuscript. M.F. conceived the original idea.

**Notes**

The authors declare no competing financial interest.

**Biographies**

Maurizio Fagnoni is currently an Associate Professor at the PhotoGreen Lab (Department of Chemistry, University of Pavia, Italy). His academic and professional background is in organic photochemistry and his activity has always been focused on the exploration of the photochemistry of organic molecules and the attending applications in various fields. The photochemical generation of intermediates, e.g., radicals and cations and radical ions by photocatalytic means, is the main topic of his research. Particular attention has been given to the significance of such mild synthetic procedures in the frame of the increasing interest for sustainable green chemistry. He was the recipient in 2019 of the "Elsevier Lectureship Award" from the Japanese Photochemical Association. He was recently coeditor of the book *Photoorganocatalysis in Organic Synthesis* (World Scientific, 2019). Since 2019, he has been the President of the Didactic Council in Chemistry of the University of Pavia.

Stefano Crespi received his Ph.D. in 2017 at the University of Pavia (Italy) under the supervision of Maurizio Fagnoni. He won a two-year fellowship as a Post-Doc in the same University focusing on the study of novel heteroaryl azo photoswitches. He joined the workgroup of Burkhard König at the University of Regensburg, where he studied new scaffolds based on heteroaryl azo dyes and novel photocatalytic transformations. In 2019, he moved to Groningen to work on molecular motors in the group of Ben Feringa as a Marie Skłodowska-Curie fellow. His research interests lie in the combination of reaction design in organic (photo)chemistry with computational models.

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ABBREVIATIONS

Acr’Mes          9-mesitylene-10-methylacridinium  
alil-DHPs         4-alkyl-1,4-dihydropyridines  
BDE              bond dissociation energies  
BI-OAc           benzoiodoxole acetate  
BI-OH            hydroxybenzoiodoxole  
4CzIPN           1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene  
DABSO            1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide)  
DBAD            di-tert-butylazodicarboxylate  
DCN              1,4-dicyanophthalene  
DIAD            disopropyl azodicarboxylate  
DMAc            N,N-dimethylacetamide  
DMAP            4-dimethylaminopyridine  
EY               Eosin Y  
HAT               hydrogen atom transfer  
d-HAT           direct hydrogen atom transfer reaction  
i-HAT           indirect hydrogen atom transfer reaction  
HDAC          histone deacetylase  
HE              Hantzsch ester  
Ir[dpF(CF3)ppy]2(dtbbpy)2+  bis(2-(2,4-difluorophenyl)-5-trifluoromethylpyridine)(di-tert-butyllpyridine)iridium  
fac-Ir(ppy)3  fac-(tris(2,2′-phenylpyridine))-iridium  
[Ir(ppy)2(dtbbpy)]+  bis(2-phenylpyridine) (di-tert-butyllpyridine)iridium  
LB               Lewis base  
NFSI            N-fluorobenzensulfonimide  
NHPI        alkyl N-hydroxpyrrolimidine esters (Pthh-ester)  
PC               photocatalyst  
PCET            proton-coupled electron transfer  
PFBI–OH   perfluoroxybenzoxazole  
PCC            photoorganocatalysts  
RFTA           riboflavin tetracetate  
Ru(bpy)32+  tris(2,2′-bipyridine)ruthenium  
SET              single electron transfer  
TBACN        tetrabutylammonium cyanide  
TBADT      tetrabutylammonium decatungstate  
TBD           1,5,7-triazacyclononane  
TMHD            tetramethylheptanedione  
TMSCN         trimethylsilyl cyanide  
TTMSS           tris(trimethylsilyl)silane  
XAT            halogen atom transfer reaction

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