C-C Bond Forming Reactions

via Photogenerated Intermediates

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1. INTRODUCTION

1.1. Photogeneration of Reactive Intermediates

Reactions via intermediates are widely used in organic synthesis.[1] However, the generation of these highly reactive species under mild conditions and in a predictable way, in accordance with the general principles of Green Chemistry,[2] is not an easy task. Photochemistry is the elective method, since the absorption of a photon leads to the selective delivery of a large amount of energy into an

absorbing molecule and leaves no waste to get rid of after the process, thus offering a smart way to generate active intermediates under controlled conditions.[3]

The mild conditions required, with no need of heating and aggressive chemicals, allows for the control of the fate of the intermediates generated (e.g. by limiting the decomposition processes), thus directing the reaction towards the chosen target. The great advantage of photochemistry is that in most cases other reagents (or impurities) present in solution as well as the reaction medium did not interfere in the formation of the desired intermediate. The use of a photochemical approach has the further advantage that the species can be formed either in the singlet or in the triplet (e.g. for carbenes and cations) state according to the multiplicity of the excited state involved. Actually, among the possible photogenerated species, carbon-based intermediates are by far the most applied in organic synthesis. Typical intermediates are radicals, biradicals, radical ions (radical cations or anions), carbocations, carbanions and carbenes. In the following, a brief description of the photogeneration of these species is offered.

1.1.1 Radicals. The *thermal* generation of carbon-centered radicals is achieved by transfer of an atom (or group of atoms) X from a precursor R-X to a radical M$^{\bullet}$, in turn obtained from the fragmentation of a suitable initiator. The C-X bond to be broken has to be relatively weak (e.g. X = I, Br in alkyl halides) or liable to activation (e.g. the N-O bond in *N*-acyloxythiopyridones, Barton esters[4]). Photochemistry offers several alternatives. Homolytic cleavage of a precursor (typically involving a C-Br, C-I or C-SePh bond, Scheme 1a, path a)[3] is not often adopted due to the poor light absorption of the starting halide and by the occurring of a competitive heterolytic fragmentation to give an ion pair (R^{+} + X^{-}). Barton esters are a convenient choice in this case, because of their strong UV/visible absorption and the easy preparation. The process involves the photocleavage of the N-O bond and carbon dioxide loss from the acyloxy radical to give radical R$^{\bullet}$ (Scheme 1a, path b[4]). Irradiation of (diacyl-oxyiodo)arenes[5] is another way to generate the desired

radical R$^\bullet$ through a similar mechanism. Alternatively, a preformed metal complex (e.g. a Co^I complex) can afford the desired radical upon irradiation (path c).

The main breakthrough, however, is the formation of radicals by the cleavage of a strong C-H bond. Otherwise, this is possible by using a suitable excited photocatalyst (PC*) through an hydrogen atom transfer, HAT (path d).[6-9] Scheme 1b shows a typical photocatalytic cycle where the radical generated added to a radical trap (a double or a triple bond) to form an adduct radical that upon hydrogen back-donation from PC-H$^\bullet$ regenerates PC and gives the end product. Only a few classes of photocatalysts were used for this purpose, namely aromatic ketones (e.g. benzophenone, xanthone, fluorenone, etc.)[6] or polyoxometalates (e.g. the decatungstate anion[8,10]).

Scheme 1. a) Modes of Photogeneration of Radicals b) General Scheme of a Photocatalyzed Hydrogen Atom Transfer (HAT) Reaction
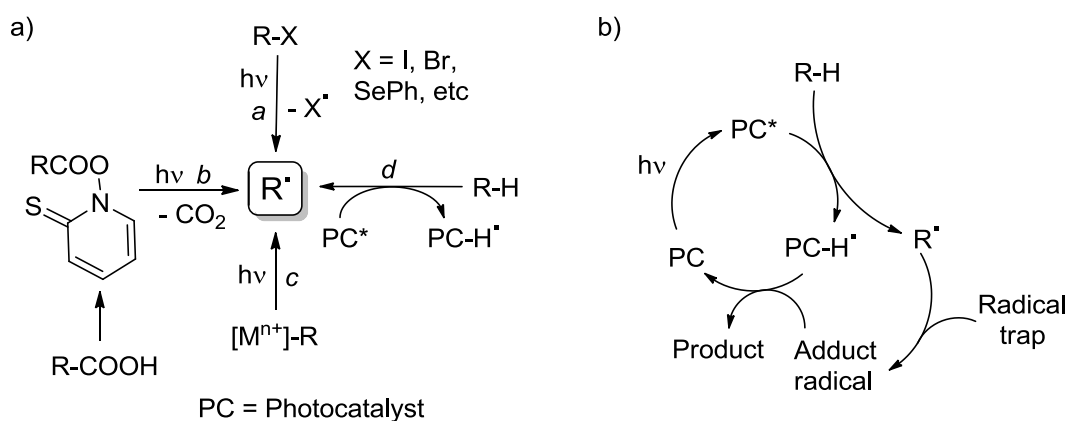
Heteroatom-based radicals (Y$^\bullet$) can be conveniently exploited for the generation of carbon-based radicals. Indeed, the former were generated by the photohomolytic cleavage of a weak bond Y-Z in analogy to carbon-centered analogues (Scheme 2).[3] Usually, the bond broken connects either two heteroatoms, as is the case for N-X (in *N*-halo- amines or amides), S-S (in disulfides), X-X (in dihalogens) or N-O bonds in Barton esters (path a). The direct cleavage of an Y-H bond (path b) is not common and remains mainly limited to S-H or P-H bonds, albeit the process can be promoted

by an excited photocatalyst PC* (path *b'*). Radical Y• can then be exploited for generating a C-centered radical in a secondary process either by hydrogen abstraction (e.g. by thiol radicals from a weak C-H bond in allyl derivatives, path c),[3] or by addition to a double or a triple bond (Scheme 2, path d).
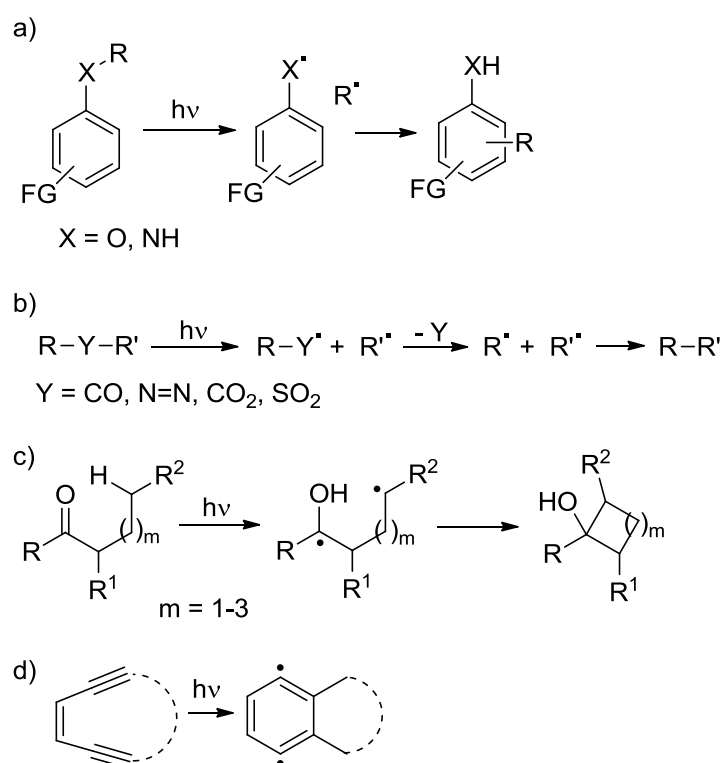
Scheme 2. Use of Photogenerated Heteroatom Based Radicals for the Formation of Carbon Centered Radicals
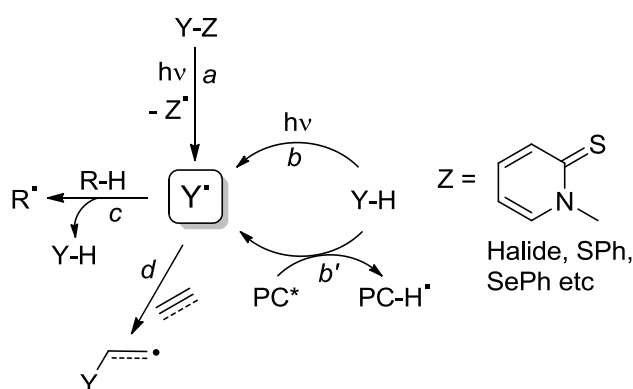
1.1.2. Biradicals or Radical Pairs. The use of biradicals in synthesis is quite rare due to their limited accessibility by thermal reactions. A significant example is the cycloaromatization of enediynes (Bergman reaction) and of allene-enynes (Myers-Saito reaction).[11] On the other hand, the high energy of excited states makes the photofragmentation of a single bond viable,[3,12] and offers an entry to a radical pair or to a biradical when the fragments are linked by a tether. The end products can be obtained either by a reaction at one of the radical centers or by radicals recombination as illustrated in Scheme 3. An example of the latter case is the photo-Fries reaction,[13] where the initial homolytic fragmentation leads to arylated products upon radical recombination (Scheme 3a). In aliphatic derivatives, elimination of a small molecule (CO, nitrogen, etc.) may precede the recombination resulting in an overall extrusion process (Scheme 3b).[14] The Norrish Type II reaction[3,15-17] is widely used for the construction of *n* membered rings induced by the intramolecular hydrogen abstraction from an excited carbonyl and cyclization of the 1,*n*-biradical formed. The

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reaction is well suited for the preparation of cyclobutanes (via hydrogen abstraction from the γ position), but different rings may be accessible when the γ-position bears no hydrogen or it is not geometrically favoured (Scheme 3c). Sparse examples deal with the generation of *p*-benzyne via photoinduced Bergman reaction (Scheme 3d).

Scheme 3. Modes of Photogeneration of Biradicals (Radical Pairs)

a)

b)

R−Y−R' $\xrightarrow{h\nu}$ R−Y$^\bullet$ + R'$^{\bullet\bullet}$ $\xrightarrow{-Y}$ R$^\bullet$ + R'$^{\bullet\bullet}$ $\longrightarrow$ R−R'

Y = CO, N=N, CO_2, SO_2

c)

m = 1-3

d)

1.1.3. Radical Ions. The most intriguing and useful intermediates that are accessible by photochemical means are radical ions. This is because thermal redox processes are not common among organic compounds and often require (apart from electrochemical methods) harsh conditions due to the use of inorganic strong oxidants or reductants (e.g. sodium). Actually, the best way for generating radical ions is making use of photoinduced electron transfer (PET) reactions[3,9,18-22] recently indicated as photoredox catalysis.[23-29] Typically, single electron transfer (SET) is achieved by irradiation of one of two organic molecules (A-Y and D-X) to form a radical ion pair (A-Y$^{\bullet-}$ and D-X$^{\bullet+}$, Scheme 4, path a). A major drawback of the reaction is the facile back electron transfer (bet)

that strongly limits the efficiency of the overall chemical reaction (path b). In successful cases, one of the radical ions is a stable species, whereas the other one undergoes a chemical reaction (path c), such as addition, rearrangement, or fragmentation to give a radical when either the radical anion bears a nucleofugal group (Y^-) or the radical cation bears an electrofugal group (X^+, Scheme 4, path d).

Scheme 4. Photogeneration and Fate of Radical Ions

$$A\text{-}Y \xrightarrow{h\nu} A\text{-}Y^* \xrightarrow[a]{D\text{-}X} A\text{-}Y^{\bullet-} + D\text{-}X^{\bullet+} \xrightarrow{b} A\text{-}Y + D\text{-}X$$

$$D\text{-}X \xrightarrow{h\nu} D\text{-}X^* \underset{A\text{-}Y}{\overset{a}{\nearrow}} \qquad \underset{\substack{\text{Fragmentations} \\ \text{(Radicals)}}}{\overset{d}{\searrow}} \overset{c}{\searrow} \text{Reactions}$$
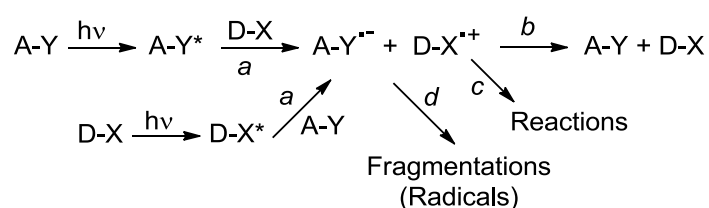
Alternatively, a radical ion (or a radical from it) can be formed through a SET reaction with an excited photocatalyst (PC*), as illustrated in Scheme 5. Thus, PC* oxidizes or reduces an organic molecule R-X to the corresponding radical ion (path a') that then reacts according to paths b' or c', d', with the concomitant formation of the reduced (PC_{red}) or oxidized (PC_{ox}) form of the photocatalyst. A purposely added sacrificial electron donor or acceptor E is responsible for the regeneration of the starting PC (Scheme 5a, path e'). On the other hand, a SET reaction between PC* and E (path a'') may generate PC_{red} or PC_{ox} that functions as a ground state reductant (or oxidant), respectively, causing the conversion of a reagent (R-Y) into the corresponding radical ion (path b'') or radical from it (Scheme 5b, path d''). However, the most convenient situation occurs when PC is regenerated at a different point in the reaction mechanism, with no need of E and thus resulting in a redox neutral reaction.[24] A radical chain process can, however, explain the fate of the reaction as recently reported in the reinvestigation of the mechanism of some photoredox processes.[30] In most cases it would be convenient to incorporate suitable X or Y groups in order to make the organic compounds more oxidizable or reducible. These electroauxiliary groups[31] have

the advantage to be lost in the fragmentation of radical ions (if any), thus allowing an easy formation of the corresponding radicals (paths c' and d'').

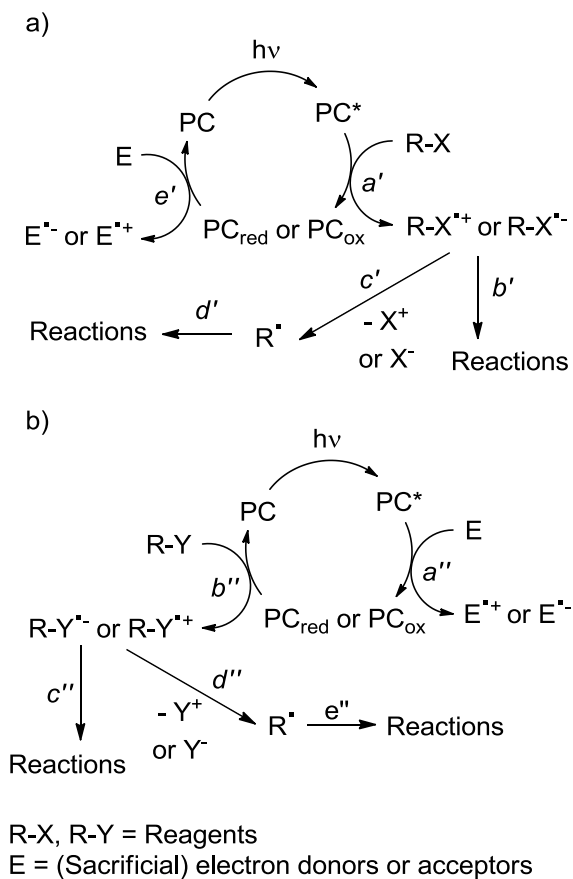**Scheme 5. General Scheme of Photoredox Catalysis**

a)

$h\nu$

PC → PC*

E →

PC* $\xrightarrow{a'}$ R-X

e'

PC$_{red}$ or PC$_{ox}$

E$^{\bullet-}$ or E$^{\bullet+}$

R-X$^{\bullet+}$ or R-X$^{\bullet-}$

c'

d'

b'

Reactions ← R$^{\bullet}$

- X^{+} or X^{-}

Reactions

b)

$h\nu$

PC → PC*

R-Y →

PC* $\xrightarrow{a''}$ E

b''

PC$_{red}$ or PC$_{ox}$

R-Y$^{\bullet-}$ or R-Y$^{\bullet+}$

E$^{\bullet+}$ or E$^{\bullet-}$

c''

d''

- Y^{+} or Y^{-}

R$^{\bullet}$ $\xrightarrow{e''}$ Reactions

Reactions

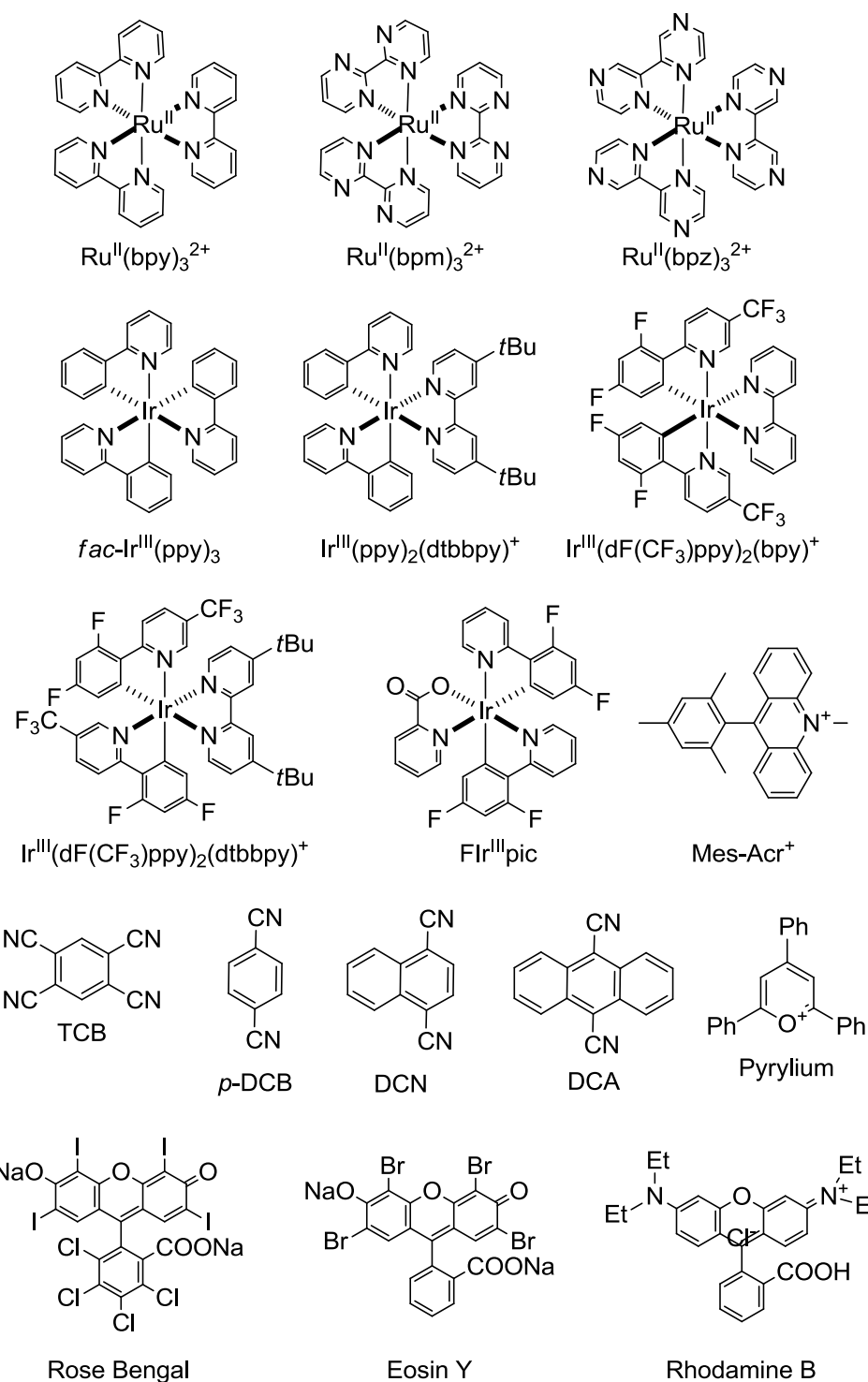R-X, R-Y = Reagents
E = (Sacrificial) electron donors or acceptors

Chart 1 collects most of the photoredox catalysts used in synthesis.

Chart 1. Common Photoredox Catalysts Used for (Visible Light) C-C Bond Formation in Synthesis

Ru^{II}(bpy)$_3^{2+}$ Ru^{II}(bpm)$_3^{2+}$ Ru^{II}(bpz)$_3^{2+}$

fac-Ir^{III}(ppy)$_3$ Ir^{III}(ppy)$_2$(dtbbpy)$^+$ Ir^{III}(dF(CF$_3$)ppy)$_2$(bpy)$^+$

Ir^{III}(dF(CF$_3$)ppy)$_2$(dtbbpy)$^+$ FIr^{III}pic   Mes-Acr$^+$

TCB   *p*-DCB   DCN   DCA   Pyrylium

Rose Bengal   Eosin Y   Rhodamine B

Ru^{II}(bpy)$_3^{2+}$ = tris-(2,2'-bipyridine)ruthenium; Ru^{II}(bpm)$_3^{2+}$ = tris-(2,2'-bipyrimidine)ruthenium; Ru^{II}(bpz)$_3^{2+}$ = tris-(2,2'-bipyrazine)ruthenium; *fac*-Ir^{III}(ppy)$_3$ = *fac*-(tris-(2,2'-

phenylpyridine))iridium; $Ir^{III}(ppy)_2(dtbbpy)^+$ = bis-(2-phenylpyridine)(di-*tert*-butylbipyridine)iridium; $Ir^{III}(dF(CF_3)ppy)_2(bpy)^+$ = bis-(2-(2',4'-difluorophenyl)-5-trifluoromethylpyridine)(2,2'-bipyridine)iridium; $Ir^{III}(dF(CF_3)ppy)_2(dtbbpy)^+$ = bis-(2-(2',4'-difluorophenyl)-5-trifluoromethylpyridine)(di-*tert*-butylbipyridine)iridium; $FIr^{III}pic$ = bis-(2-(4,6-difluorophenyl)pyridine)(picolinato)iridium; $Mes-Acr^+$ = 9-mesityl-10-methylacridinium salt; TCB = 1,2,4,5-tetracyanobenzene; *p*-DCB = 1,4-dicyanobenzene; DCN = 1,4-dicyanonaphthalene; DCA = 9,10-dicyanoanthracene; Pyrylium = 2,4,6-Triarylpyrylium salt.

The feasibility of the initial PET reaction depends on the reduction (E_{RED} $R/R^{•-}$) or oxidation (E_{OX} $R^{•+}/R$) potential of the reagent R to be reduced or oxidized. Figures 1 and Figures 2 gather the oxidation and reduction potentials, respectively, of some organic molecules in comparison with the reduction (E^*_{RED} $PC^*/PC^{•-}$) or oxidation (E^*_{OX} $PC^{•+}/PC^*$) potential in their excited states of common photocatalysts. Thus, apart from ascorbate anion, the only easily oxidized organic compounds are amines,[32,33] carboxylate anions and thiolate ion (E_{OX} ca. 1V vs SCE), whereas olefins are easily oxidized only when susbstituted with one or more electron-donating groups (e.g. vinyl ethers or ketene silyl acetals) or with three or four alkyl groups (e.g. tetramethylethylene). Unsubstituted alcohols, ethers, ketones, nitriles and hydrocarbons are generally very difficult to oxidize (E_{OX} > 3V vs SCE, Figure 1). On the contrary, carbon based radicals are more easily oxidized with respect to the neutral molecules if the resulting cation is sufficiently stabilized (e.g. the benzyl radical).

As for the photocatalysts, cyanoarenes are the most powerful oxidants (see the case of TCB with a E^*_{RED} of 3.44 V vs SCE). Visible light absorbing $Mes-Acr^+$ and pyrylium salts have been used when a good oxidant was required, since Ru^{II} or Ir^{III} complexes are modest oxidants in their excited states. However, the possible derivatization of the ligands and the formation during the reaction of

metal species having different oxidation states (e.g. Ru^I or Ru^{III} in the former case) expands the applications of these photoredox catalysts.[23,24]

Figure 1. Oxidation Potential of Selected Organic Molecules (and Radicals) in Comparison with the Reduction Potential in the Excited State of Common Photocatalysts
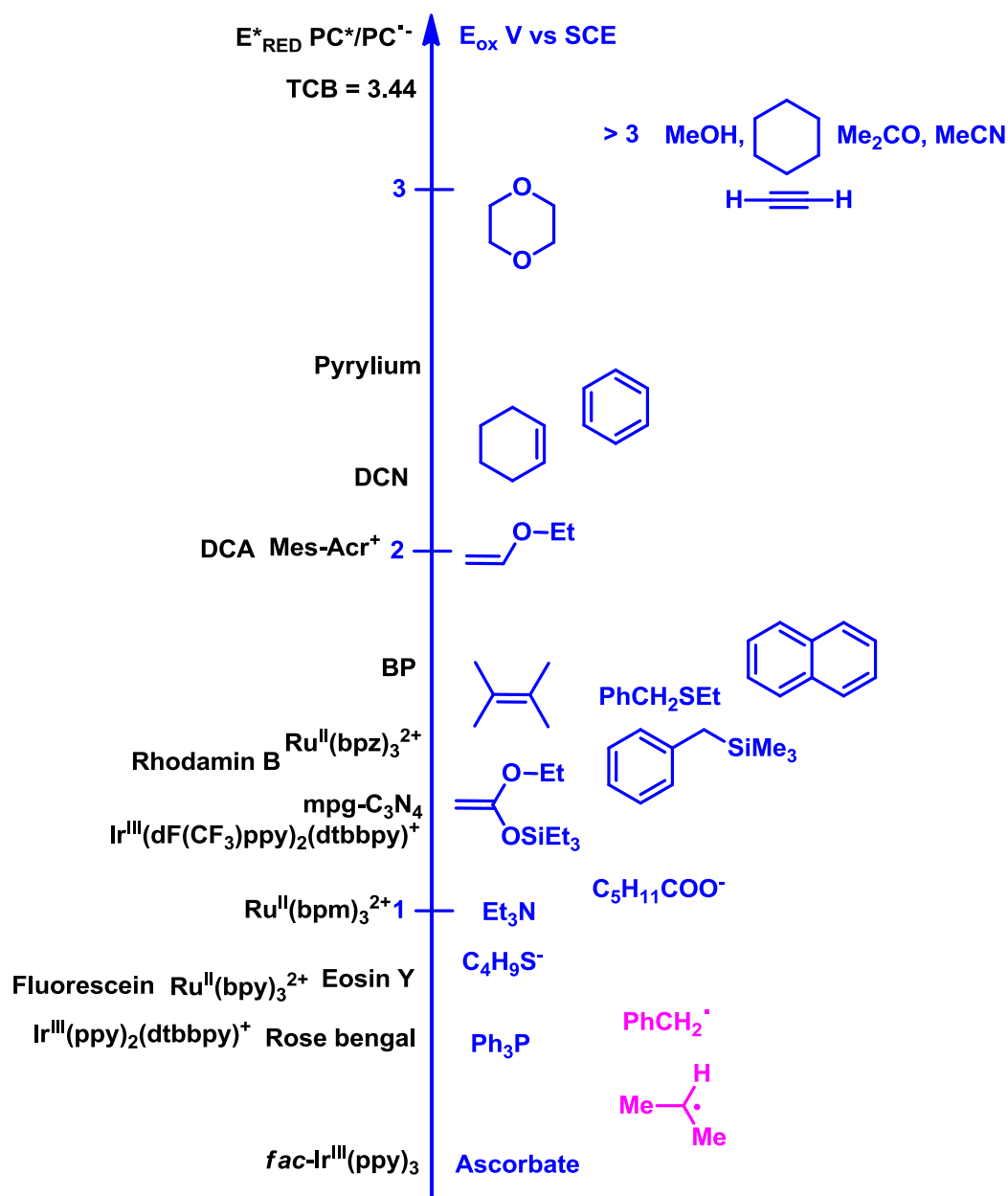
BP = Benzophenone; mpg-C_3N_4 = mesoporous graphitic carbon nitride (see also Chart 1).

Positively charged derivatives such as aryl diazonium salts are smoothly reduced and the same holds true for α-bromo carbonyls ($E_{RED} > -1V$ vs SCE, Figure 2). Electron-poor olefins have roughly E_{RED} ca. -2V vs SCE, except particular cases such as maleic anhydride. As for aromatic halides, the order of reducibility is ArI > ArBr > ArCl. Even in this case radicals giving stabilized anions upon reduction, have a favorable reduction potential (e.g. $^{\bullet}CH_2COOEt$, Figure 2). Notably, Cu^I or dimeric $Au^I_2{}^{2+}$ based complexes performed better than Ru^{II} based complexes as reductant in the excited state.

Figure 2. Reduction Potential of Selected Organic Molecules (and Radicals) in Comparison with the Oxidation Potential in the Excited State of Common Photocatalysts
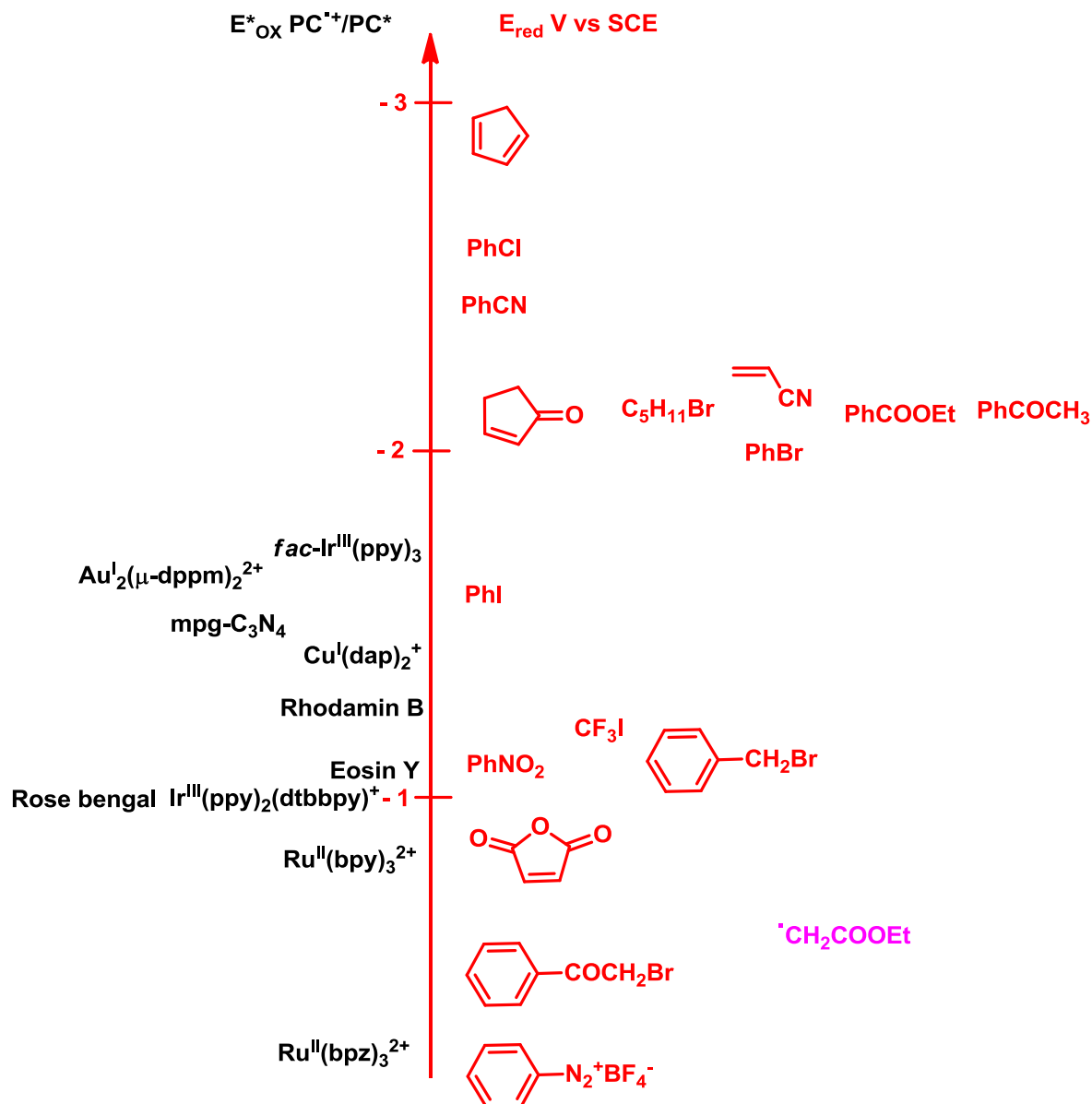

dap = 2,9-bis(*para*-anisyl)-1,10-phenanthroline; dppm = 1,1-bis(diphenylphosphino)methane (see also Chart 1).

The $S_{RN}1$ mechanism is another important source of radical anions for valuable nucleophilic substitution reactions initiated by an electron transfer process.[34] A simplified general scheme of an

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$S_{RN}1$ reaction is depicted in Scheme 6a, where the radical anion of the substrate R-X is formed by (photostimulated) reaction with a (carbon) charged nucleophile (Nu^-) or other electron sources (e.g. a strong base). Fragmentation of the thus formed radical anion and addition of the resulting radical onto the nucleophile affords R-Nu$^{\bullet-}$. The propagation cycle is assured by the release of the end product (R-Nu) with the concomitant formation of R-X$^{\bullet-}$. The radical anions of (hetero)aromatics have an important role in Ar-C bond formations via the $ArS_{RN}1$ reaction.[34-37] The general mechanism is depicted in Scheme 6b where the photoinduced electron transfer between an aryl halide and an enolate anion generates the radical anion of the aromatic ($ArX^{\bullet-}$) that upon halide anion release and coupling with the enolate gives the desired α-arylated carbonyl.

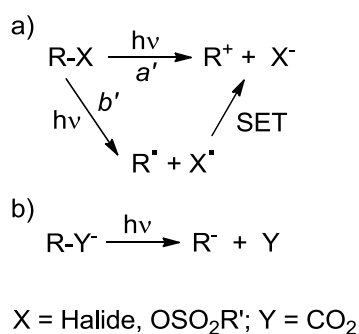**Scheme 6. General Scheme of an $S_{RN}1$ Reaction**
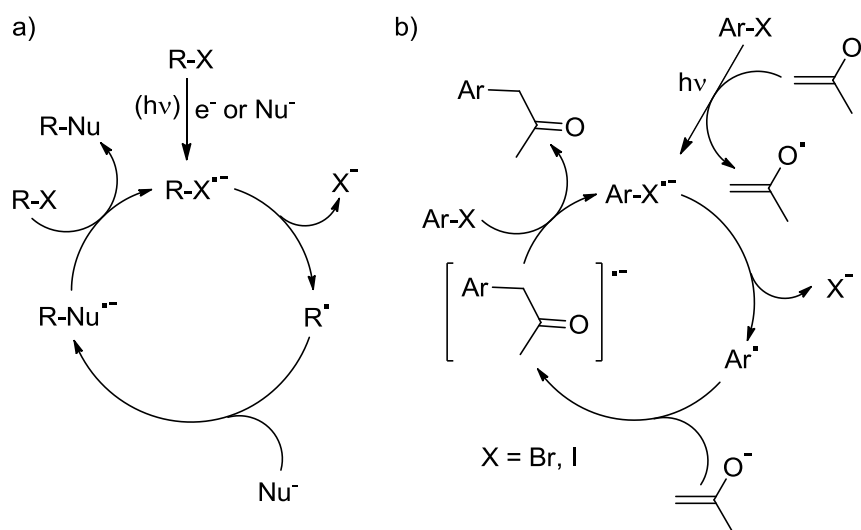
1.1.4. Cations and Anions. Carbocations and carbanions have been most often generated by photoheterolysis (Scheme 7).[3] The thermal formation of carbocations is restricted to the S_N1 reaction involving the solvolysis of C-halogen (or C-O) bond in alkyl halides (or sulfonates). The process, however, is only applicable for the formation of stable (usually tertiary or benzylic) carbocations. The high energy of excited states makes the formation of unstable (e.g. vinyl or aryl[38]) carbocations viable via cleavage of a C-halide bond (Scheme 7a, path a') or to a lesser extent of a C-

O bond (e.g. in sulfonates or phosphates). As mentioned before, competitive photohomolysis could be a severe limitation for a clear cut process unless an electron transfer within the radical pair leads to the desired ion pair (Scheme 7a, path b'). The two pathways to carbocations have not always been clearly distinguished.[3]

On the other hand, carbanions have a tremendous role in organic chemistry for building C-C bonds, in particular for the case of enolates (or related anions) formed by deprotonation of a C-H bond. The photogeneration of anions for synthetic purposes has a very limited scope and mostly involves photodecarboxylation reactions (Scheme 7b).[3,39]

Scheme 7. Modes of Photogeneration of Carbocations and Carbanions

a)

$$R\text{-}X \xrightarrow[a']{h\nu} R^+ + X^-$$

$$R\text{-}X \xrightarrow[b']{h\nu} R^{\bullet} + X^{\bullet} \xrightarrow{SET} R^+ + X^-$$

b)

$$R\text{-}Y^- \xrightarrow{h\nu} R^- + Y$$

$$X = \text{Halide, } OSO_2R'; \; Y = CO_2$$

1.1.5. Carbenes. The role of photogenerated carbenes in the formation of C-C bonds is not as important as that of carbon-centered radicals.[3,40] The simplest way to form a carbene is by photolysis of either the corresponding diazo compound or of a diazirine (Scheme 8a). The typical reactivity of the resulting carbene is the addition onto a double or a triple bond to form a three membered ring. A particular case is that of the Wolff rearrangement where a carbene (and a ketene from it) is formed starting from α-diazocarbonyl or carboxyl compounds.[41,42] Ketenes have been used for the synthesis of four membered rings via [2+2] cycloadditions and, more recently, in multicomponent reactions.[43] A recent approach makes use of the photoinduced conversion of acyl silanes into the corresponding siloxycarbenes (Scheme 8b).

Scheme 8. Modes of Photogeneration of Carbenes

Wolff rearrangement
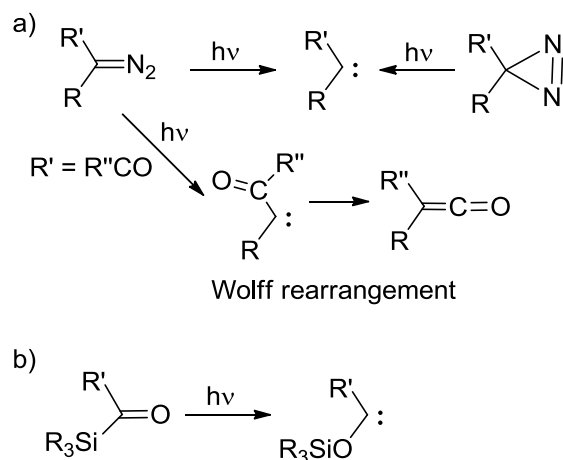
Aim of this review is to collect the most significant applications of photogenerated intermediates for the formation of C-C bonds with particular regards to publications reported from year 2000 onwards.

2. FORMATION OF A RING

The construction of a ring (from three membered to medium-sized or larger rings) can be accessed via ring contraction, ring enlargement as well as by a cyclization reaction.[3] Several reactions belong to this class, witnessing the importance of photogenerated intermediates for this important target.

2.1. Three Membered Rings

The formation of three membered rings is limited to cyclopropanes. Ring contraction by photoextrusion of CO, N_2 and SO_2 is a largely adopted strategy.[14] An early example involved the irradiation of 2-phenylthietan-1,1-dioxides (**1a-c**) to give phenyl cyclopropanes, (**3a-c**) where the stabilization imparted by the phenyl group on the biradical intermediates **2a-c** was the driving force of the reaction (Scheme 9).[44]

Scheme 9. Synthesis of Cylopropanes via Photogenerated Biradicals

3a, R = Me, 95%
b, R = C$_6$H$_5$CH$_2$, 92%
**c**, R = H, 95%
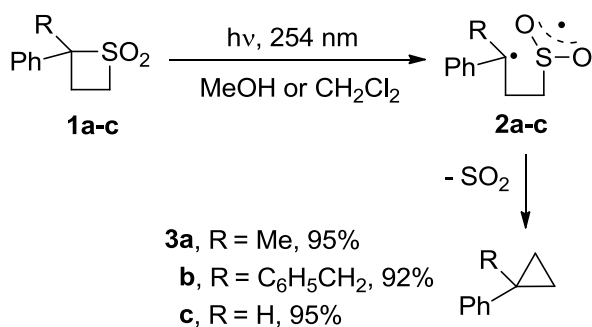
The multiplicity of the excited state has a role in the photoextrusion process, as demonstrated in the reaction of cyclobutanone **4** where the synthesis of cyclopropane **5** was successful only under acetone sensitization, while direct photolysis led to the corresponding decarbonylated alkene. Again, the photodecarbonylation reaction was promoted by the stabilizing effect exerted by the presence of α-substituents (e.g. the methyl groups in **4**, Scheme 10).[45]

Scheme 10. Formation of a Three Membered Ring via Photoextrusion of CO


5, 85%
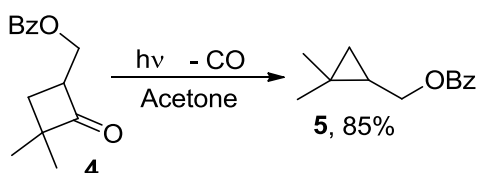
The same approach was used as the key step in the preparation of natural compounds. Recent examples are the total synthesis of terpenoids echinopines A and B, where the smooth photoextrusion of nitrogen in diazoderivative **6** afforded ester **7** via a biradical intermediate (Scheme 11),[46] and the synthesis of prostratin (12-deoxyphorbol-13-acetate).[47]

Scheme 11. Synthesis of Echinopines A and B

$$\text{6} \xrightarrow[\text{C}_6\text{H}_6,\ 6\text{h}]{h\nu\quad -\text{N}_2} \text{7, 66\%}$$

R = H, Echinopine A
R = Me, Echinopine B
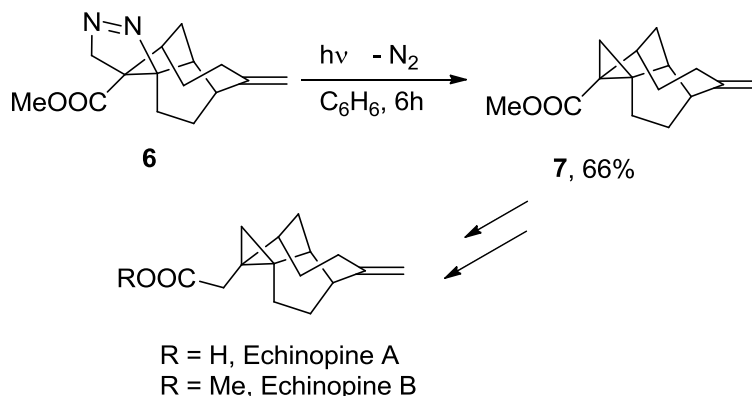
In rare instances, three-membered rings were formed by a Norrish II reaction involving aromatic ketones bearing a good leaving group (e.g. a mesyloxy group) in the α-position (**8a,b**). Thus, γ-hydrogen abstraction was followed by the elimination of MsOH and cyclopropylketones **10,b** were formed upon cyclization of the resulting 1,3-biradicals (**9a,b**, Scheme 12).[48,49] The reaction required *N*-methylimidazole in order to buffer the acidity liberated and gave exclusively the *trans*-adducts depending on the substituent R.

Scheme 12. Synthesis of Cyclopropylketones Promoted by a Norrish II Reaction

10a, R = Me, 90%
b, R = COOMe, 59%
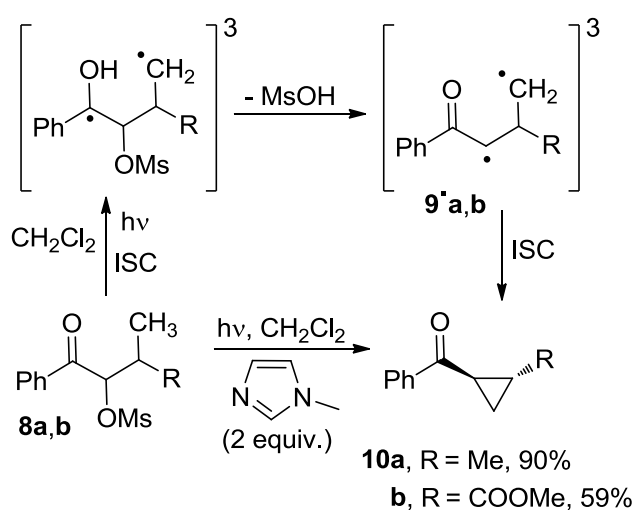
Photoredox catalysis was used for the cyclopropanation of alkenes. The strategy relied on the formation of carbanion **14⁻** via a double mono-electronic reduction of dibromomalonate **11** by

$Ru^I(bpy)_3^+$ generated from the corresponding Ru^{II} complex in the presence of a reductive quencher (iPr$_2$NEt, Scheme 13).[50] The overall yields were very good and the fact that the process could be carried out under sunlight irradiation is an added bonus.

Scheme 13. Photoredox Catalyzed Cyclopropanation of Alkenes
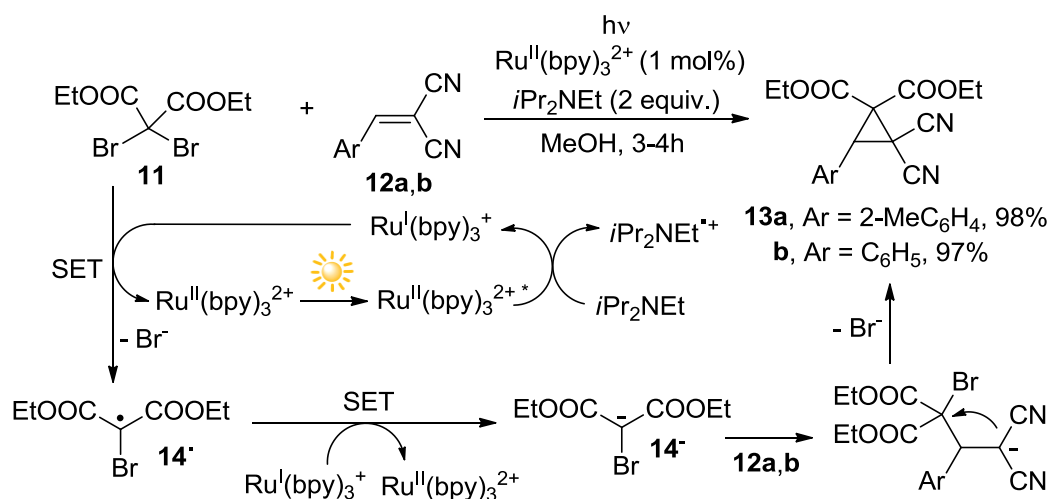
Another possible pathway for the construction of three membered rings makes use of an intramolecular addition of a radical ion onto a C=N bond via a PET induced 1-aza-di-π-methane rearrangement.[51]

A single case deals with the formation of cyclopropenes. 3-(p-Cyanophenyl)-5,5-dimethyl-4-phenyl-5H-pyrazole (**15**) was photochemically converted to the vinyldiazo **16** that upon further irradiation gave **18** in an almost quantitative yield with the intermediacy of carbene **17** (Scheme 14).[52]

**Scheme 14. Preparation of Cyclopropenes via Photogenerated Carbenes**
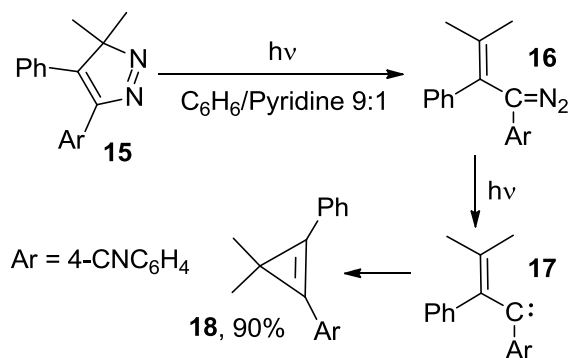
2.2. Four Membered Rings

Cyclobutane or, to a lesser extent, azetidines and lactams are mainly formed by cyclization, cycloaddition or ring expansion. In the former case, biradical intermediates were largely used in the construction of the cyclobutane moiety, in most cases with a high degree of stereoselectivity. The Norrish-Yang cyclization, when applied to carbohydrate models[53,54] such as 1-glycosyl-2,3-butandiones (**19**), gave chiral cyclobutanols (**20**) in a quantitative yield (Scheme 15).[53] The presence of the 1,2-diketone moiety in **19** allowed for the use of sunlight. A related cyclization was later applied to the total synthesis of (+)-lactacystin.[55]

Scheme 15. Chiral Cyclobutanols from Solar Irradiation of 1-Glycosyl-2,3-butandiones
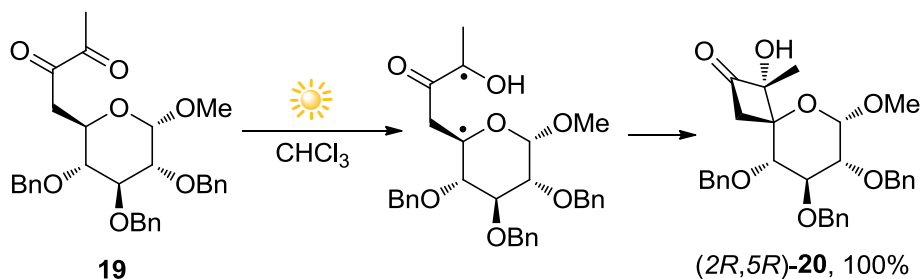
The diastereoselectivity of the Norrish-Yang cyclization was increased when the starting ketone was irradiated in the solid state. As an example, photolysis of the chiral derivative of 2,4,6-triisopropylbenzophenone (**21**) in acetonitrile led to an equimolar amount of the (*S*,*S*)-**22** and the

(*R*,*S*)-**22** isomers (Scheme 16). On the contrary, the irradiation of crystals of **21** formed the (*R*,*S*)-**22** isomer exclusively.[56] Similarly, the chiral ammonium salts of 2,2-diethyl-1-tetralone-6-carboxylic acid gave an enantioselective cyclobutanol formation upon reaction at -43 °C in the solid state.[57]

Scheme 16. Enantioselective Cyclobutanol Formation in the Solid State
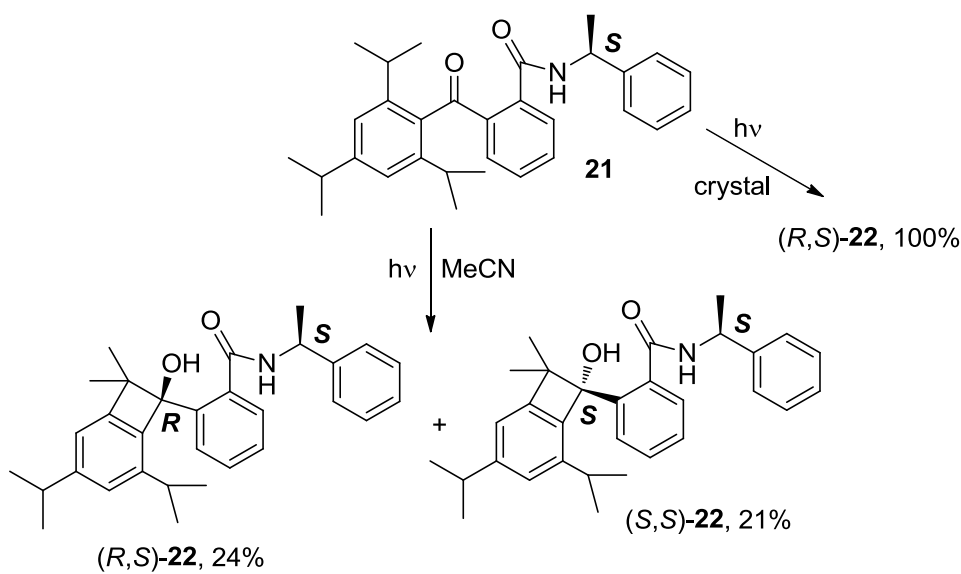
In alternative, the solid compound could be irradiated in an aqueous suspension, as it was reported for the synthesis of **25**, a key compound for the preparation of the bioactive cardenolide ouabagenin (Scheme 17).[58] In details, adrenosterone **23** was converted into diketal **24** and the ensuing irradiation in the presence of a surfactant (SDS) caused the clean formation of cyclobutanol **25** (2.5 g scale).

Scheme 17. Synthesis of Ouabagenin
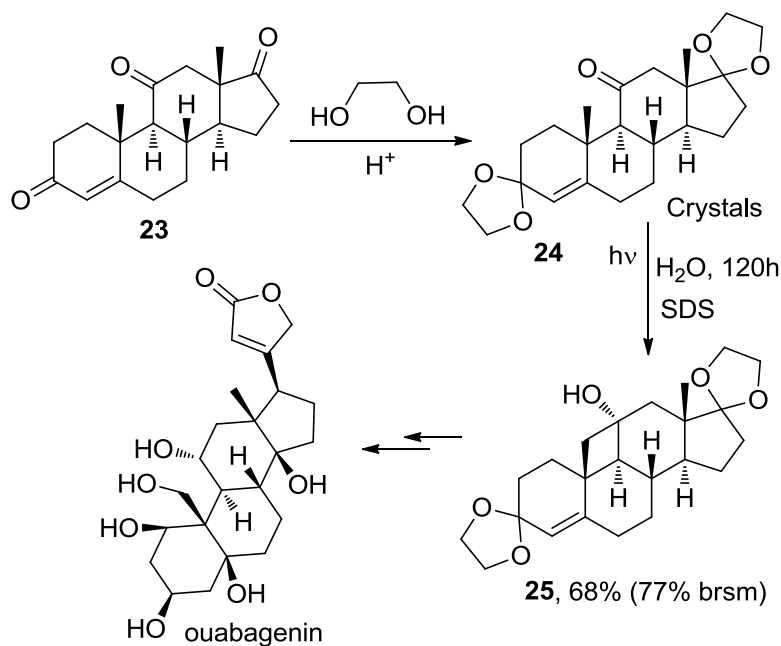
The photoinduced intramolecular γ-hydrogen abstraction process was found to be suitable for the synthesis of nitrogen containing four membered rings, as demonstrated in the preparation of azetidinols.[59] β-lactams were likewise accessible with a good ee (*ca.* 60%) when a water suspension of a glyoxylamide precursor was irradiated in the presence of a chiral host and hexadecyltrimethylammonium bromide as the surfactant.[60]

Another widely employed approach for the formation of four-membered rings is the [2+2] photocycloaddition of alkenes initiated by a SET process.[6,22] The reaction has been applied both to electron-rich **27** and electron-poor alkenes **26**, as shown in Scheme 18, and both cyclodimerizations (by using a single alkene) and cross cycloadditions between two different olefins have been carried out. Indeed, the cyclodimerization of phenyl(aryl) vinyl ethers has been studied under both homogeneous[61,62] and heterogeneous[63,64] conditions.

Scheme 18. Synthesis of Cyclobutanes via Photoredox [2+2] Cycloaddition

PC = Photocatalyst
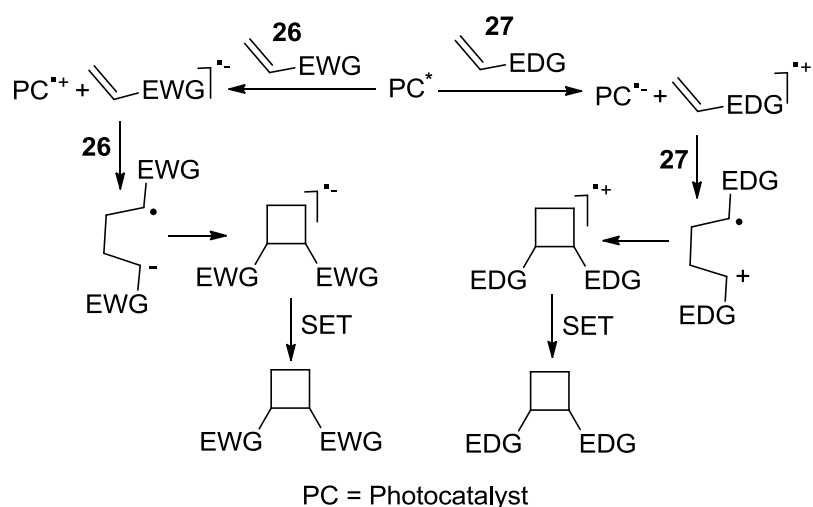
Recently, cross cycloaddition reactions based on the different redox properties of the two electron-poor olefins have been developed. Accordingly, the coupling of enone **28** with enone **29** was successful because of the easier reducibility of the former (Scheme 19).[65] A Ru^{II} complex was used here in the role of photocatalyst and ambient sunlight was sufficient to promote the reaction. The lithium cation functioned as Lewis acid and it was postulated to activate the enone toward one-electron reduction.

Scheme 19. Cross Cycloaddition Reactions of Enones

30, 84%, dr > 10:1
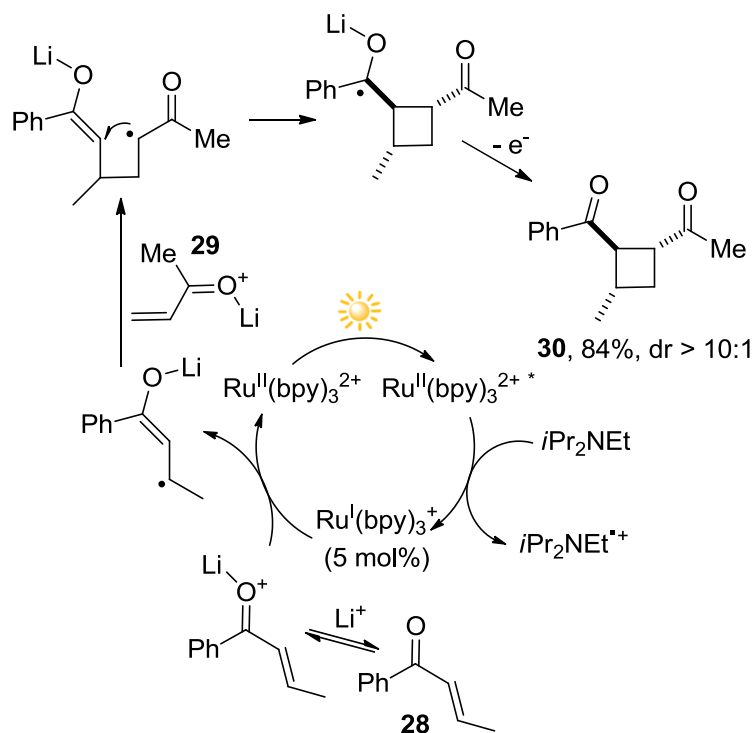
When the starting compound contains two olefinic moieties, an intramolecular reaction can take place, as in the case of the preparation of macrocyclic 2,ς-dioxabicyclo[n.2.0] ring systems.[66] In a related case, the intramolecular reaction led to the formation of another ring along with the four membered one (see also Section 2.6).[67,68]

A recent approach makes use of a dual photoredox and gold-catalyzed reaction through an arylative ring expansion of cycloalkanols (**31a,b**, Scheme 20). The photocatalyst generated an aryl radical (from an aryl diazonium salt) that was trapped by an Au[I] complex. Subsequent oxidation and reaction with **31a,b** gave the hoped for cyclobutanones **32a,b** upon ring expansion.[69]

Scheme 20. Dual Catalytic Approach for the Preparation of Cylobutanones
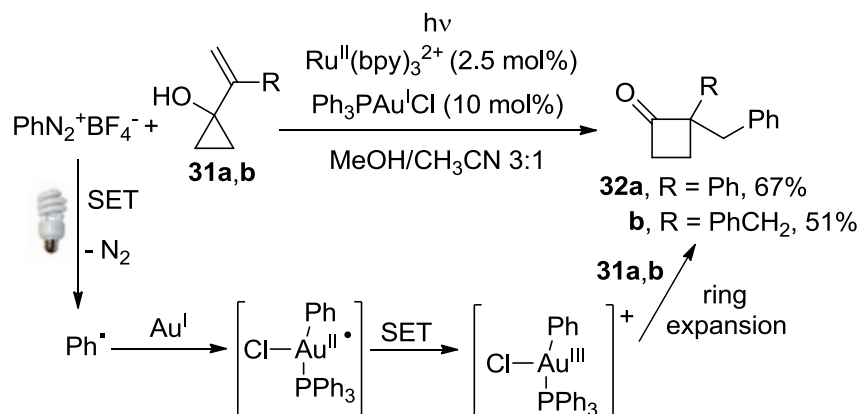
A different smooth strategy to β-lactams is based on the photogeneration of ketenes by Wolff rearrangement.[42,42] Thus, irradiation of diazo ketone **33** in the presence of imine **34** gave the lactam ring (compounds **35** and **36**), preferentially in the *trans* configuration (Scheme 21).[70,71]

Scheme 21. Synthesis of Lactams

72%, **35:36** = 92:8
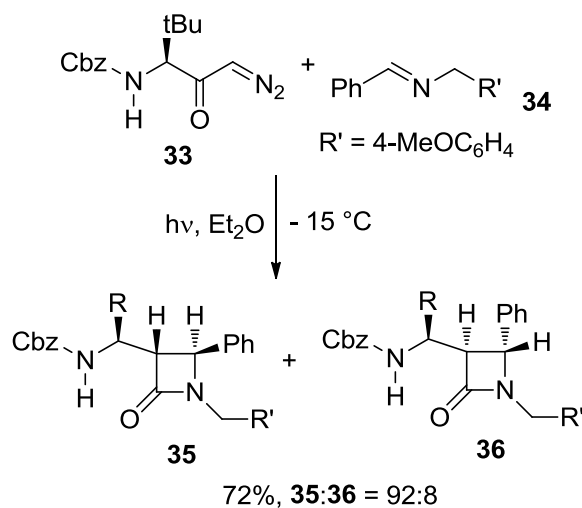
2.3. Five Membered Rings

The versatility in the photochemical formation of five membered rings is witnessed by the formation of both carbocyclic (cyclopentanes and cyclopentenes) and various heterocyclic

compounds, in some cases containing even more than one heteroatom. Ring contraction or enlargement or having recourse to a cyclization reaction are the elective strategies used.

2.3.1. Carbocycles. A valuable approach for the synthesis of cyclopentanes involves the ring contraction of cyclohexanone derivatives through a decarbonylation process induced by a Norrish I reaction, especially when the process is carried out in the solid state.[14] A typical example is the preparation of α-cuparenone (±-**38**) by photoelimination of CO from cyclohexadienone **37** either in the racemic form (Scheme 22) or in the chiral form by making use of chiral difluorodioxaborinane complexes.[72] Related decarbonylations were applied to the synthesis of (±)-herbertenolide[73] and of bicyclo[3.2.1]octane derivatives.[74]

Scheme 22. Synthesis of (±)-α-Cuparenone by Photoinduced Ring Contraction
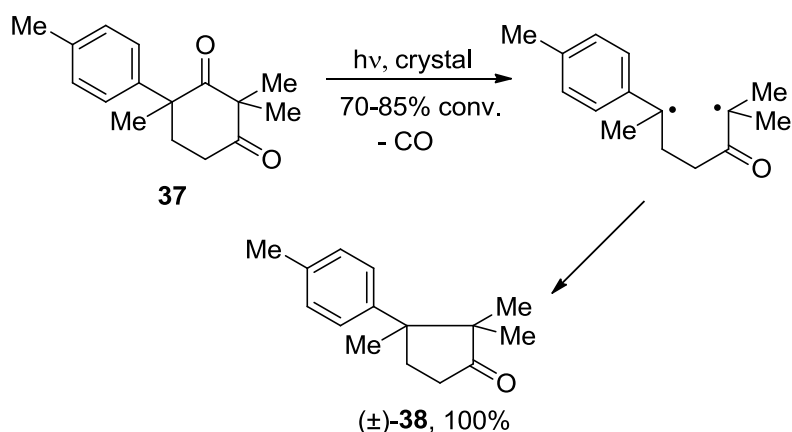
Different ways have been reported to accomplish the synthesis of cyclopentanes by a cyclization process. As an example, 2-aroylaryl radicals were photogenerated by homolytic Ar-Br cleavage in 2-halobenzophenones. The resulting radical cyclized affording fluorenones in an almost quantitative yield.[75]

The construction of five membered rings was easily promoted by the intermediacy of radical ions, either by radical cyclization or by ring opening of cyclopropanes under photocatalyzed conditions. In the first case, the initial oxidation of a vinyl ether bearing a selenyl group caused the elimination

of the PhSe$^•$ radical and the resulting cation gave the final cyclopentyl ketone upon cyclization onto a vinyl moiety.[76] Cyclization reactions were also promoted by a monoelectronic reduction (Scheme 23). The process could be initiated by the radical anion of 9,10-dicyanoanthracene (DCA) that was able to reduce the carbonyl moiety present in enone **39**. The thus formed enolate radical anion **39$^{•-}$** underwent a radical cyclization to form cyclopentane **40** (*trans*-1,2-stereochemistry preferred) via a C-C bond formation.[77] Triphenylphospine **41** was used here as reductive quencher (Scheme 23).

Scheme 23. DCA Photocatalyzed Construction of a Cyclopentane Ring

40, 98%,
(*trans/cis* 85:15)
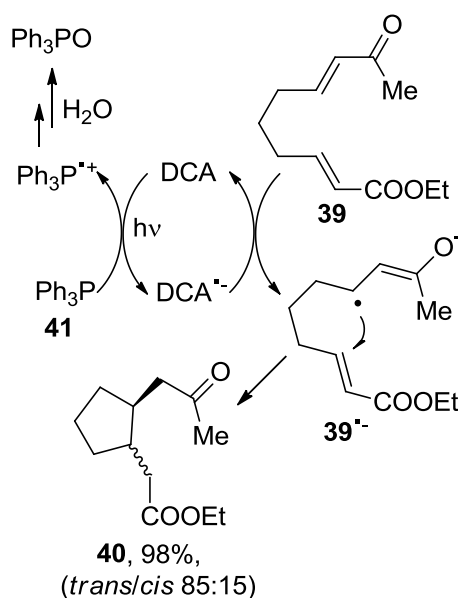
Another recent example is shown in Scheme 24, where mesoporous graphitic carbon nitride (mpg-C$_3$N$_4$) was used in the role of heterogeneous photocatalyst. Functionalized cyclopentanes (**43a,b**) were easily formed under flow conditions and LED irradiation by a radical cyclization starting from substituted 2-bromo-1,3-dicarbonyls (**42a,b**). THF was used as the solvent in the double role of electron and hydrogen donor.[78]

Scheme 24. Mesoporous Graphitic Carbon Nitride Photocatalyzed Synthesis of Substituted Cyclopentanes
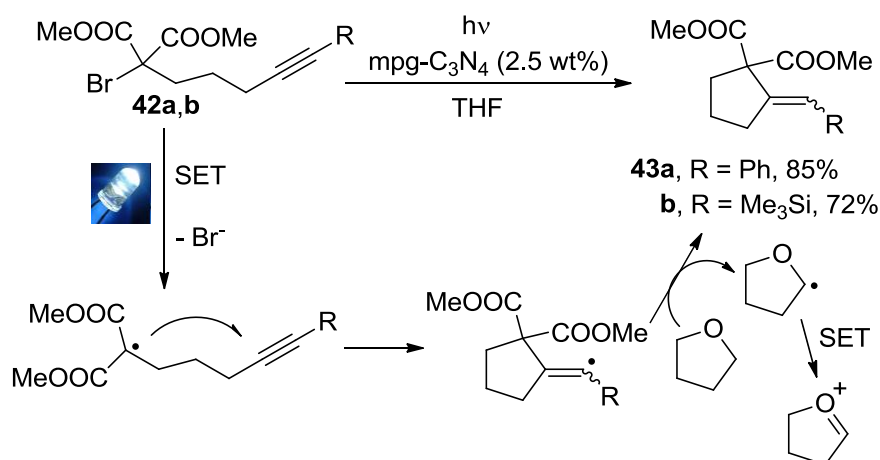
A photogenerated carbene was found useful for the construction of a cyclopentene ring. Thus, photolysis of acyl silane **44** generated the siloxycarbene **46** that in turn underwent a 6-π electrocyclization to **47** and a 1,5-hydride shift to give the desired enol ether **45** (Scheme 25). However, the reaction was only tested so far in small amounts in a NMR tube.[79]

Scheme 25. Cyclopentenes via Photogenerated Siloxycarbenes
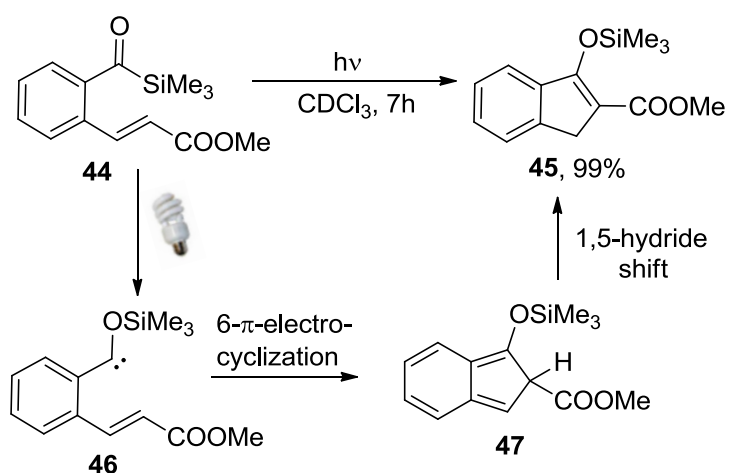
Scheme 26 illustrates a representative case of ring opening of cyclopropanes in the synthesis of cyclopentenes. The aniline **49** was oxidized by the Ru[II] catalyst causing a ring opening to the

distonic radical cation **51**[·+] that upon addition to propiolate **48** and cyclization, formed the five membered ring and the desired cyclic allylic amine **50** upon SET with Ru[I] complex.[80] Related [3+2] cycloadditions have been reported for the synthesis of cyclopentanes or cyclopentenes by oxidative or reductive ring opening of three membered rings.[81-83]

Scheme 26. Photocatalyzed Addition of a Cyclopropyl Amine onto Methyl Propiolate
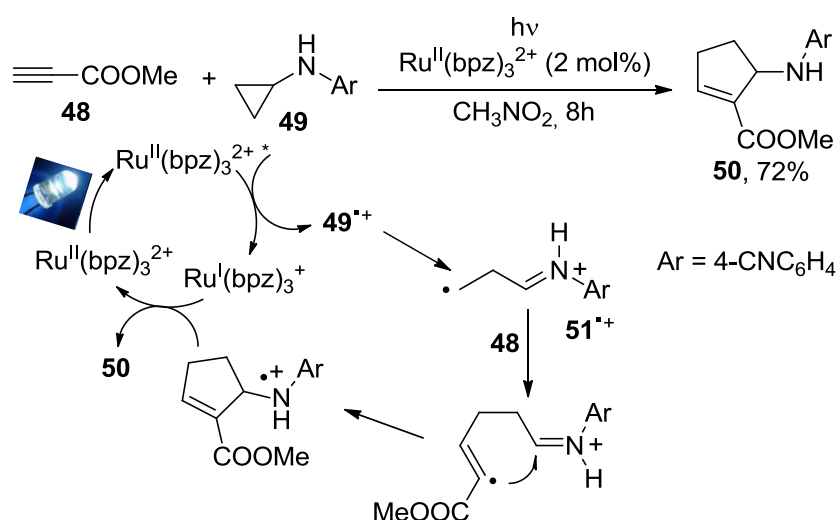
2.3.2. Nitrogen Containing Heterocycles. The Norrish-Yang cyclization was used for the preparation of nitrogen containing heterocycles (mainly pyrrolidines, a key motif in natural occurring compounds), provided that an efficient intramolecular δ-hydrogen abstraction took place.[16,17] An intriguing case was the photocyclization of the *N*-trialkylanilinium cation (**52**[+], as the tetrafluoroborate salt) that smoothly occurred both in solution (MeCN) and in the solid state to afford **54**[+], in up to quantitative yield due to the favoured formation of the 1,5-biradical **53**[+] (Scheme 27).[84] In a similar way, the core of the pyrrolizidine alkaloid (±)-isoretronecanol[85] as well as substituted tetrahydropyrrolo[2,1-*a*]isoindol-5-ones[86] have been prepared.

Scheme 27. Photocyclization of *ortho*-Benzoyl *N*-Trialkylanilinium Cations
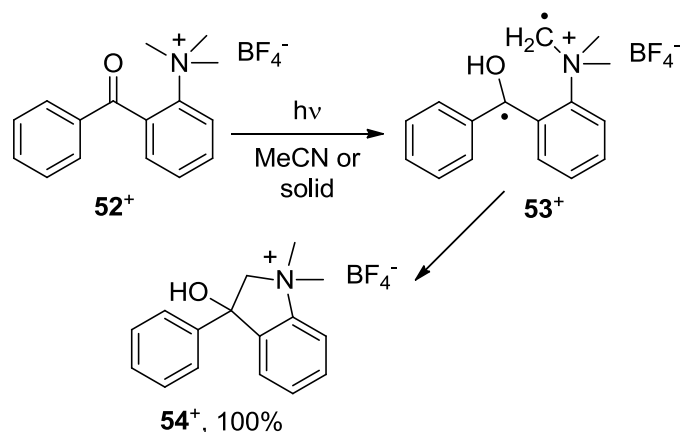
Another approach makes use of the intramolecular formation of an Ar-C bond. A photostimulated intramolecular S$_{RN}$1 reaction was reported for the synthesis of carbolines (**56a-c**) from the corresponding anilinohalopyridines **55a-c** (Scheme 28).[87]

Scheme 28. Synthesis of Carbolines from Anilinohalopyridines

55a, X = Br, R = H, R^1 = 3-Me
   b, X = Br, R = 6-COO*t*-Bu, R^1 = H
   c, X = Cl, R = R^1 = H

56a, 90%
   b, 79%
   c, 75%
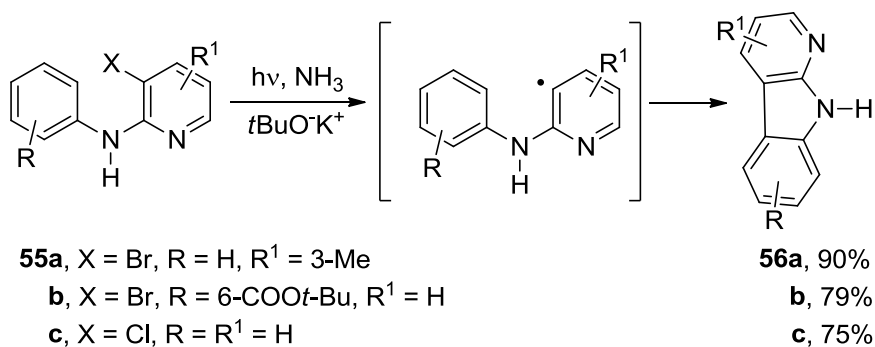
Another example deals with the preparation of oxindoles by irradiation of a solution of 2-bromo-anilides **57** with a 40 W household fluorescent lamp in the presence of visible light photocatalyst *fac*-Ir^{III}(ppy)$_3$ (Scheme 29). Bromide elimination and radical addition onto the aromatic ring led to nitrogen heterocycles **58** in *ca.* 95% yield, independently on the substituent R present on the aromatic ring.[88]

Scheme 29. Formation of a Five Membered Ring via Photocatalyzed Reaction of 2-Bromo-anilides
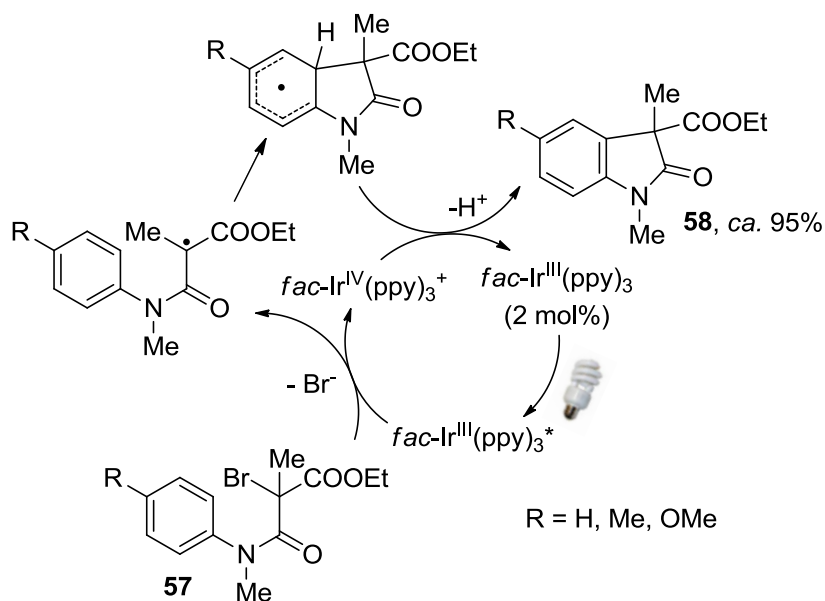
Related oxindoles bearing a quaternary carbon center (**61a-c**) were prepared upon radical trifuoromethylation of the double bond in *N*-aryl acrylamides (**59a-c**) followed by intramolecular cyclization (Scheme 30). Togni's reagent (**60**) was used as the source of F$_3$C$^\bullet$.[89] The oxindole core was also prepared via 1,2-alkylarylation of *N*-aryl acrylamides by α-keto and α-cyano radicals formed from acetone and acetonitrile, respectively.[90]

Scheme 30. Synthesis of Trifluoromethylated Oxindoles
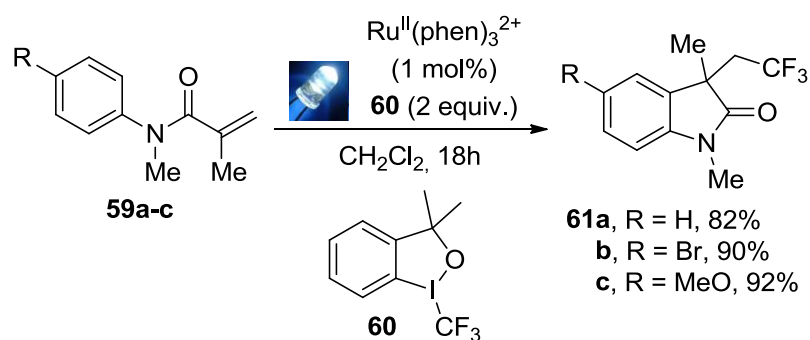
Different 1,3-dipoles can be photogenerated and used in the synthesis of nitrogen heterocycles via 1,3-dipolar cycloadditions.[3] A particular case is the photochemical cascade reaction starting from vinyl bromides **62a-c** (Scheme 31). The reaction was performed in a biphasic system (water-DCM) making use of $Bu_4N^+Cl^-$ in the role of phase-transfer catalyst. Photolysis of **62a-c** gave the corresponding vinyl cations that in turn formed **63a-c** upon addition of the azide anion. The azides were photochemically converted to azirines **64a-c** and then to nitrile ylides **65a-c** that were trapped by a dipolarophile (dimethyl fumarate in Scheme 31) causing the formation of 1-pyrroline derivatives (**66a-c**) in a good yield.[91]

Scheme 31. Synthesis of 1-Pyrroline Derivatives from Photogenerated 1,3-Dipoles
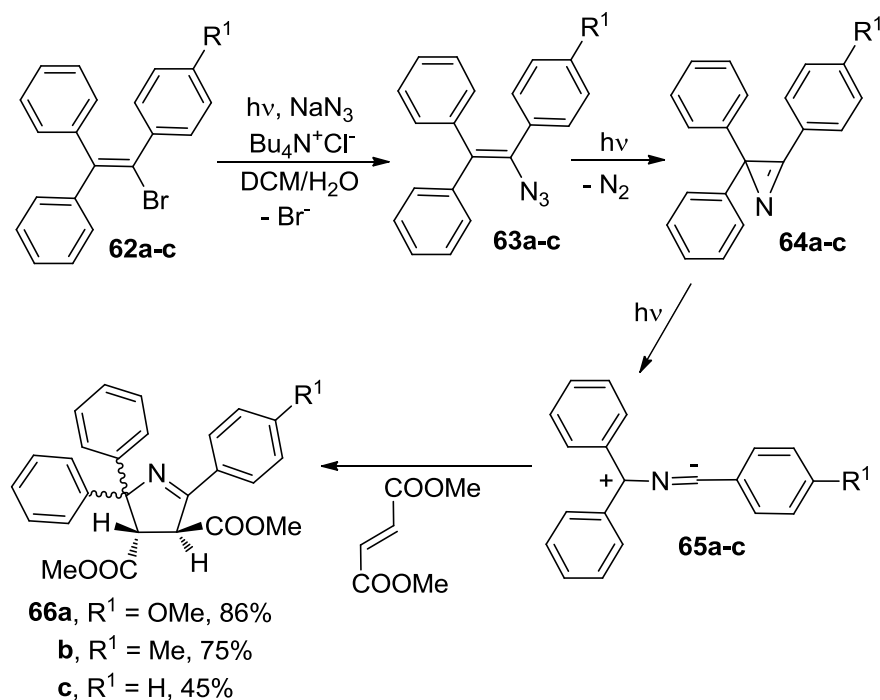
Azomethine ylides can be obtained under photoredox conditions both from α,α'-bis-(trimethylsilyl)-amines (upon two sequential desilylation steps)[92] and from *N*-substituted tetrahydroisoquinolines[93] by using DCN and a Ru^{II} complex as the photocatalyst, respectively. α,β-Unsaturated esters and amides or maleimides were employed as the dipolarophiles.

A formal [3+2] cycloaddition was used for the preparation of the HMG-CoA reductase inhibitor **70** starting from *2H*-azirine (**68**) (Scheme 32). 9-Mesityl-10-methylacridinium perchlorate (Mes-Acr$^+$ClO$_4^-$) was adopted as photoredox catalyst. The mono-electronic oxidation of **68** caused ring opening of the nitrogen heterocycle and the resulting radical cation was trapped by dimethyl acetylenecarboxylate **67** to yield pyrrole **69** in a modest yield. The latter compound was then elaborated to **70**.[94]

Scheme 32. Photocatalyzed Ring Opening of Azirines
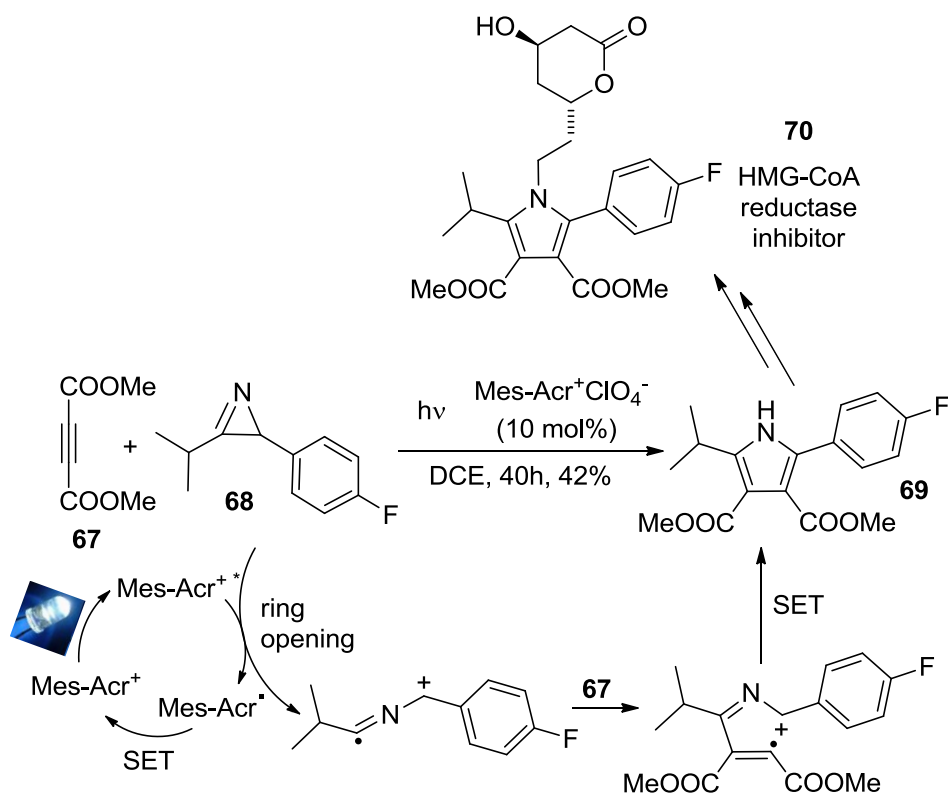
Dyes can be valid substitutes for metal-based photoredox catalysts. Thus, rhodamine B was successfully employed in the generation of perfluoroalkyl radicals from the corresponding iodides. The ensuing addition onto diallyl amines gave the corresponding pyrrolidines after a cyclization step upon LED irradiation. Water (as the solvent) was required for the process to occur.[95]

Metal/photoredox dual catalysis has been recently applied for the synthesis of benzofused nitrogen heterocycles. The coupling of iodoacetanilides (**71a,b**) with alkenes was performed with the

cooperation of both a Ni^0 catalyst and a Ru^{II} *photo*catalyst with the help of the *N*-heterocyclic carbene ligand **72**. The role of the first catalyst was to activate the Ar-I bond allowing the addition onto the alkene, whereas the excited Ru^{II} species had the role to oxidize the Ni^{II} complex intermediate to Ni^{III}, thus causing the release of the indoline products (**73a,b**, Scheme 33).[96] Furthermore, the combination of Pd^{II}(OAc)$_2$ and of an Ir-based photocatalyst enabled the preparation of indoles by a cyclization reaction of aromatic enamine esters via Ar-H activation.[97]

Scheme 33. Metal/Photoredox Dual Catalysis for the Synthesis of Benzofused Nitrogen Heterocycles
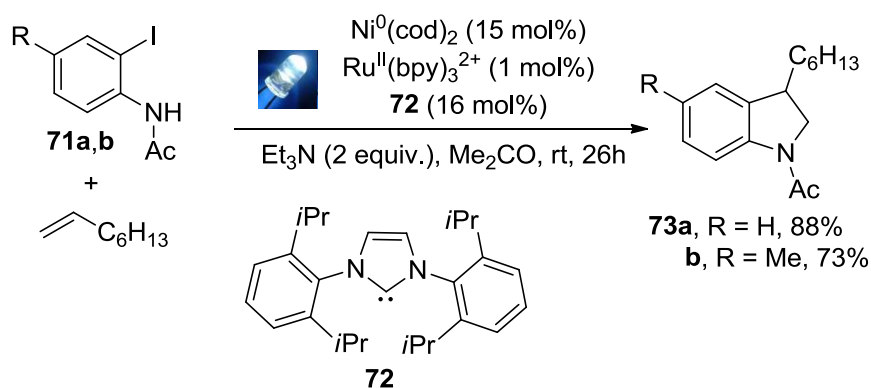
2.3.3. Oxygen Containing Heterocycles. The use of the Norrish-Yang reaction via 1,5-biradical cyclization has been reported as the key step for the synthesis of natural occurring derivatives having a tetrahydrofuran moiety. In detail, the syntheses of coumestrol from a glyoxylate ester,[98] of racemic (±)-isogmelinol and (±)-paulownin from 5-aryl-tetrahydrofuran-3-ones[99] and of *trans*-dihydrobenzofuranols from 2-benzyloxy-acylbenzenes were reported.[100]

The presence of an oxygen nucleophilic moiety (e.g. a COOH or an OH group) in one of the reactants can allow for the preparation of substituted tetrahydrofurans and γ-lactones via a cyclization reaction. As an example, the phocatalyzed addition of alcohols onto maleic acid was used for the synthesis of terebic acid (**75**). The UV-A absorption of the photocatalyst (the water

soluble benzophenone disodium disulfonate salt, **74**) allowed the use of solar light to promote the process in a mixed aqueous solvent (Scheme 34).[101]

Scheme 34. Synthesis of Terebic Acid 75
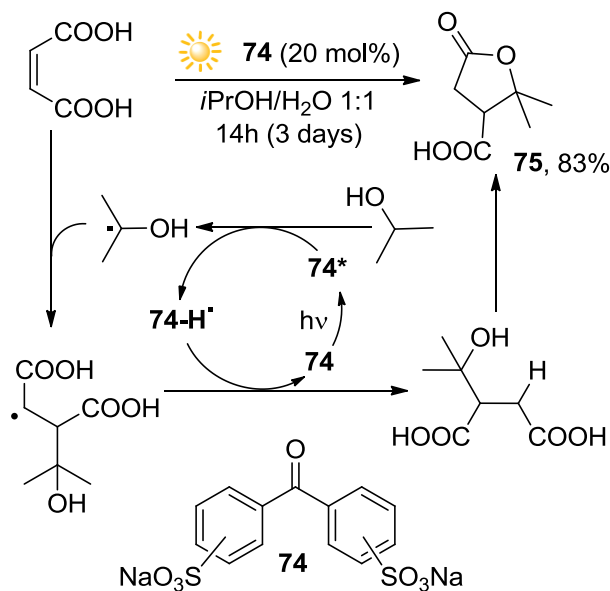
An alternative approach to oxygen heterocycles makes use of the reaction of photogenerated triplet phenyl cations (obtained by photoheterolysis of an Ar-Cl bond) with alkenes bearing a tethered oxygen based nucleophile. The addition onto the double bond was followed by intramolecular attack of the oxygen nucleophile, resulting in the tandem formation of an aryl-carbon and a C-O bond (Scheme 35). The 4-hydroxyphenyl cation reacted both with pentenol (to give benzyl tetrahydrofuran **76**)[102] and with 2-cyclopentenyl acetic acid to form furanone **77**[103] in a satisfying yield.

Scheme 35. Photogenerated Triplet Phenyl Cations as Intermediates for the Synthesis of *O*-Based Heterocycles
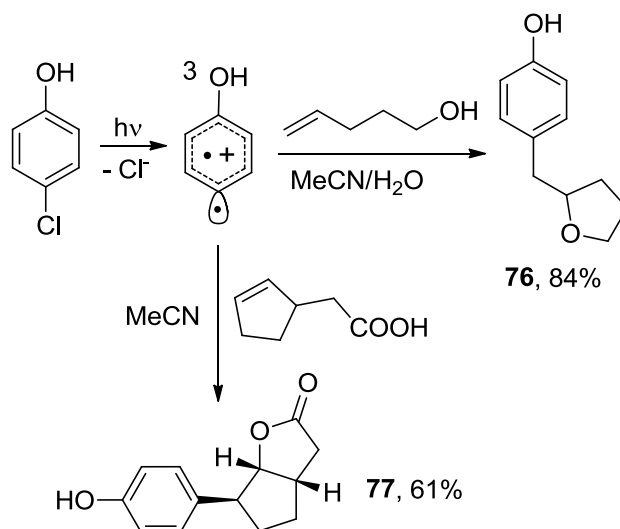
Aryl radicals rather than aryl cations were likewise used for the straightforward preparation of benzyl tetrahydrofurans (**79a,b**) thank to a dual photoredox and gold catalytic approach (Scheme 36). The strategy was based on the intramolecular oxyarylation of alkenol (**78a,b**) initiated by the addition of the Au^I catalyst onto **78a,b** to give an alkylgold(I) intermediate that underwent the attack of an aryl radical (from the Ru catalyzed photoredox decomposition of the diazonium salt).[104] Analogously, the Ru^{II} based photocatalyzed addition of aryl radicals onto alkenoic acids gave γ,γ-disubstituted butyrolactones in a good yield through an arylation-lactonization sequence.[105]

Scheme 36. Synthesis of 2-Benzyltetrahydrofurans
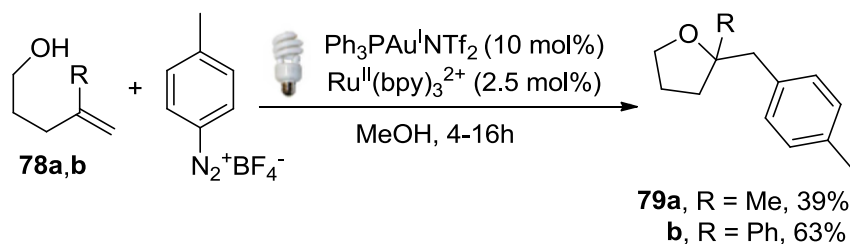
A direct route for the formation of γ-lactones was recently developed by the photocatalyzed addition of styrenes to α-bromo esters under mild conditions. The radical derived from the latter

compounds added onto the double bond of styrenes and ensuing oxidation, water addition and intramolecular formation of a C-O bond gave the desired heterocycle.[106]

Another interesting approach for the construction of tetrahydrofuran based compounds makes use of an oxidative [3+2] cycloaddition of phenols and alkenes as illustrated in Scheme 37. In the presence of a ruthenium polypyridyl complex, phenols (**81a-c**) were phocatalytically oxidized and added to styrene **80** to form potentially bioactive dihydrobenzofurans (**82a-c**).[107] The insoluble $Ru^{II}(bpz)_3(S_2O_8)$ was proposed as the active catalyst.

Scheme 37. Photocatalyzed Route to Dihydrobenzofurans
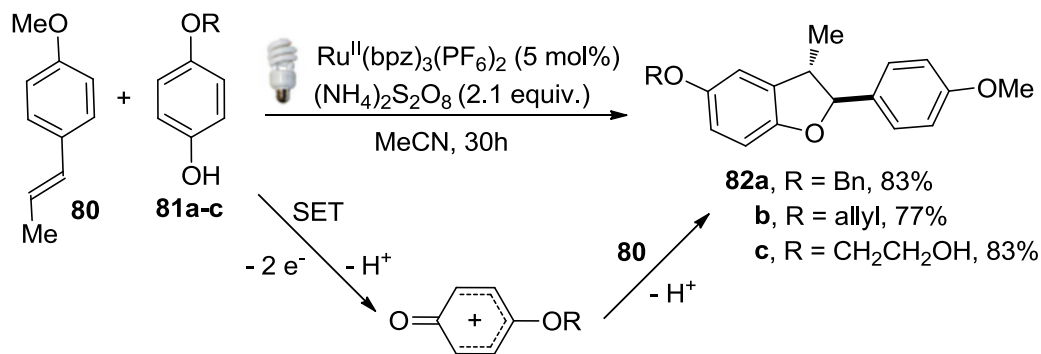
Sparse reports deal with the preparation of furans. One approach made use of the photoredox coupling between alkynes and 2-bromo-1,3-dicarbonyl compounds under LED irradiation (Scheme 38). An excited Ir^{III} complex was responsible for the reduction of bromodiketone **84**. Addition of radical **86·** onto alkyne **83** and cyclization of the vinyl cation obtained from the oxidation of **87·** afforded furan **85** in a very good yield.[108]

Scheme 38. Synthesis of Arylfurans
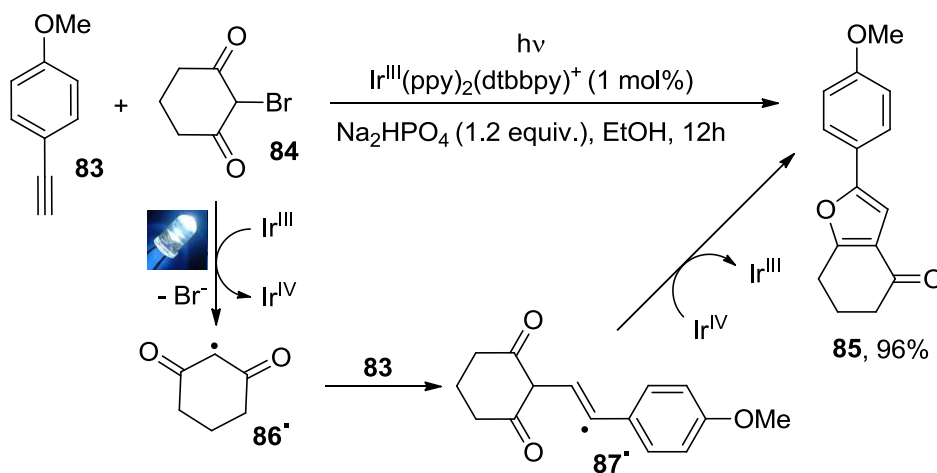
Furthermore, 2-substituted benzo[b]furans were prepared by addition of photogenerated 2-hydroxyphenyl cations (from the photolysis of 2-chlorophenols) onto an alkyne followed by an intramolecular cyclization.[109]

2.3.4. Sulfur Containing Heterocycles. Sparse examples deal with the synthesis of S-heterocycles. The homolytic cleavage of the Ar-Cl bond in phenylthiotetrachloropyridine (**88**) followed by intramolecular addition onto the phenyl ring caused the formation of pyridobenzothiophene (**89**) in 68% yield. The success of the reaction was ascribed to the absence of ensuing photodechlorination of **89** (Scheme 39).[110]

Scheme 39. Preparation of Pyridobenzothiophenes
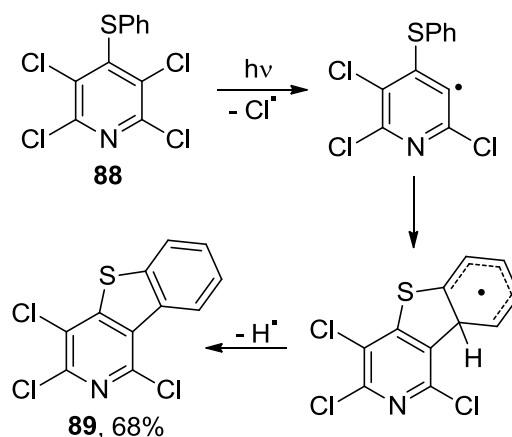
Diazonium salts (e.g. **90**$^+$) are again a suitable source of aryl radicals, in turn used for the preparation of benzothiophenes (**92**). Eosin Y (an inexpensive visibile light-absorbing dye) was adopted in the role of photocatalyst causing the reduction of the salts. Addition of the thus formed aryl radicals (e.g. **91**$^•$) onto an alkyne followed by the vinyl radical addition onto a vicinal SMe group led to disubstituted thiophenes (**92**, 61% yield, Scheme 40).[111]

Scheme 40. Photocatalyzed Preparation of Disubstituted Thiophenes
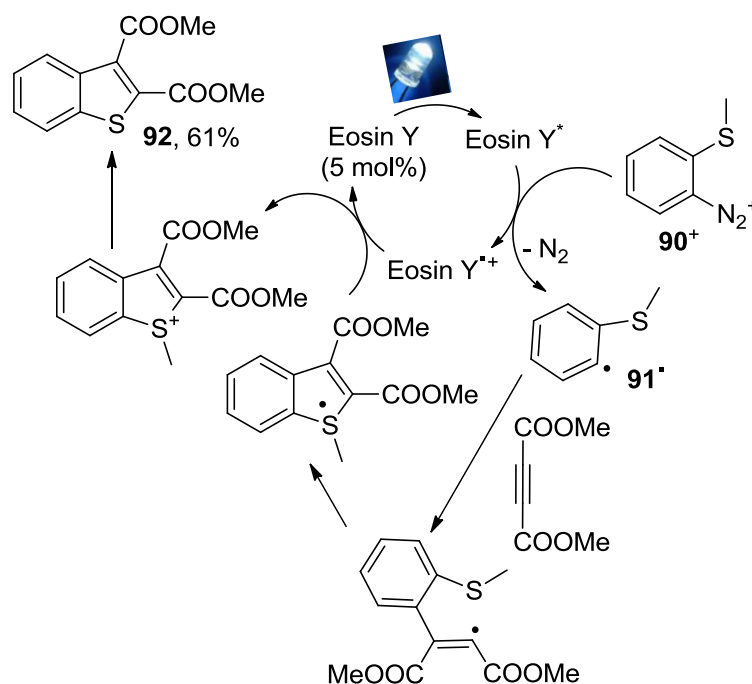
2.3.5. More than One Heteroatom in the Ring. A representative case belonging to this category is the synthesis of imidazoles via a photocatalytic aerobic oxidation/[3+2] cycloaddition/aromatization cascade starting from secondary amines and isocyanides. The reaction was applied to the preparation of **97**, a novel protein tyrosine kinase (PTK) inhibitor candidate (Scheme 41).[112] The reaction was initiated by the photocatalytic oxidation of the α-amino-substituted lactam **93** to **96** that reacted with isonitrile **94** to afford the [1,5-*a*]quinoxalin-4(5*H*)-one derivative **95** in 85% yield. **97** was then obtained by removal of the *p*-methoxybenzyl group.[112]

Scheme 41. Visible Light Induced Synthesis of [1,5-*a*]Quinoxalin-4(5*H*)-ones

R = 4-MeOC$_6$H$_4$
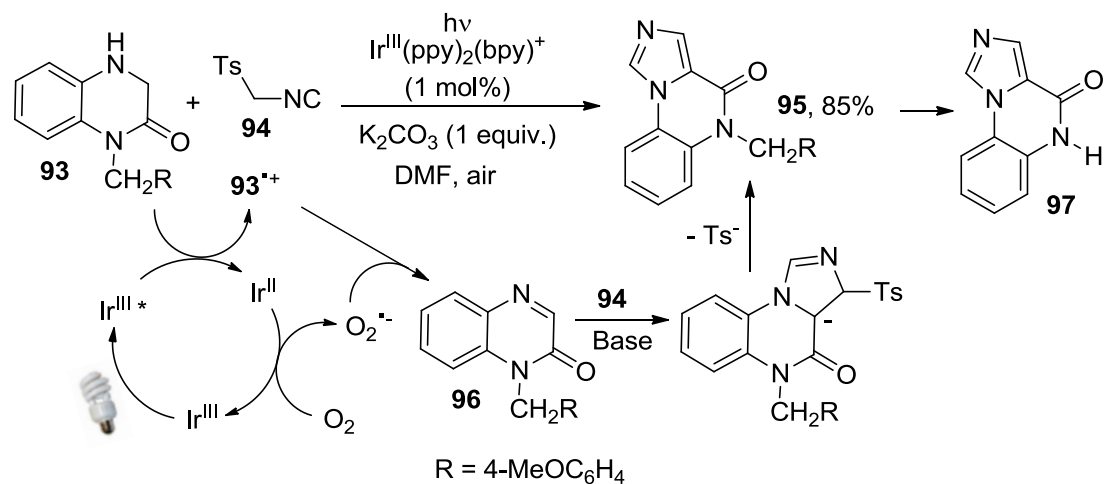
2.4. Six Membered Rings

2.4.1. Carbocycles. As previously described, intramolecular C-H hydrogen abstraction by an excited ketone takes place preferably from the geometrically favoured γ-position (see Section 1.1.2). The generation of a 1,6 biradical was thus possible only if no hydrogen was present in either γ- or δ- positions.[16,17,113] The Norrish-Yang coupling then resulted in the formation of the corresponding six-membered ring, as observed in the photochemical synthesis of variously substituted tetralols from β-arylpropiophenones.[114]

Vinyl radicals are widely used as intermediates in ring formation, and different generation strategies have been developed in these years. The simplest approach involved photohomolysis of vinyl halides, although heterolytic cleavage of the C-X bond often competed.[3,115,116] Substituted phenanthrenes have been prepared in high yields by exploiting this approach.[117] In a recent application, a vinyl radical was obtained from α-bromo-cinnamates or -chalcones employing a visible light photoredox strategy (Scheme 42). Mono-electronic reduction of the starting substrate **98** and subsequent detachment of bromide anion afforded vinyl radical **99˙** that, upon addition onto heteroarenes (such as furan) and ensuing cyclization, gave intermediate **100˙**. The latter underwent

oxidation and deprotonation to yield benzocondensed heterocycles (e.g. **101**) in which two C-C bonds were consecutively formed through the activation of three different C-H bonds.[118] A similar strategy has been adopted in the visible light photoredox catalyzed Heck-type coupling of α-bromochalcones with alkenes.[119]

Scheme 42. Photocatalyzed Synthesis of Benzocondensed Heterocycle 101 from a Bromocinnamate
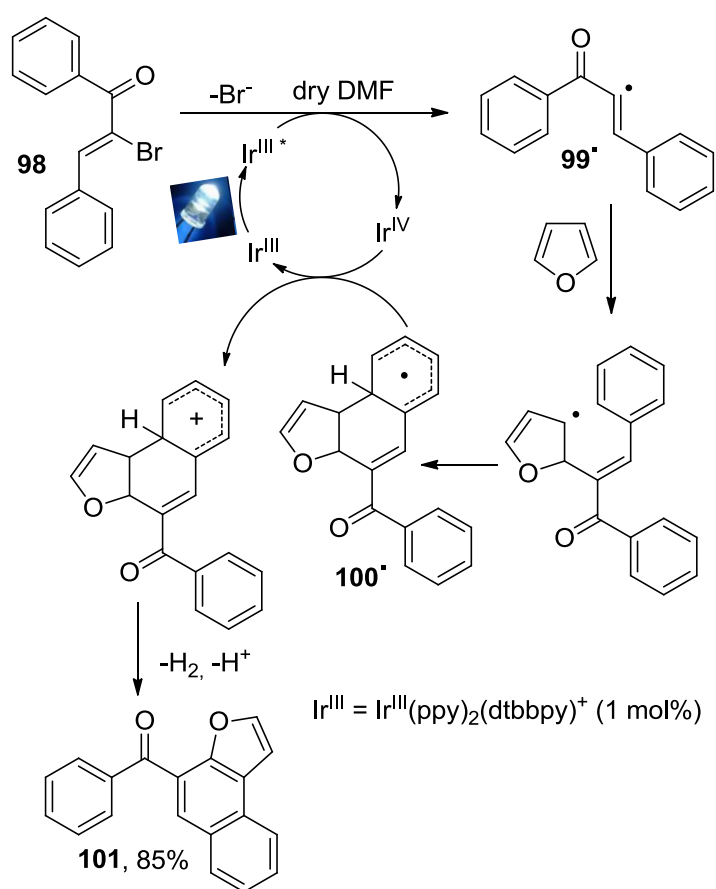
Vinyl radicals have also been generated through the selective addition of an electrophilic thiyl radical onto an aryl-acetylene moiety. The approach has been exploited in a diastereoselective radical addition/cyclization sequence for the conversion of benzodioxole **102** to sulfide **103**, a precursor in the synthesis of ent-lycoricidine, a compound structurally related to pancratistatin (Scheme 43).[120] An enantioselective variant of this strategy has been adopted for the synthesis of both (–)- and (+)-ent-lycoricidine, as well as of (+)-narciclasine.[121]

Scheme 43. Total Synthesis of ent-Lycoricidine
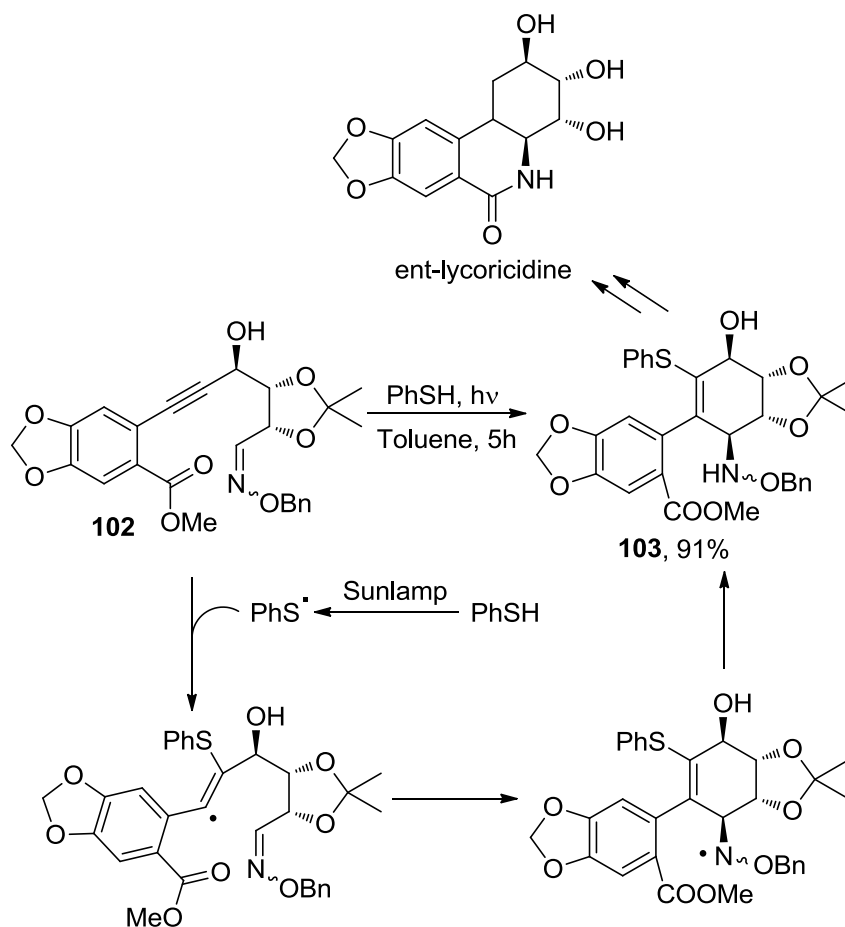
Similarly, a 1,3-dioxolan-2-yl radical was generated via benzophenone photocatalysis and used to initiate a tandem radical addition-carbocyclization in alkynyl ketoxime ethers.[122]

The synthesis of aporfine **105** (a precursor of alkaloid thalicmidine **106**) involved a $S_{RN}1$ mechanism[34] and occurred via cyclization of (2-bromobenzyl)-substituted tetrahydroisoquinoline **104** (Scheme 44). However, the feasibility of the reaction was limited to compounds bearing an electron withdrawing substituent on the nitrogen atom.[123]

Scheme 44. Synthesis of Thalicmidine

thalicmidine
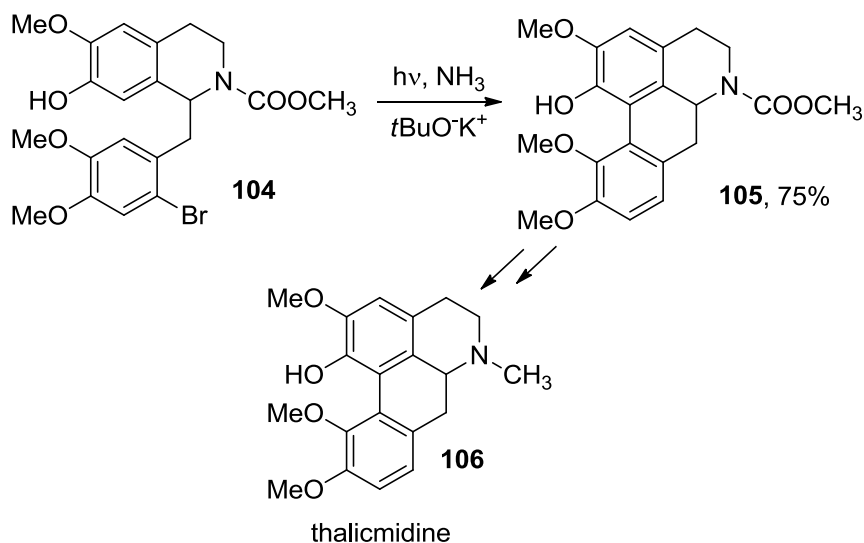
Diels-Alder reactions do not occur when both the diene and the dienophile are electron-rich or electron-poor compounds. However, monoelectronic oxidation/reduction resulted in the Umpolung of one of the reactants, thus giving access to the desired cycloadduct.[3,25,124] This is the case of phenyl vinyl sulfide that, in the presence of *p*-DCB as photocatalyst, was photooxidized to the corresponding radical cation and trapped by diene **107** to form the octahydronaphthalene core in compound **108** (60% yield, Scheme 45a), a precursor of sesquiterpene (−)-β-selinene **109**.[125] In some cases 2,4,6-triphenylpyrylium[126] and triphenyl(thia)pyrylium[127] tetrafluoroborates were successfully used as an alternative to cyanoarenes. In this case the irradiation time was significantly reduced and involved the use of a wavelength > 345 nm. Furthermore, a lower amount of the photocatalyst (0.1-1.5 mol% rather than 20 mol% usually required for DCB) could be used.[126] Recently, the use of Cr^{III} complexes as photoredox catalysts to promote Diels-Alder cycloadditions was reported.[128] Thus, near UV (300-419 nm) irradiation of a solution of diene **110** and styrenes **111a-c** in oxygen-equilibrated nitromethane in the presence of chromium complex $Cr^{III}(Ph_2phen)_3^{3+}$ resulted in a diastereoselective (dr > 19:1) cycloaddition (Scheme 45b). A similar protocol, involving a Ru^{II} based photocatalyst, was developed and exploited as the key step in the multistep synthesis of natural compound heitziamide A.[129]

Scheme 45. Diels-Alder Reactions Promoted by Photoredox Catalysis

a)

107 **108**, 60%

3 steps

109

(-)-β-selinene

b)

110

111a-c

hν (Near UV)
Cr^{III}(Ph$_2$phen)$_3^{3+}$ (1 mol%)

air, CH$_3$NO$_2$

112a, R = 4-MeO, R^1 = nPr, 88%
b, R = 2-MeO, R^1 = Me, 76%,
c, R = 4-MeO, R^1 = (CH$_2$)$_3$OMe, 52%
in all cases dr > 19:1

Ph$_2$phen =
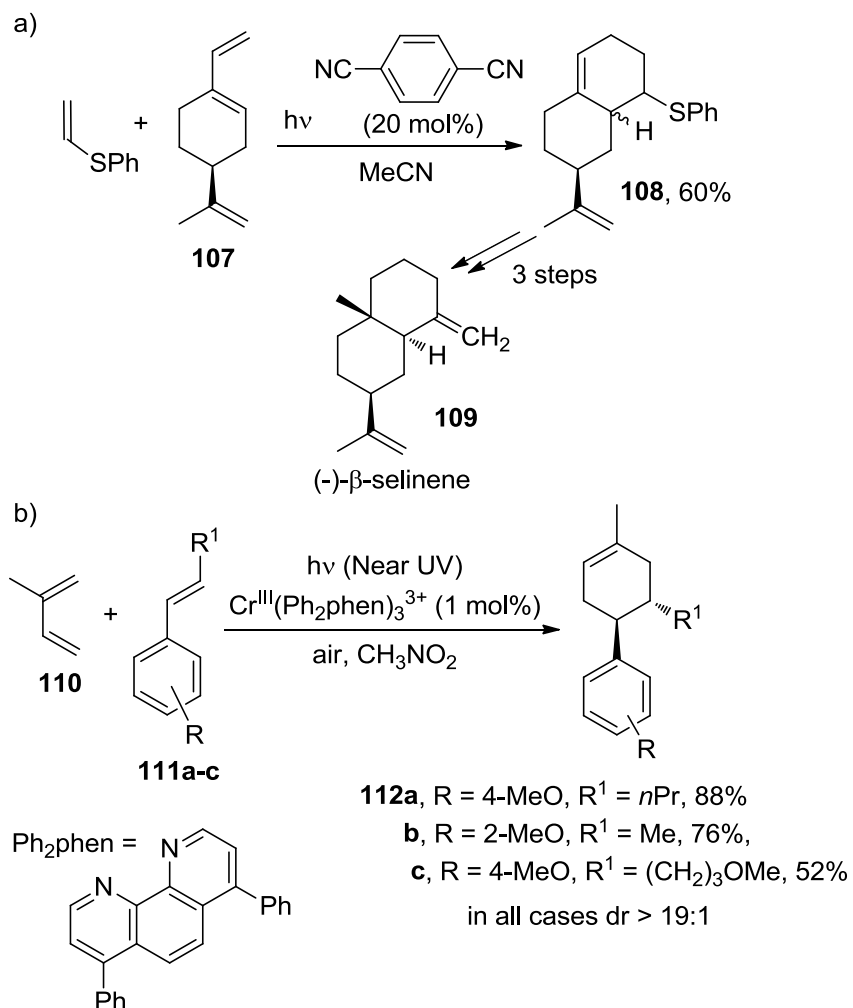
syn-1,2-Hydroxy hydrazines **116a-e** have been obtained via Ir^{III} photocatalyzed enantioselective aza-pinacol cyclization of hydrazones **113a-e**, which was enabled by proton-coupled electron transfer (PCET) to form radical/ion pair **117·a-e** in the presence of chiral phosphoric acid (*R,R*)-**114**-OH.[130] Cyclization to radical **118·a-e** and hydrogen transfer from Hantzsch ester **115**-H$_2$ gave the desired chiral aminoalcohols **116a-e**. Radical **115**-H· underwent oxidation and deprotonation, regenerating at the same time the Ir^{III} photocatalyst and acid (*R,R*)-**114**-OH (Scheme 46).

Scheme 46. Enantioselective Synthesis of 1,2-Hydroxy Hydrazines 116a-e

116a, R = H, 83%, ee 93%
b, R = 4-CF$_3$, 58%, ee 90%
c, R = 2-Me, 63%, ee, 94%
d, R = 3-Me, 78%, ee, 90%
e, R = 4-Me, 81%, ee 95%
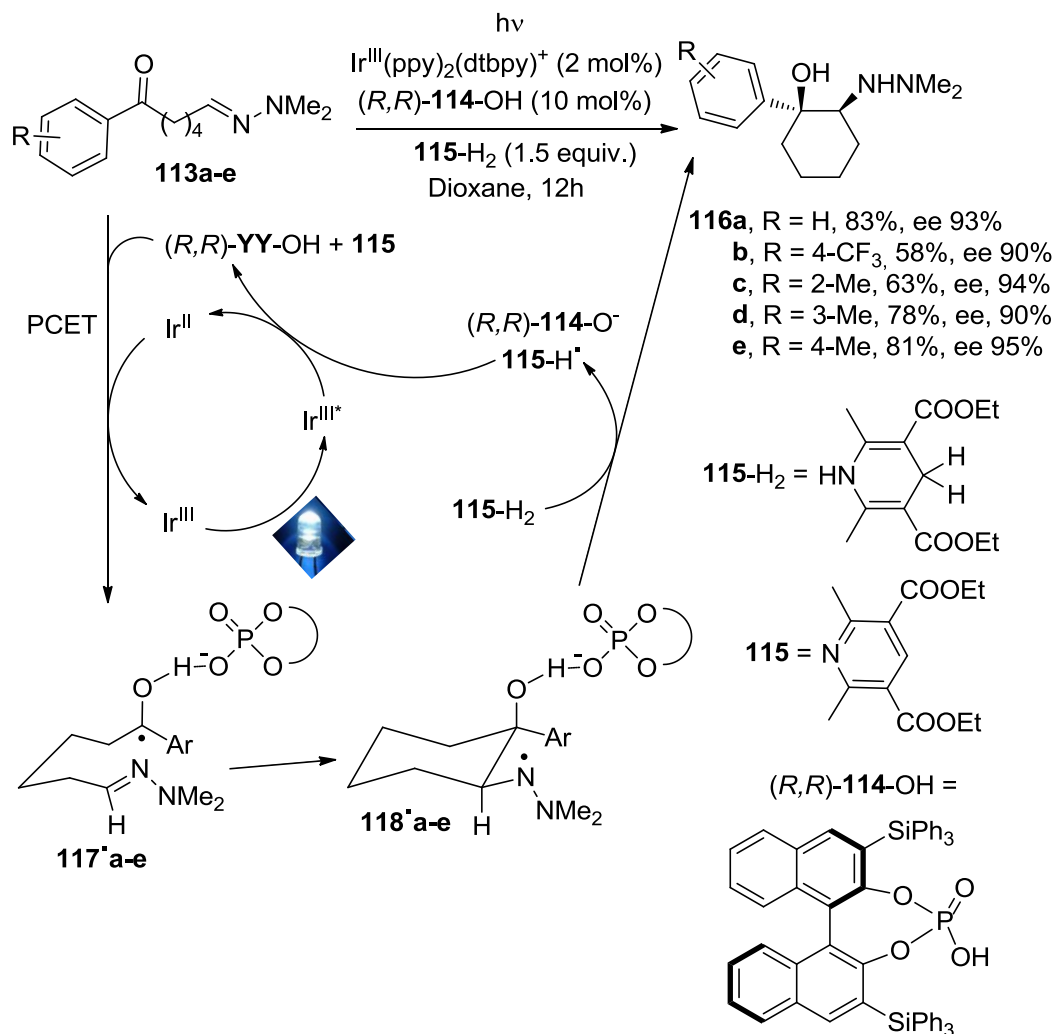
2.4.2. Nitrogen Containing Heterocycles. Nitrogen containing six-membered rings can be likewise accessed via a Norrish-Yang cyclization. As an example, δ-lactams **121a,b** were obtained as a single diastereoisomer by irradiation of chiral α-acylamino γ-ketoamides **119a,b** (Scheme 47).[131] The chair-like conformation of 1,6-biradicals **120a,b** was responsible for the excellent diastereoselectivity observed.[131] Analogously, a remarkable selectivity in hydrogen abstraction from the ε-position was observed in the case of 4-oxo-4-phenyl-butanoyl amines and exploited for the photochemical synthesis of δ-lactams[132] and ornithine lactams.[133]

Scheme 47. Synthesis of δ-Lactams

121a, R = COOMe, 75%
b, R = Ph, 90%
in all cases dr > 97:3
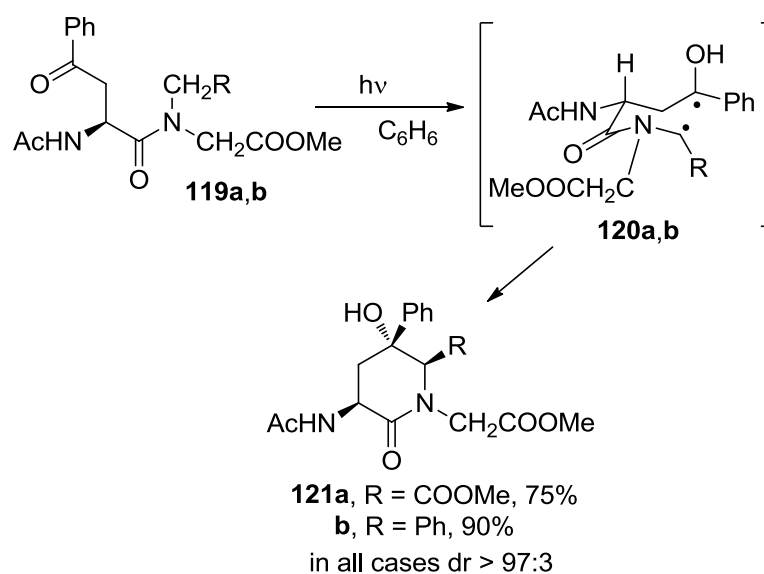
Direct photolysis of 2-iodo-*N*-(2-arylethyl)imidazoles **122a-c** in nitrogen saturated MeCN resulted in an intramolecular cyclization via aryl radical to afford 5,6-dihydroimidazo[2,1-a]isoquinolines **123a-c** (Scheme 48a).[134] Analogously, the photohomolysis occurring in *N*-(2-iodobenzyl)anilines **124a-c** in degassed acetonitrile has been exploited in the synthesis of phenanthridines **125a-c** (Scheme 48b).[135]

Scheme 48. Photochemical Synthesis of a) 5,6-Dihydroimidazo[2,1-a]isoquinolines and b) Phenanthridines via Direct Homolysis of an Aryl-Iodine Bond

a)

122a-c

hν, 254 nm
MeCN, 4-10h

123a, R = H, 70%
b, R = Cl, 66%
c, R = CF$_3$, 53%

b)

124a-c

hν, 254 nm
MeCN, 2h

125a, R = H, 85%
b, R = COOMe, 95%
c, R = OH, 90%
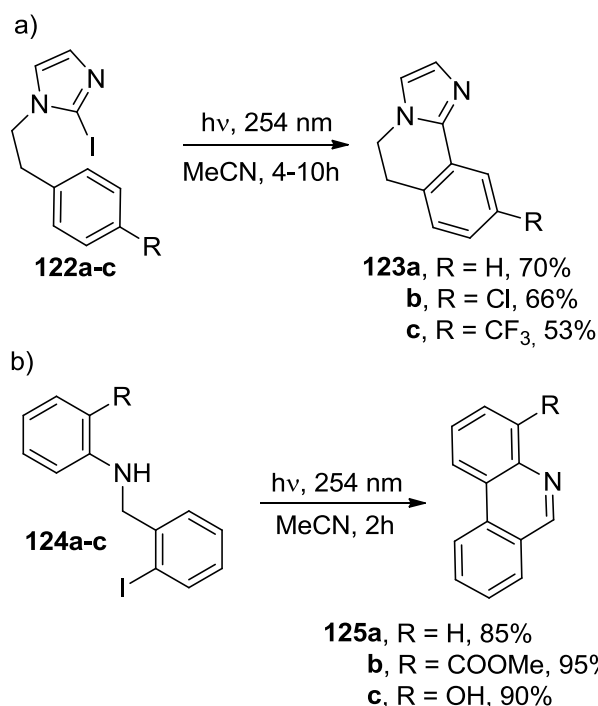
Heteroatom based radicals were used in the preparation of nitrogen containing heterocycles. Thus, isoquinolines **129a,b** have been synthesized through a radical chain reaction involving the intermolecular addition of the iminyl radical **127˙** (photogenerated by homolysis of acyl oxime **126**) onto the triple bond of an alkyne, followed by the intramolecular addition of the resulting vinyl radical **128˙a,b** onto the aromatic ring (Scheme 49).[136]

Scheme 49. Synthesis of Isoquinolines via Nitrogen Based Radicals
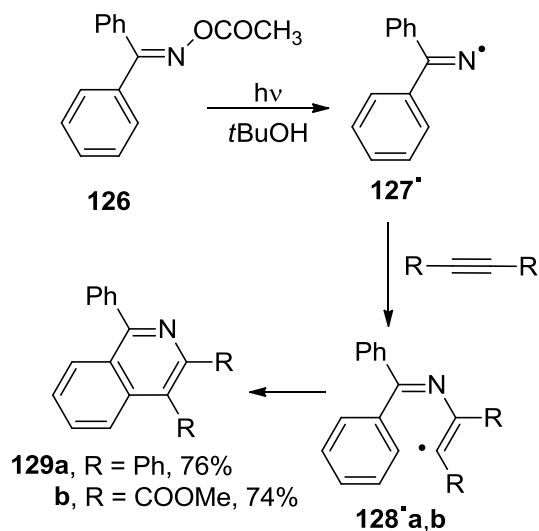
The versatile access to alkyl and aryl radicals offered by photoredox catalysis was exploited for the preparation of indoles starting, respectively, from unactivated bromoalkanes or bromoarenes and having recourse to dimeric gold cation complex $Au^I_2(\mu\text{-dppm})_2{}^{2+}$.[137] This complex exhibits an absorption maximum in the UV region (295 nm) and, when irradiated, produces a long-lived excited state $[Au^I\text{-}Au^I]^{2+}$ * with a quantum yield Φ of 0.23. Thus, UV-A ($\lambda = 365$ nm) irradiation of indoles **130a-c** in the presence of dimeric $Au^I_2(\mu\text{-dppm})_2{}^{2+}$ afforded the corresponding indolines **131a-c** in a highly satisfactory yield (Scheme 50).

Scheme 50. Gold Dimeric Complexes for the Photocatalytic Preparation of Indoles
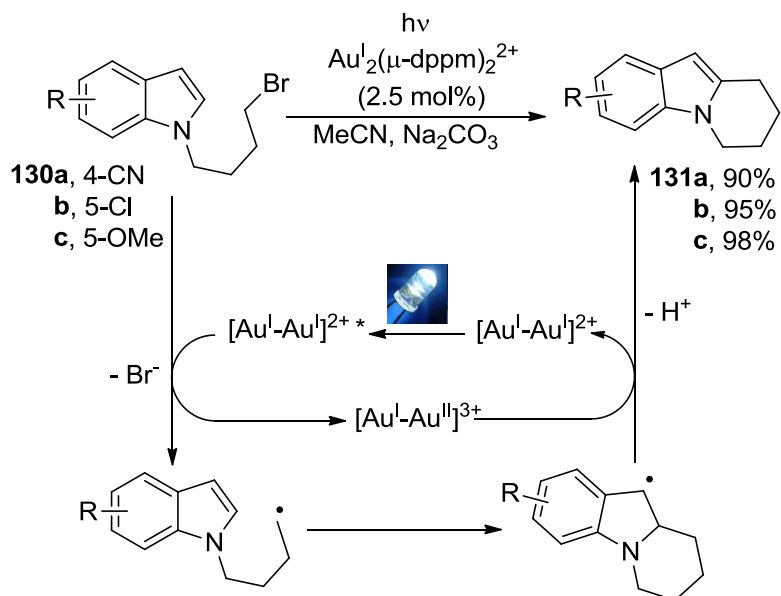
6-Substituted phenanthridine **133** was obtained by addition of photogenerated electrophilic α-carboxy radical **134·** onto 2-aryl-phenylisonitrile **132**. The obtained imidoyl radical **135·** underwent intramolecular attack onto the aryl ring (Scheme 51) followed by oxidation (by Ir^{IV}) and deprotonation to yield **133** in satisfactory yield, with the concomitant regeneration of the initial Ir^{III}photocatalyst.[138] A similar strategy has been adopted in the synthesis of substituted isoquinolines from vinyl isocyanides and diaryl iodonium salts.[139]

Scheme 51. Synthesis of 6-Substituted Phenanthridines
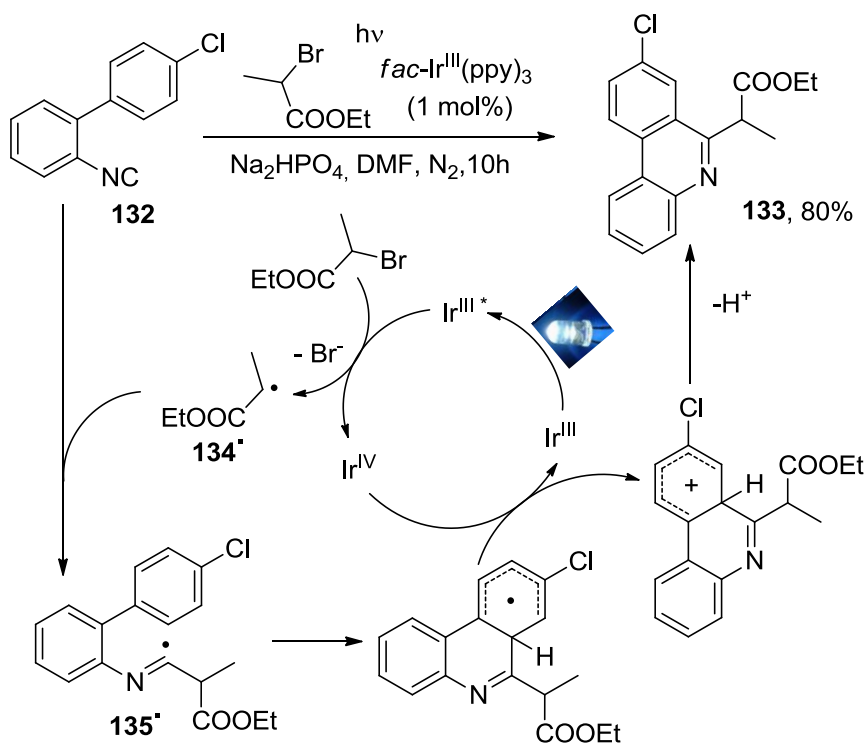
A different approach was reported for the synthesis of phenanthridone alkaloid (+)-2,7-dideoxypancratistatin **139** and was based on a PET reaction as the key step. Excited DCN caused the oxidation of the silyl enol ether moiety present in compound **136**. Cyclization of the resulting radical cation **136**[•+] onto the benzodioxole ring and formal loss of a hydrogen atom from radical **138**[•] gave reduced phenanthridone **137** (Scheme 52).[140]

Scheme 52. Synthesis of (+)-2,7-Dideoxypancratistatin precursor 137

139
(+)-2,7-dideoxypancratistatin

TBS = SiMe₂*t*Bu
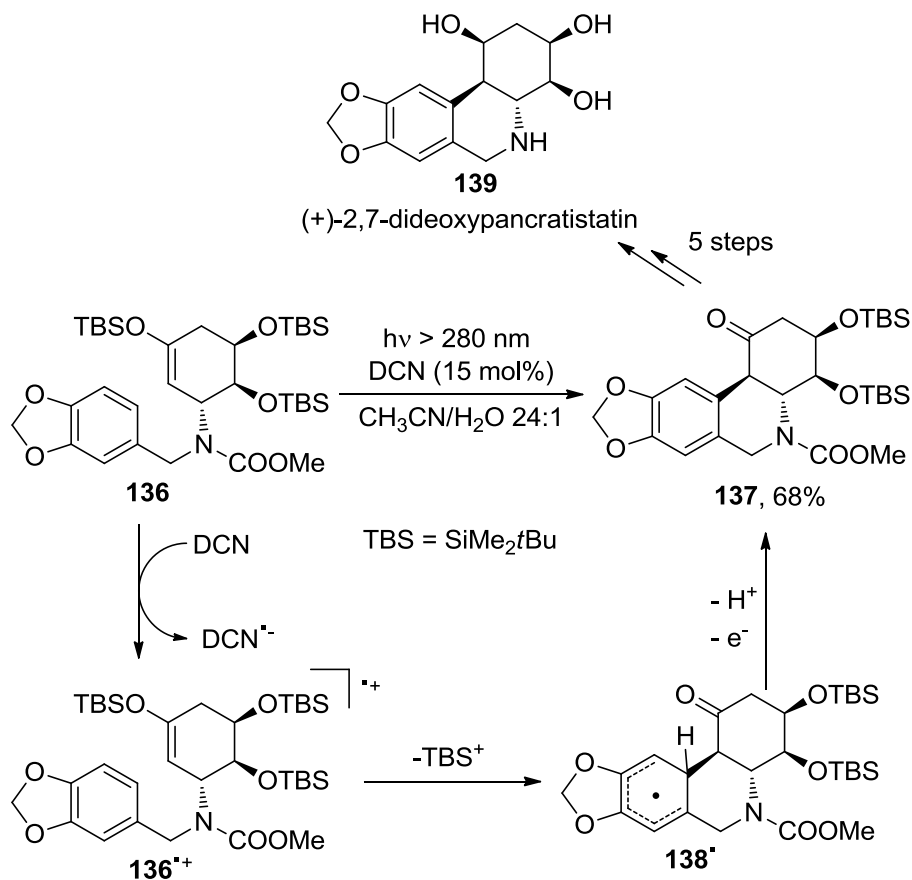
2.4.3. Oxygen Containing Heterocycles. Chromanone derivatives were found to be accessible through either photochemical or thermal rearrangement of aryl esters of α,β-unsaturated carboxylic acids. Thus, the photochemical synthesis of chroman-4-ones was carried out via a photo-Fries rearrangement followed by cyclization under basic conditions in a biphasic water/benzene system.[141] As indicated in Scheme 53, aromatic esters **140a,b** underwent photo-Fries rearrangement in the organic phase to give the corresponding phenols **141a,b**. Migration of the latter compounds to the aqueous basic phase induced an oxa-Michael addition reaction and chromanones **142a,b** were thus formed in excellent yields. Benzochroman-4-ones and heteroarylchroman-4-ones were likewise obtained in a one-pot procedure in cyclohexane/aqueous KOH biphasic system from the corresponding (hetero)aryl 3-methyl-2-butenoate esters.[142]

Scheme 53. Synthesis of Chromanone Derivatives
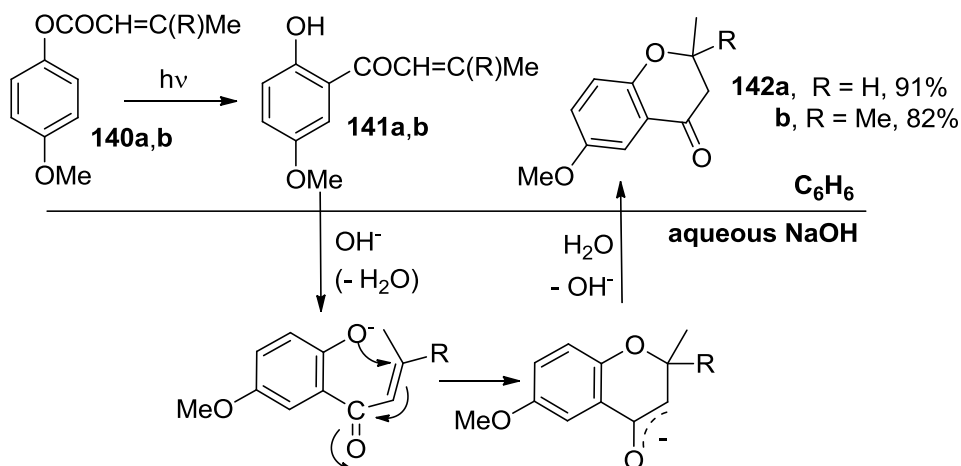
As reported in Scheme 54, 4-substituted benzochromane (**144**) was likewise accessible via intramolecular cyclization taking place in napthyl derivative **143** by following a $S_{RN}1$ mechanism (see further Scheme 6).[143]

Scheme 54. Synthesis of Oxygenated Heterocycles via $S_{RN}1$ Reaction
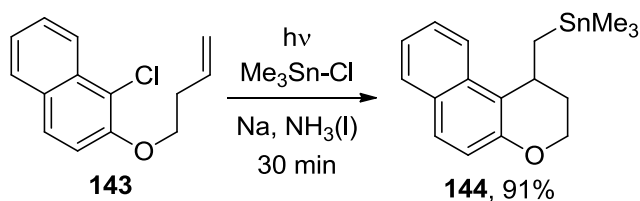
The coumarin skeleton is found in a wide range of both natural and artificial bioactive compounds, including anti-HIV and anti-cancer drugs.[144] Among the impressive number of proposed approaches, only a few protocols have been carried out in the absence of metals. As an example, eosin Y photocatalyzed the synthesis of differently substituted coumarines **149a-d** from phenyl propiolate **147** in the presence of *tert*-butyl hydroperoxide as an oxidative quencher. The process was initiated by an aryl sulfonyl radical (see **146˙a-d** in Scheme 55) generated by hydrogen atom abstraction from the corresponding arylsulfinic acid (**145a-d**) by *tert*-butoxy radical. The latter was in turn produced from *t*BuOOH via reductive cleavage by excited eosin Y.[145] Compounds **149a-d**

were then formed by addition of radicals **146˙a-d** onto the triple bond of **147** followed by intramolecular attack of the so formed vinyl radical onto the aromatic ring to give **148˙a-d**.

Scheme 55. Eosin Y Photocatalyzed Preparation of Coumarins
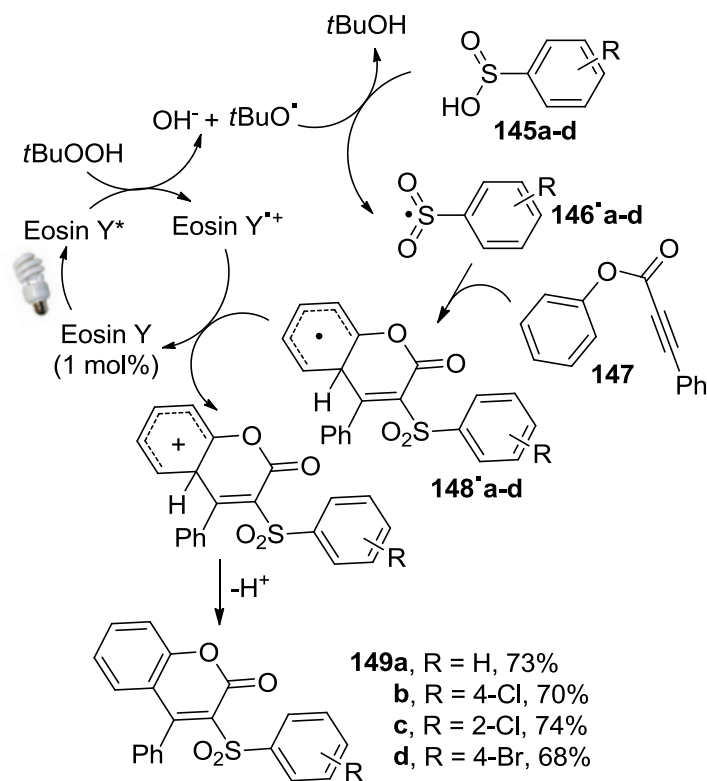
Substituted tetrahydropyrans and δ-lactones have been synthesized via intramolecular anti-Markovnikov hydroetherification of alkenols in the presence of 9-mesitylacridinium perchlorate (Mes-Acr⁺ClO4⁻) as photocatalyst.[146] A photoredox catalyst was also involved in the difunctionalization of electron rich styrenes **150a,b**.[147] In this case, reduction of diethyl 2-bromomalonate by excited *fac*-Ir^{III}(ppy)$_3$ resulted in the formation of radical **151˙**, after loss of a bromide ion. **151˙** in turn added regioselectively onto the double bond of **150a,b** and gave benzyl radicals **152˙a,b** that were further oxidized to carbocations **153⁺a,b**. Finally, nucleophilic cyclization afforded the desired oxygen containing ring (compounds **154a,b**, Scheme 56).

Scheme 56. Synthesis of Substituted δ-Lactones and Tetrahydropyrans
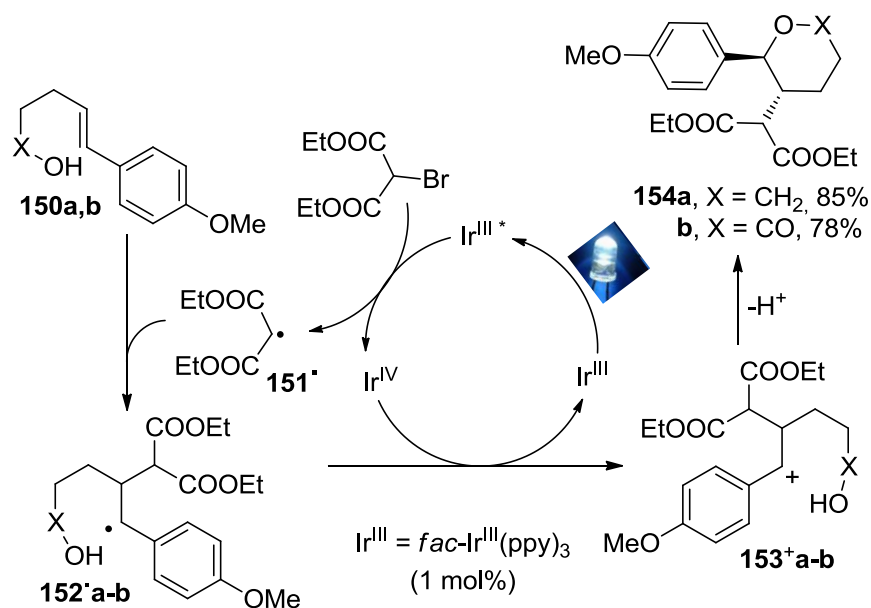
Siloxycarbenes were obtained through the atom-economical Brook rearrangement occurring in colored acyl silanes, when irradiated with a household 23W compact fluorescent lamp (CFL). The process has been exploited for the synthesis of benzopyran-4-ones **156a-c** through the intramolecular addition of the *in situ* generated siloxycarbene **157a-c** onto an alkyne moiety, to form unstable cyclopropenones **158a-c** that gave vinyl silanes **156a-c** upon ring opening and silyl migration (Scheme 57). The process, however, was efficient only when using electron withdrawing substituted alkynes and required a long irradiation time (12h).[148]

Scheme 57. Synthesis of Benzopyran-4-ones 156a-c via Photogenerated Siloxycarbenes
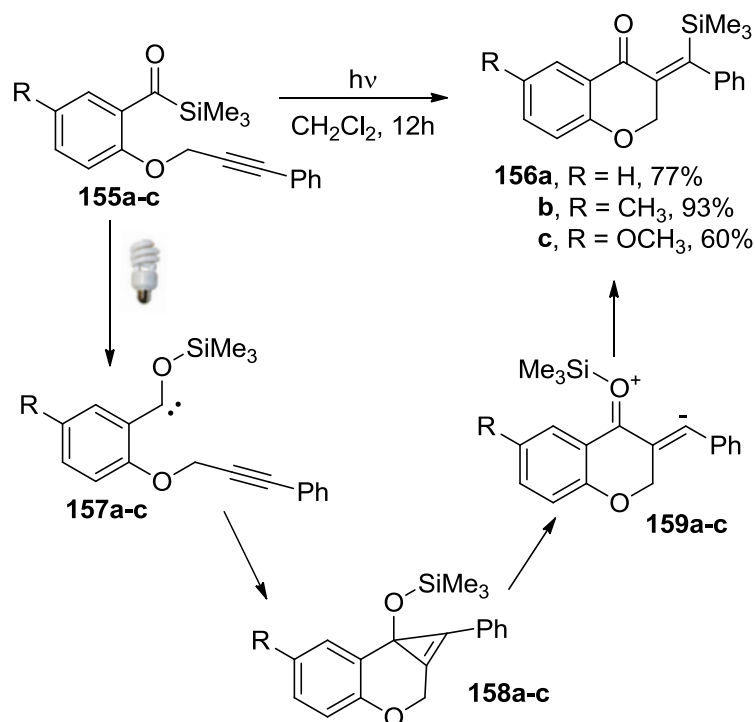
2.4.4. More than One Heteroatom in the Ring. Benzothiazine *S,S*-dioxides **161a,b** have been obtained via the photostimulated $S_{RN}1$ coupling of *ortho*-iodobenzenesulfonamide **160** with ketone or ester enolates (see an example in Scheme 58), although in the latter case reduction of **160** to sulfonamide in part competed with the desired cyclization.[149]

Scheme 58. Synthesis of Benzothiazine *S,S*-Dioxides 161a,b
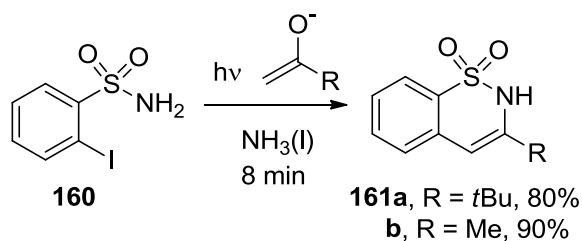
As previously stated, dimeric gold cation complex $Au^{I}_2(\mu\text{-dppm})_2{}^{2+}$ can be exploited as photoredox catalyst in cyclizations starting from alkyl and aryl bromides. As an example, irradiation in the presence of 2-bromoaryl sulfonate or phosphinate **162a,b** with either artificial or solar light afforded

the corresponding tricylic compounds **163a,b** in high yields via a radical cyclization (Scheme 59).[150]

Scheme 59. Gold Photocatalyzed Cyclization of Aryl Bromides

162a,b → **163a**, X= P(O)Ph, 90%
b, X = SO$_2$, 81%

Reagents: Au$^I_2$(μ-dppm)$_2^{2+}$ (2.5 mol %), iPr$_2$NEt (2 equiv.), MeCN, 2-24h
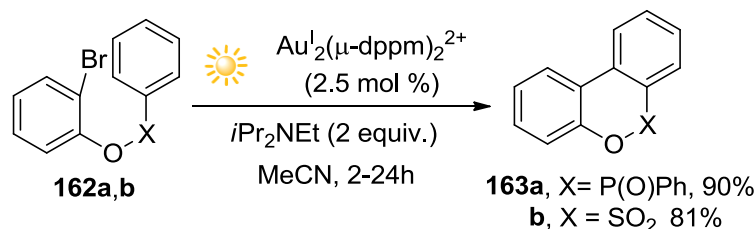
Nitrogen-containing heterocycle-fused compounds including pyrrolo[1,2-a]quinoxalines **168a-d** have been obtained via visible-light induced decarboxylative radical cyclization involving (diacyl-oxyiodo)arenes **164a-d** and aryl isocyanide **165**, by using the iridium complex *fac*-Ir^{III}(ppy)$_3$ as the photocatalyst (Scheme 60).[151] Oxidative quenching of excited Ir^{III}(ppy)$_3$ resulted in the decomposition of **164a-d** into iodobenzene, CO_2, carboxylate anion and alkyl radicals R$^\bullet$. The latter reacted with aromatic isonitrile **165** to generate imidoyl radicals **166$^\bullet$a-d**, that in turn underwent cyclization with the nearby pyrrole ring. Oxidation of the obtained intermediates **167$^\bullet$a-d** to the corresponding Wheland carbocations **167$^+$a-d** allowed to regenerate the catalyst. Finally, 4-substituted pyrrolo[1,2-a]quinoxalines **168a-d** were obtained via deprotonation of **167$^+$a-d** by the R-COO$^-$ anion. Notably, the process was also optimized under continuous flow conditions, in a three-step process in which isocyanide was generated in situ from the corresponding aniline, thus minimizing the risks of exposure to this toxic and foul-smelling reactant.[151] A photochemical multi-component reaction involving *N*-substituted thioureas, aromatic aldehydes and tetrahydrofuran (or dioxane) has been likewise exploited for the synthesis of a library of 2-pyrimidinethiones.[152]

Scheme 60. Synthesis of Pyrrolo[1,2-a]Quinoxalines

168a, R = C_6H_{11}, 73%
b, R = tBu, 74%
c, R = $(CH_2)_2Ph$, 66%
d, R = $(CH_2)_3COOMe$, 56%
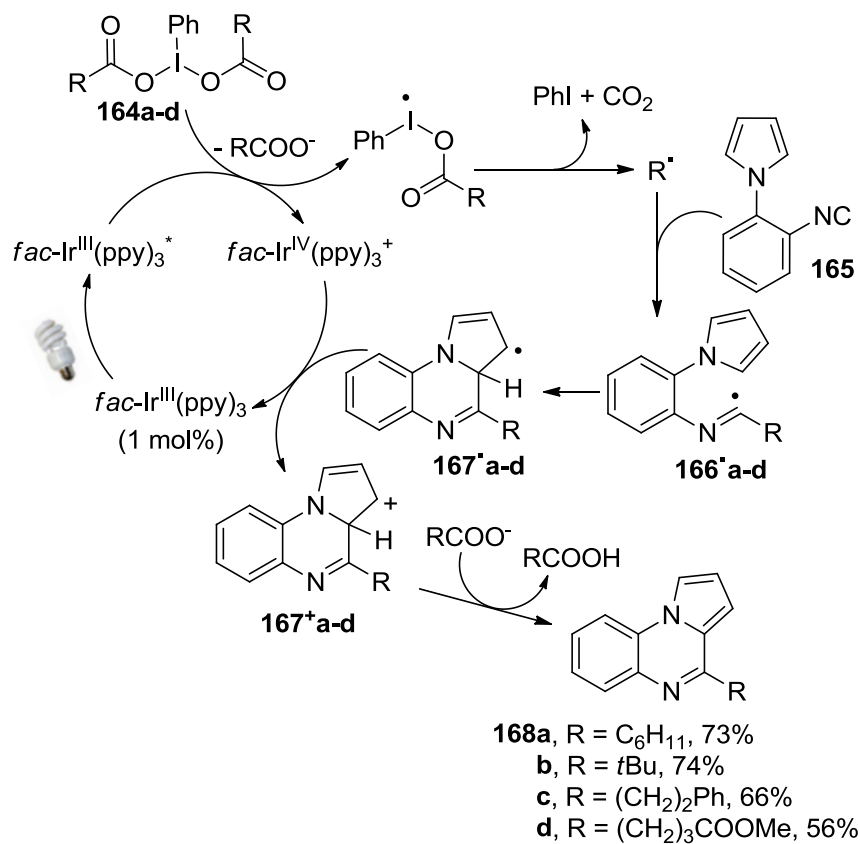
2.5. Larger than Six Membered Rings

As seen above, atom economical photo-Fries processes have been exploited in the synthesis of biologically active compounds.[13,153] Photochemical rearrangement in neat cyclohexane of macrocyclic lactone **169** via biradical **170** (Scheme 61), gave the corresponding acyl phenol **171** in a 75% yield, in turn employed as a key intermediate in the preparation of antibiotic kendomycin **172**.[154]

Scheme 61. Synthesis of Antibiotic Kendomycin 172 via Photo-Fries Rearrangement of Lactone 169
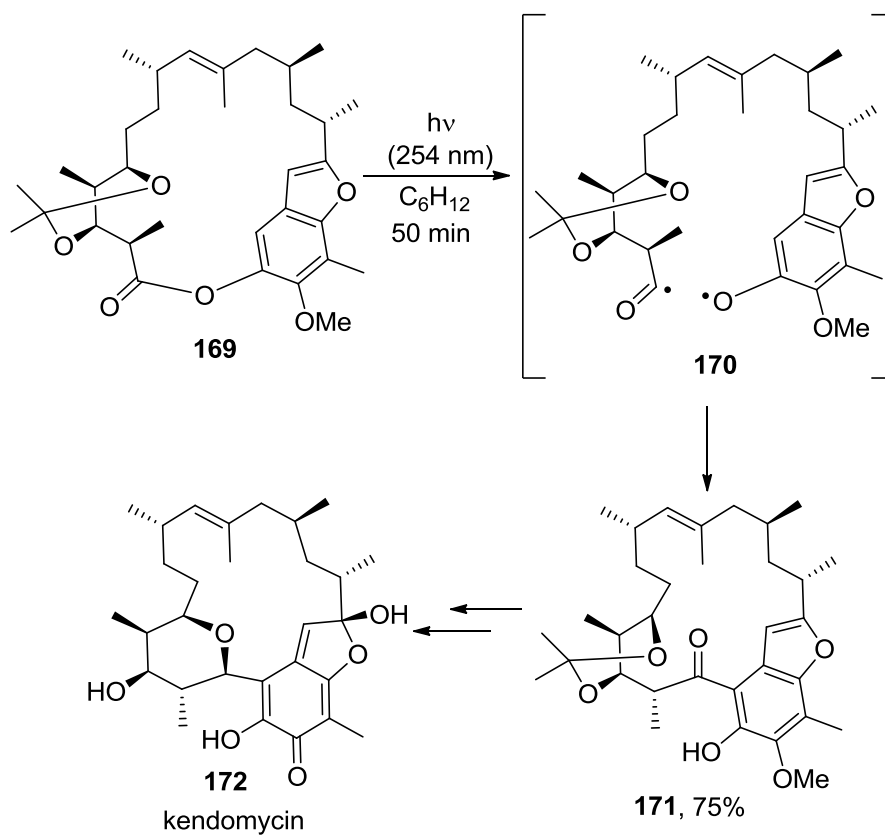
Cobalt complex **174** (Scheme 62) has been recently exploited for the base-mediated alkyl Heck type coupling via generation of carbon centered radicals from the corresponding alkyl iodides.[155] In a recent application, the octahydroazulene ring in the vasorelaxant daphmanidin E (**178**) was formed starting from iodide **173**.[156] The initial step of the process involved a photostimulated reaction between **174** and **173** to form Co^{III} derivative **176** that underwent intramolecular cyclization to **177**. Loss of a Co^{III}-H species ensued, affording the desired product **175**.

Scheme 62. Synthesis of the Vasorelaxant Daphmanidin E (178)
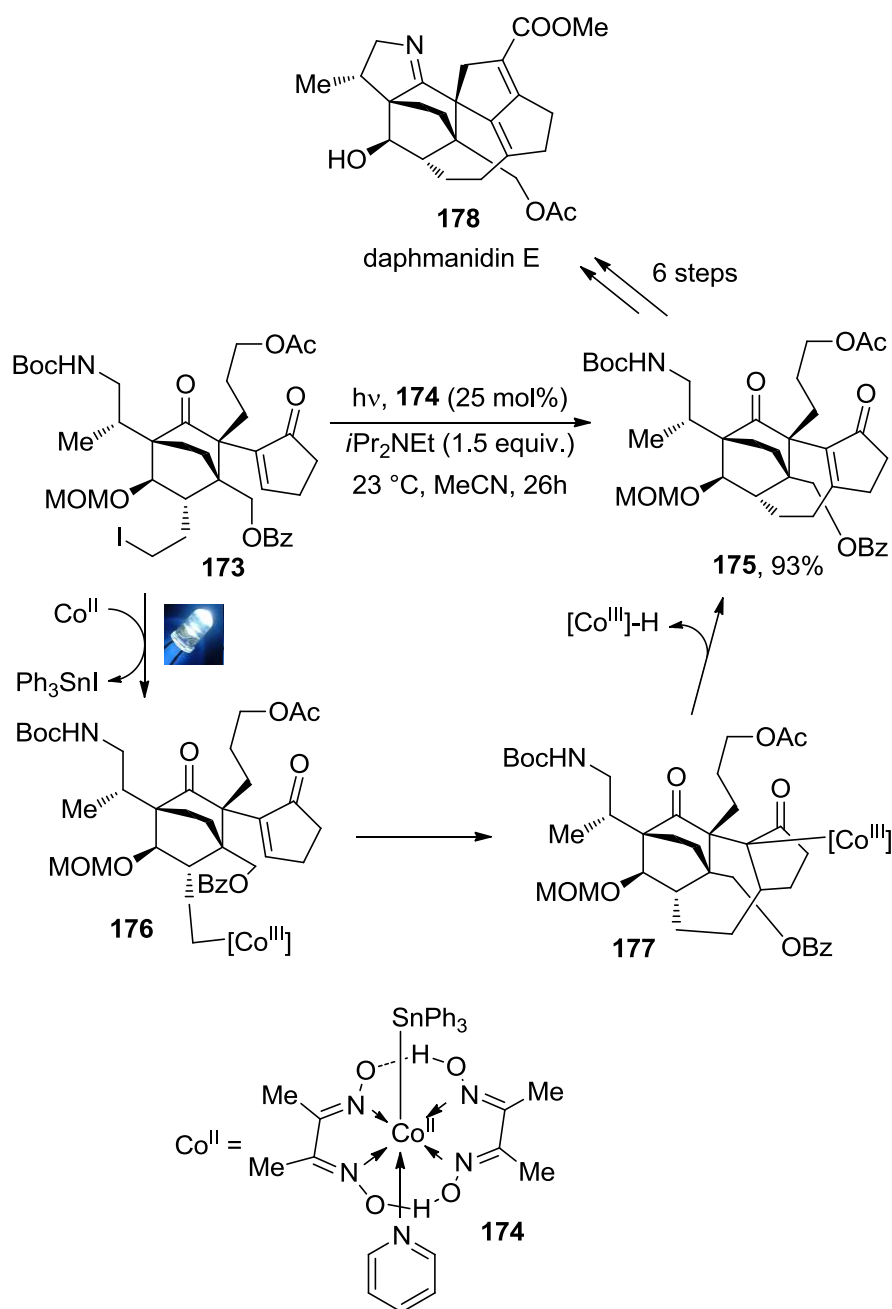
The excellent properties of the trimethylsilyl substituent (or a carboxylate) as electroauxilary group (Section 1.1.3)[31] has been exploited for the preparation of macrocyclic polyethers, polythioethers and polyamides.[157,158] As illustrated in Scheme 63, irradiation of *N*-substituted phtalimides **179a,b** caused an intramolecular SET reaction (see intermediates **180a,b**) that was followed by loss of the trimethylsilyl cation and protonation to form biradicals **181a,b**. The desired macrocycles **182a,b**

were then obtained from radical recombination.[157] An intramolecular photoinduced electron transfer was also reported in the Witkop cyclization applied to the multistep synthesis of monoterpenoid indole alkaloid (−)-leuconoxine.[159]

Scheme 63. Photochemical Synthesis of Macrocycles via Intramolecular SET Reaction

182a, n = 1, 82%
b, n = 3, 76%
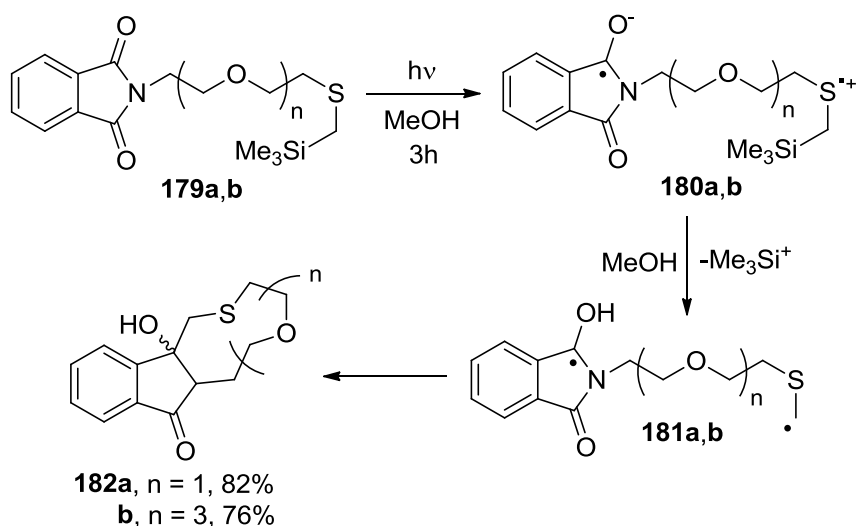
Intramolecular arylation of photogenerated vinyl cations **184⁺a-c** from β-bromostyrenes **183a-c** resulted in the selective formation of a vinyl-aryl bond, with the subsequent formation of a dibenzo[*b,f*]oxepin ring (see compounds **185a-c** in Scheme 64). The same reaction could be carried out thermally, but required the use of a large excess of base, high temperatures (up to 160 °C) or of AgOTf to favour solvolysis. In any case, a lower yield of **185b** was obtained under thermal conditions.[160]

Scheme 64. Photochemical and Thermal Synthesis of Dibenzo[*b*,*f*]oxepins

185a, R = H
b, R = CH₃   in all cases
c, R = Cl   100% yield
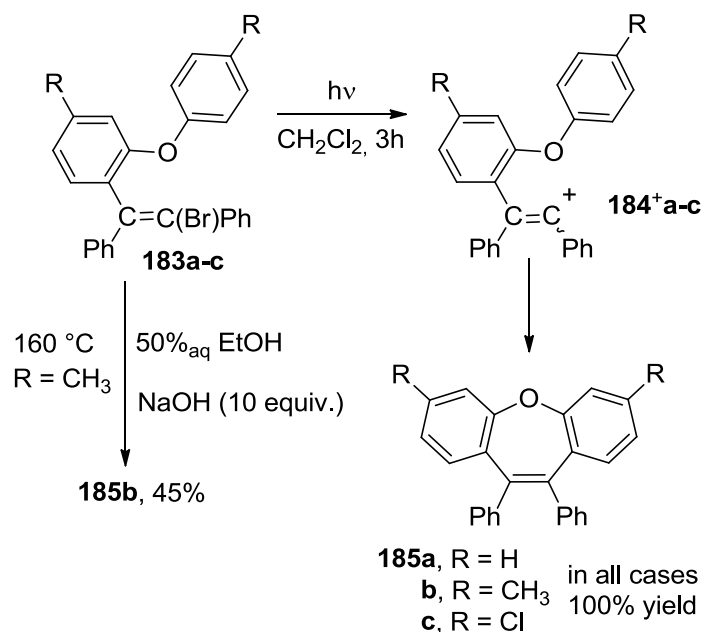
2.6. Two Rings

The Bergman cyclization in cyclic endiynes requires a relatively low activation energy and takes place under mild conditions, resulting in the simultaneous formation of 2 cycles.[11] Thus, cyclization of 10-membered pyrimidine enediynes **186** (Scheme 65), with a carbinol group adjacent to the triple bond, afforded tricyclic compound **188** in a satisfactory yield by using either a photochemical (83% yield) or a thermal approach (93% under reflux), via formation of *para*-benzyne **187**.[161]

Scheme 65. Photogeneration of Biradical via Bergman Cyclization
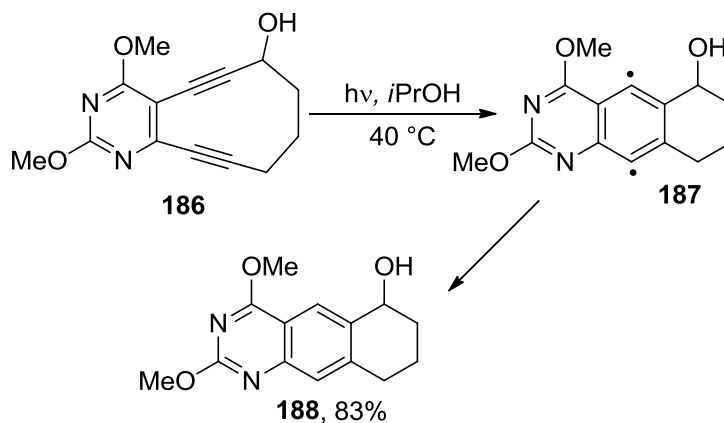
Caged hydrocarbon **190** (Scheme 66) has been synthesized in an almost quantitative yield via photoextrusion of SO$_2$ in sulfone **189** upon irradiation in an acetone-benzene 1:1 mixture.[162]

Scheme 66. Photoextrusion of SO$_2$ for the Formation of two Cyclobutane Rings
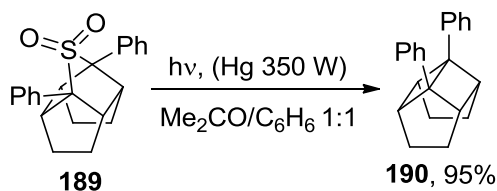
Ketenes arising from Wolff rearrangement of α-diazoketones and esters are considered as useful intermediates in organic synthesis.[41,163] Photodecomposition of Meldrum's acid diazo derivative **191** afforded ketene **192** that was efficiently trapped by substituted cyclohexenes **193a-d** to form cyclobutanones **194a-d** (Scheme 67a).[41,164] Intramolecular [2+2] cycloaddition of ketenes, however, is more often used in the synthesis of strained molecules, as in the case of **196** (Scheme 67b).[165]

Scheme 67. Wolff Rearrangement of α-Diazoketones in a) Intermolecular and b) Intramolecular Formation of Rings
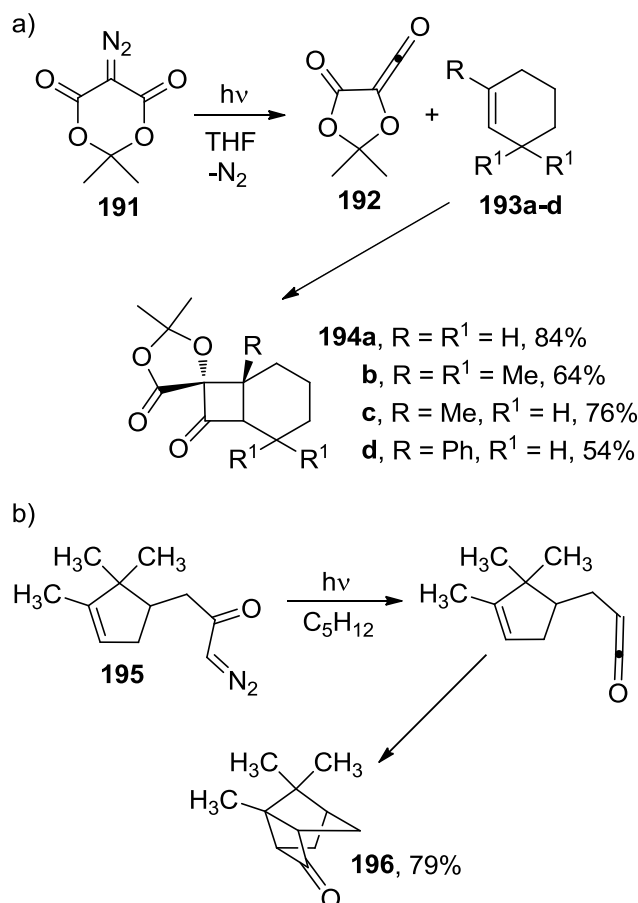
Intramolecular [2+2] cycloaddition may proceed via radical ions.[166] This is the case of bis-enones **197a,b** that were readily converted to bicyclic compounds **198a,b** in high yields and in a diasteroselective fashion (Scheme 68a) under $Ru^{II}(bpy)_3^{2+}$ photocatalysis via enone radical anion intermediate.[67] Interestingly, in order to make the formation of the radical anion easier, the reaction was repeated on α,β-unsaturated 2-imidazolyl ketone **199** containing an imidazoyl group in the role of cleavable redox auxiliary (Scheme 68b). Bicyclic derivative **200** was then smoothly formed and the auxiliary group was easily removed or functionalized at the end of the photochemical process.[167]

Scheme 68. Synthesis of Cyclobutanes via Photoredox Catalysis

a)

198a, R = R^1 = Ph, 89%, dr >10:1
b, R = Ph; R^1 = Me, 85%, dr >10:1

197a,b

b)

199

200, 90% (dr >10:1)
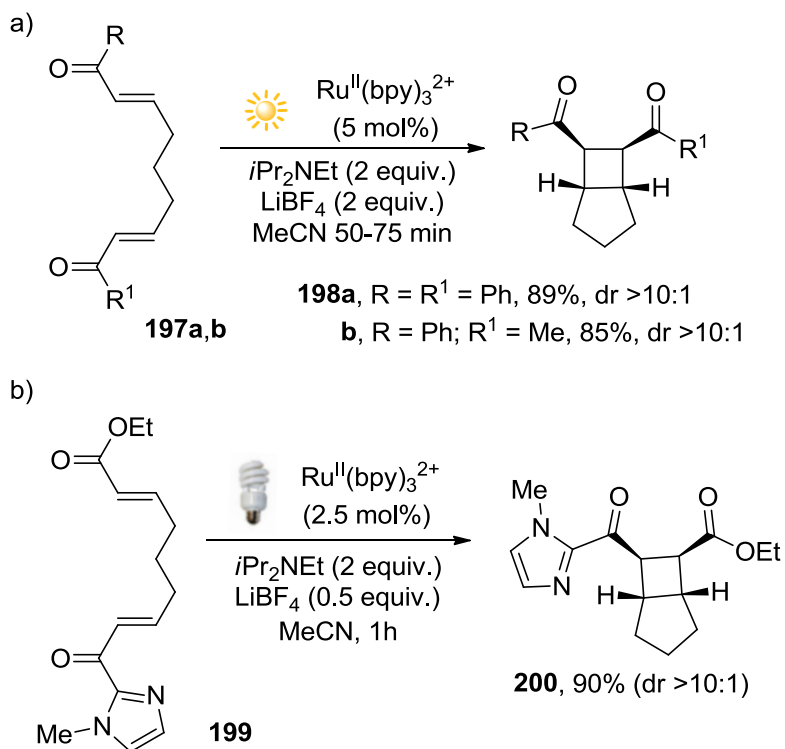
The irradiation of a Ru^{II} complex/amine system caused the photochemical reduction of the ketone moiety in phenylcyclopropylketones **201** and the opening of the α,β-cyclopropane ring to afford distonic radical ion **202**$^{\bullet-}$ (Scheme 69), which is stabilized by the presence of the lanthanum based Lewis acid. Intramolecular reaction of **202**$^{\bullet-}$ with an alkene (or alkyne) moiety led to highly elaborated bicyclo[3.3.0]octane **203**.[168]

Scheme 69. Photoredox Catalysis Route to Bicyclo[3.3.0]octanes

201, dr 1:1

TMEDA = Tetramethylethylenediamine
[La] = La(OTf)$_3$
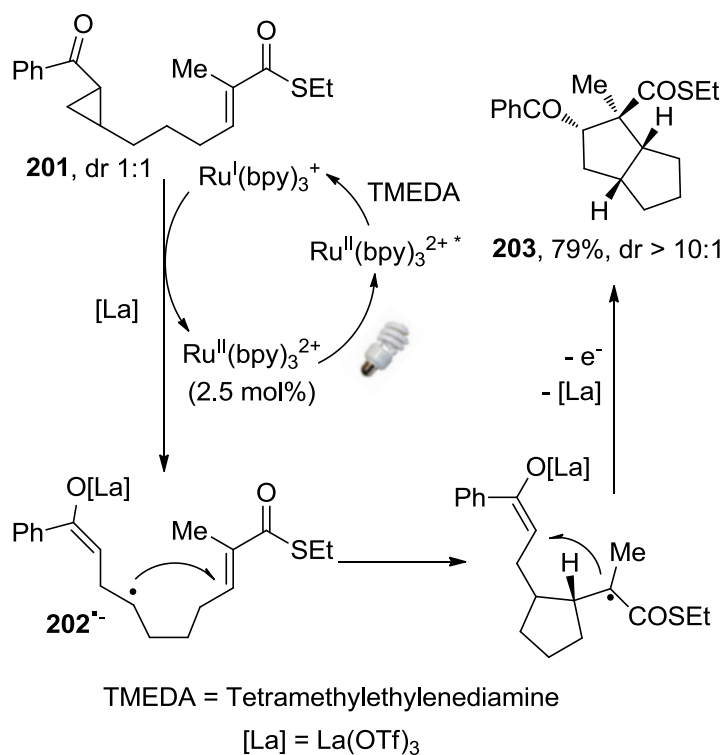
A similar distonic radical anion **205**$^{\cdot-}$ was used to trigger an intramolecular hetero-Diels-Alder reaction in tethered bis(enones) **204**, as shown in Scheme 70. Generation of **205**$^{\cdot-}$ followed by intramolecular addition on the other enone moiety gave the desired dihydropyran **206** in a highly diastereoselective fashion.[169]

Scheme 70. Intramolecular Hetero-Diels-Alder Reaction
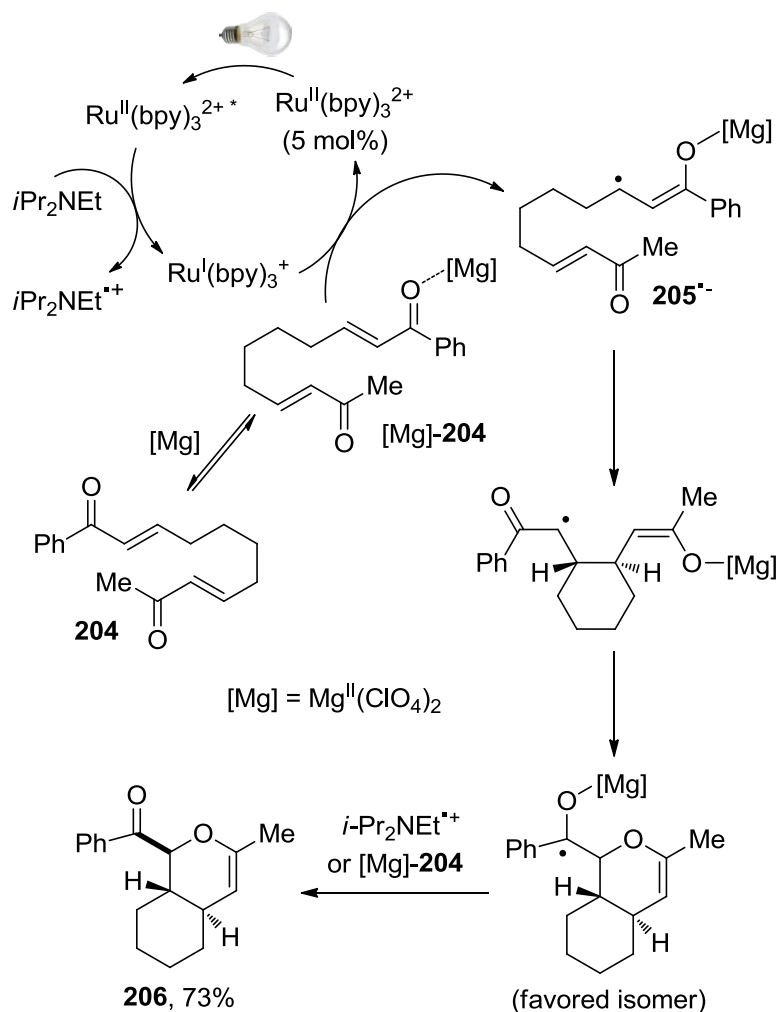
Photoinduced cycloaddition of styrenes and butadiene derivatives was found to proceed via mono-electronic oxidation of the styrene by using a Ru^{II} complex as the photocatalyst.[129] An intramolecular version of the reaction was recently described and scaled up by using either fluorescent bulbs or natural sunlight as the light source.[170]

The synthesis of bicyclic endoperoxides is of great interest due to the biological activity of several compounds belonging to this class, such as ascaridole and artemisinin.[171] The photosensitized oxygenation of dienes is definitely the elective method to achieve this target. As an example, a set of 1,5-diaryl-6,7-dioxabicyclo[3.2.2]nonanes with antimalarian activity has been obtained via photoinduced electron transfer oxygenation of the corresponding 2,6-diaryl-1,6-heptadienes[172] in

the presence of 2,4,6-triphenylpyrylium tetrafluoroborate (TPP$^+$BF$_4^-$) as photocatalyst. More recently, the single electron photoxidation of diene **207** mediated by 2,4,6-tri(4-methoxyphenyl)pyrylium tetrafluoroborate (**208**) was reported. Ensuing cyclization resulted in the formation of distonic radical cation **209**$^{•+}$ that was trapped by oxygen to form endoperoxide **210** (Scheme 71). The final reductive step was attributed to reaction either with mono-reduced **208**$^•$ or with a new molecule of **207**.[173] 1,4-Diarylendoperoxides with potential anticancer activity have been likewise synthesized by photocatalytic aerobic [2+2+2] cycloaddition occurring on dicinnamyl ethers.[174]

Scheme 71. Synthesis of Bicyclic Endoperoxide 210

210, 68%, dr 1:1
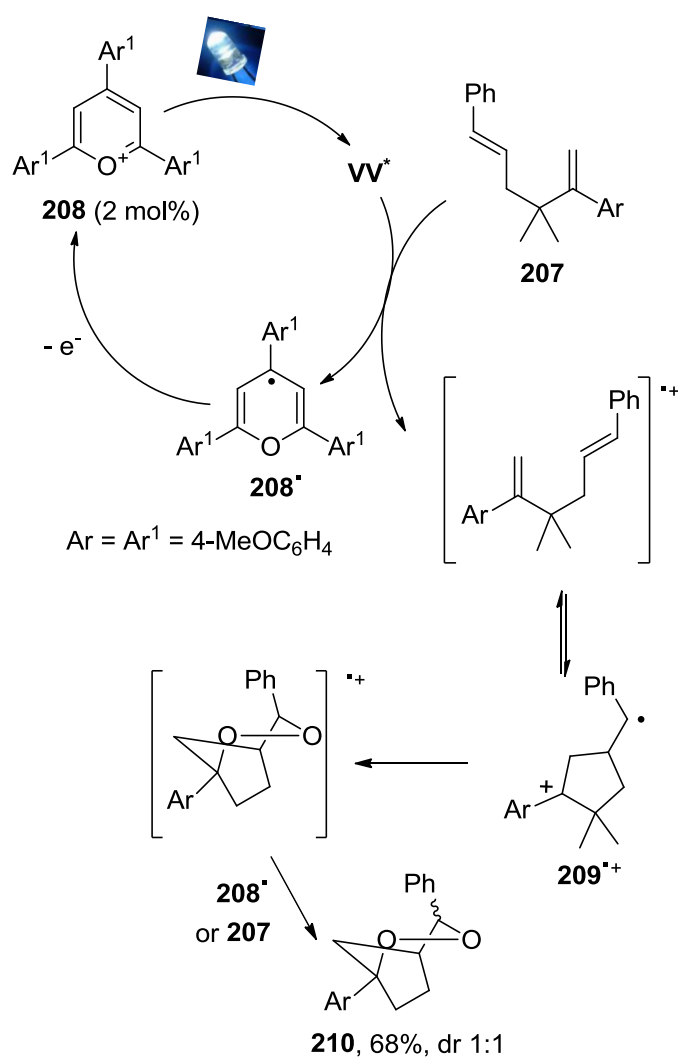
3. SYNTHESIS OF α- AND β- SUBSTITUTED CARBONYLS

3.1. Preparation of α-Functionalized Carbonyls

The most used approach for the preparation of α-functionalized carbonyls consists in the (*in situ*) conversion of the carbonyl derivative into a carbon nucleophile (enamines, enolates or enol silyl ethers) and then alkylation (or arylation) with an alkyl (or an aryl) halide. As for the latter, a $S_{RN}1$ mechanism is often involved.[37] As an example, irradiation of the enolate ion of 2-acetyl-1-methylpyrrole **212⁻** in the presence of iodonaphthalene **211** in DMSO yielded 78% of substitution product **213** (Scheme 72a). Interestingly, a sluggish reaction was observed under thermal conditions in the presence of FeBr₂, traditionally employed to promote the $S_{RN}1$ process.[175] In a related way, 2-iodoadamantane **214** reacted with different carbanions, including the enolate ion of acetophenone **215⁻**, to afford the α-alkylated product **216** in 62% yield after 3h irradiation (Scheme 72b).[176]

Scheme 72. a) Arylation and b) Alkylation of Aromatic Ketones under $S_{RN}1$ Conditions
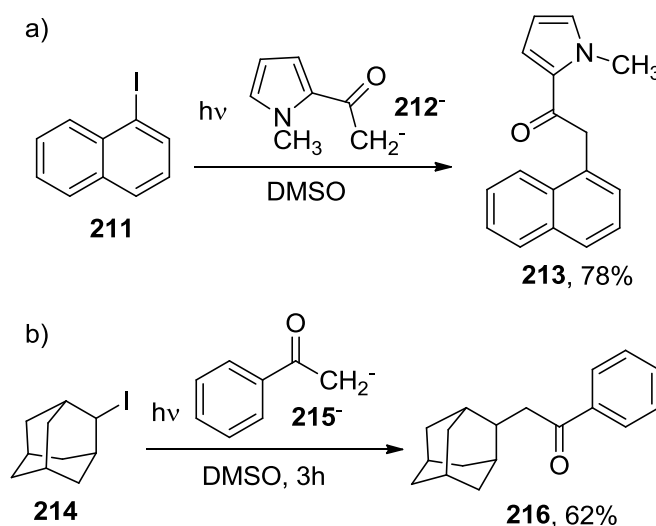
Visible light photoredox catalysis is becoming a valid tool for the enantioselective preparation of α-functionalized carbonyls, especially when photocatalysis is merged with organo- or acid-catalysis.[177]

A seminal work on this topic involved the enantioselective intermolecular α-functionalization of aldehydes, accomplished by the combined use of a photoredox catalyst (a Ru^{II} based complex) and a chiral imidazolidinone organocatalyst **219** (Scheme 73).[178] Under these conditions, aliphatic aldehydes **220a-c** reacted thermally with **219** to give enamines **221a-c** that trapped electrophilic radical **218**. The latter was in turn generated via monoelectronic reduction of bromomalonate **217** by Ru^{I} and ensuing bromide anion loss. Oxidation of the resulting α-amino radicals **222·a-c** and hydrolysis of the obtained iminium ions afforded the end alkylated aldehydes **223a-c**, in excellent yield and ee.[178] However, the mechanism of the reaction is still debated, and the participation of a chain process involving a SET between **222·a-c** and bromomalonate **217** has been recently proposed.[30] A related enantioselective approach to α-alkylated aldehydes has been later reported and involved the use of the same chiral imidazolidinone **219** and of semiconductor Bi$_2$O$_3$ (20 mol%) as the photocatalyst.[179] Carbazolic porous organic frameworks were likewise used as photocatalysts in several metal-free processes, including the α-alkylation of aldehydes, by reaction of the *in situ* formed enamines with bromomalonates and phenacyl bromides.[180]

Scheme 73. Organocatalytic Photoredox α-Alkylation of Aldehydes

223a, R = C$_6$H$_{13}$, 95%, ee 90%
  b, R = CH$_2$Ph, 92%, ee 90%
  c, R = C$_6$H$_{11}$, 83%, ee 95%

219 (20 mol%)

220a-c

221a-c

218·

222·a-c

217

218·
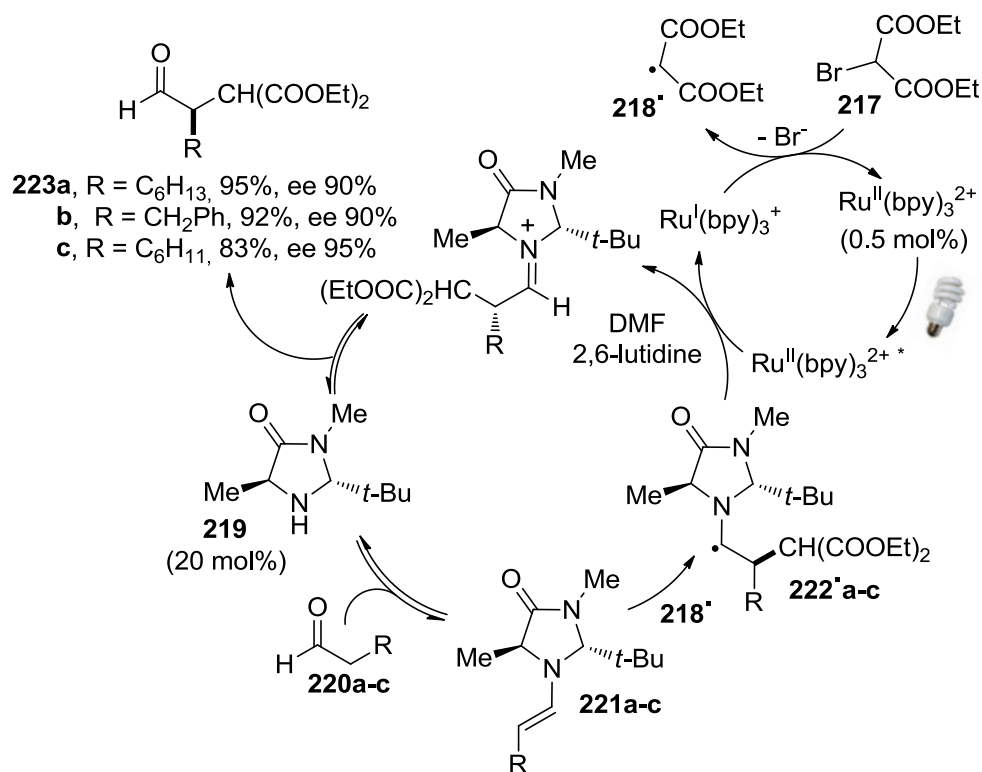
A different chiral primary amine (**226**) has been likewise used as organocatalyst in the stereoselective photocatalyzed α-alkylation of β-ketoesters and carbonyls **224a,b** (Scheme 74).[181]

Scheme 74. Photocatalyzed α-Alkylation of β-ketoesters 224a,b

224a,b

225a,b

226 (20 mol%)
NaHCO$_3$, MeCN

227a, R = Me, R^1 = Ph, 88%, ee 97%
  b, R = C$_3$H$_7$, R^1 = Ph, 52%, ee 96%
  c, R = Me, R^1 = 4-NO$_2$C$_6$H$_4$, 78%, ee 96%
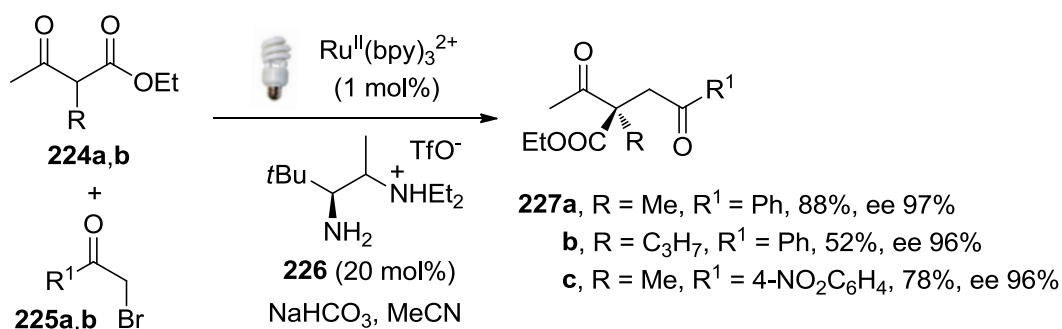
The enantioselective synthesis of α-functionalized esters **231a-c** has been also achieved by merging photoredox catalysis and asymmetric anion-binding catalysis in a one-pot, two-step process. Here, ketene silyl acetal **230** was used as carbon nucleophile. The Ru^{II}(bpy)$_3$$^{2+}$ complex photocatalyzed

the chlorination of *N*-aryl tetrahydroisoquinolines (*N*-aryl THIQ, **228a-c**) to form chloroderivatives **232a-c** that were in turn converted to the corresponding electrophilic iminium ion **233⁺a-c** via anion binding catalysis. Mannich coupling between **230** and the *in situ* generated **233⁺a-c** resulted in the desired product (Scheme 75). The use of a chiral anion binding catalyst, such as thiourea **229**, resulted in a stereoselective process.[182]

Scheme 75. Dual Catalytic Enantioselective Synthesis of β-amino Esters via Anion Binding Catalysis
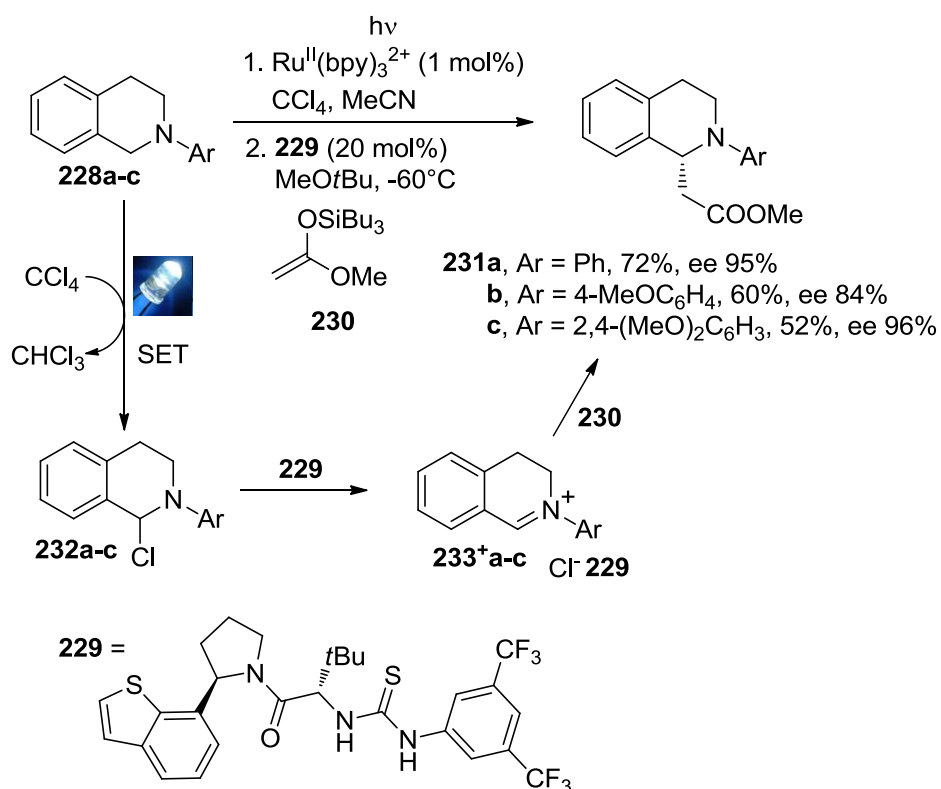
Dehydrogenative-Mannich reactions applied on substituted THIQs were also accomplished by the *in situ* generation of a nucleophilic enamine from the acid catalyzed reaction of pyrrolidine with a ketone,[183] whereas the electrophilic iminium ion of the tetrahydroisoquinoline was again obtained photocatalitically. An organic dye (Rose bengal) was successfully employed as the photocatalyst instead of toxic and expensive metal-based complexes. The substitution of (*L*)-proline for

pyrrolidine in the functionalization of cyclohexanone caused an improvement in terms of yield and also imparted a good stereoselectivity to the process.[183]

A different approach in the α-functionalization of carbonyls was based on the irradiation of an *in situ* formed colored chiral electron donor-acceptor (EDA) complex between a chiral enamine (e.g. **236**) and an electron-poor benzyl or phenacyl bromide. As an example, Scheme 76 shows the case of the derivatization of butanal **234** with benzyl bromide **237**. Thus, irradiation of the EDA complex resulted in a photoinduced electron transfer to form a radical ion pair **236•+-237•−**.[184] The coupling between benzyl radical **238•** (formed by bromide loss) and the enamine radical cation **236•+** afforded the desired product **240** in a satisfactory yield and high enantiopurity. The same approach has been successfully applied to cyclic ketones by using a cinchona-based primary amine as organocatalyst.[185]

Scheme 76. Stereoselective α-Alkylation of Aldehydes via Formation of a Donor–Acceptor Complex

240, 95%, ee 84%

234

235

236

237

238·

239⁺

236·⁺

- Br⁻

236·⁺- 237·⁻

SET

236-237

Colored EDA complex

235 =
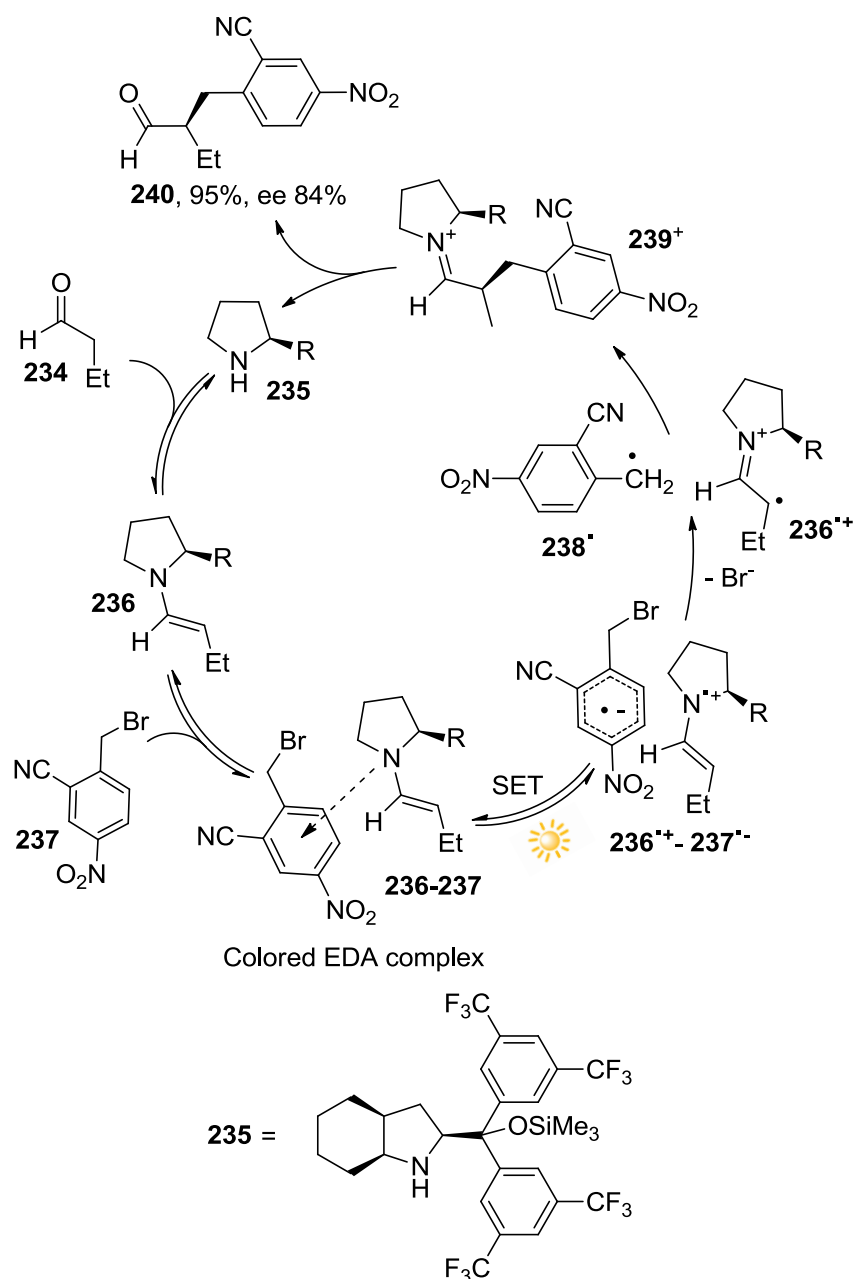
Molecules containing polyfluoroalkyl moieties often exhibit enhanced biological properties, making the development of efficient procedures for their synthesis a significant target. In recent years, great attention has been given to the development of photocatalytic procedures for the synthesis of α-trifluoromethylated or α-perfluoroalkylated carbonyls.[186,187] The achiral version of the process occurred via the reaction of an in situ formed enol silyl ether with CF$_3$I or perfluoroalkyl iodides as

alkylating agents both under batch (involving a Ru^{II} complex as the photocatalyst)[188] and continuous flow conditions (Eosin Y as the photocatalyst).[189]

However, a protocol for the valuable enantioselective α-trifluoromethylation (or α-perfluoroalkylation) of aldehydes or cyclic β-ketoesters was optimized by merging photoredox catalysis and organocatalysis[190] or by having recourse to chiral EDA complexes,[191] respectively.

An innovative photocatalytic system has been recently proposed, where an Ir^{III} complex (Ir^{III}a in Scheme 77) was found to play the dual role of photoredox and enantioselective catalyst. Indeed, the process made use of α-silylamines (e.g. **241**) as alkylating agents in the functionalization of 2-acyl-1-phenylimidazoles (e.g. **243**). Thus, reductive quenching of Ir^{III}a* by **241** afforded the corresponding iminium ion **242$^+$** via PET, loss of Me$_3$Si$^+$ and further oxidation. The iminiun ion was then trapped by chiral enolate Ir^{III}a-**244$^-$** (formed via deprotonation of the complex Ir^{III}a-**243**) and led to the formation of α-functionalized ketone **245** (Scheme 77).[192] A related Ir-based catalyst (Ir^{III}b, X = S) was applied in the coupling of acylimidazoles with benzyl bromides.[193]

Scheme 77. Photocatalytic Enantioselective Alkylation by means of Chiral Iridium Catalyst Ir^{III}a

3.2. Preparation of β-Functionalized Carbonyls

While different methods are available for the introduction of chemical functionalities at the α-positions of the carbonyl (carboxyl) moiety, the β-functionalization of esters, ketones, aldehydes, and amides has been limited for a long time to the addition of soft nucleophiles to α,β-unsaturated systems. Recently, the direct β-alkylation of saturated aldehydes, such as **220a**, has been accomplished via photoinduced oxidation of the *in situ* generated enamine **246**. The obtained β-enaminyl radical intermediate **247·** (arising via deprotonation of radical cation **246·+**) efficiently

combined with a wide range of Michael acceptors (e.g. **248**) to produce the desired β-alkylated aldehyde **249** (Scheme 78).[194] A three-component coupling of aromatic aldehydes, amines and ketones for the synthesis of γ-aminoketones through a formal β-Mannich reaction has been likewise reported, and involved the use of DABCO in the double role of base and electron transfer agent.[195] The synthetic scope of the process has also been extended to cyclic ketones.[196]

Scheme 78. β-Alkylation of Aldehydes via Photoredox Organocatalysis
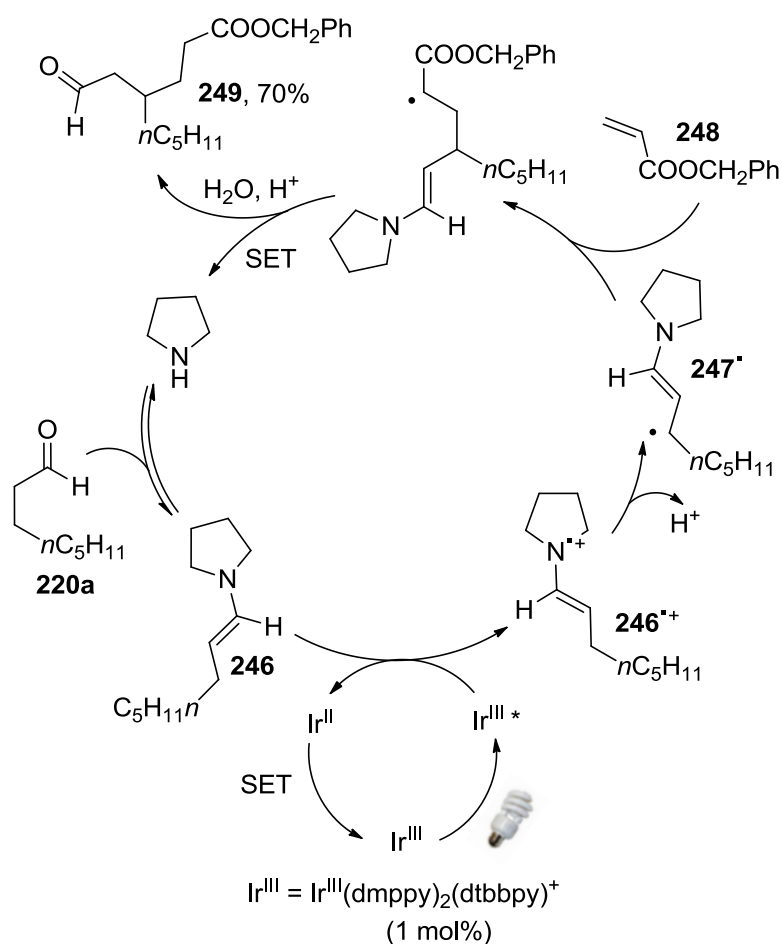
Cyclopentanones (such as **250** in Scheme 79) have been likewise functionalized in the β-position exploiting the regioselectivity of excited (nBu$_4$N)$_4$[W$_{10}$O$_{32}$] (TBADT) in abstracting β-methylene hydrogen atoms. The resulting radical **252**˙ reacted with electron-poor olefins (e.g. methyl vinyl ketone) to form 1,6-difunctionalized compounds (**251**). Notably, when the irradiation was carried

out in the presence of CO, 1,4-dicarbonyls **253** were obtained from a three-component reaction (Scheme 79).[197]

Scheme 79. Sunlight Driven β-Alkylation of Cyclopentanones
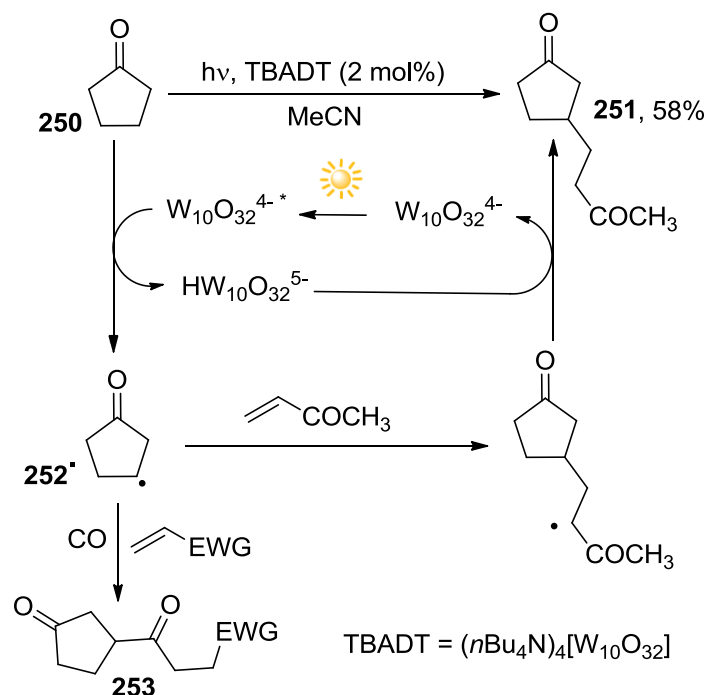
4. Ar-C BOND FORMATION

Different are the approaches (and the intermediates) potentially useful for the formation of Ar-C bonds. Aryl radicals are widely used as arylating intermediates and can be generated by homolytic cleavage of an Ar-halogen bond, by monoelectronic reduction of an aryl onium salt (e.g. a diazonium salt) and by anion loss from an aromatic radical anion (in the $ArS_{RN}1$ reaction).[34] In alternative, radical anions of polycyanoaromatics (e.g. TCB) can undergo radical addition and an ipsosubstitution results via loss of a cyanide anion.[19] Phenyl cations can be formed by photoheterolysis in aryl chlorides and fluorides.[38] In other instances, dual catalytic processes allows for the photogeneration of carbon radicals that attack a metal complex of an aryl halide. Finally, a

radical can be trapped by an (hetero)aromatic and subsequent rearomatization leads to an overall activation of an Ar-H bond.

4.1. by Ipso-substitution of an Onium Group

Aryl onium salts are highly reducible derivatives (Figure 2) and, accordingly, are widely used for the smooth photocatalytic generation of aryl radicals. In particular, arenediazonium salts have been used as the elective substrates.[198] Despite the use of $Ru^{II}(bpy)_3^{2+}$ as the photocatalyst for aryl radical formation was reported about 30 years ago and applied to promote a photo-Schorr cyclization,[199] only recently the use of onium salts has become massif.[200] As an example, arenediazonium salts **255$^+$a,b** were prepared *in situ* from the corresponding anilines **254a,b** and then irradiated in the presence of electron-rich heteroarenes (such as furan or thiophene) and eosin Y as the photocatalyst. Oxidative quenching of eosin Y* by **255$^+$a,b** resulted in the formation, after molecular nitrogen loss, of phenyl radicals **256$^•$a,b**, that were efficiently trapped by the heterocycle to generate radicals **257$^•$a-c**. The latter underwent oxidation to Wheland intermediates **257$^+$a-c**, while regenerating eosin Y, and ensuing deprotonation afforded the desired heterobiaryls (**258a-c**, Scheme 80).[200]

Scheme 80. Metal-free Arylations by Arenediazonium Salts

258a, R = 4-CN, X = O, 88%
   b, R = 4-CN, X = NBoc, 77%
   c, R = 4 Me, 2-NO$_2$, X = S, 80%
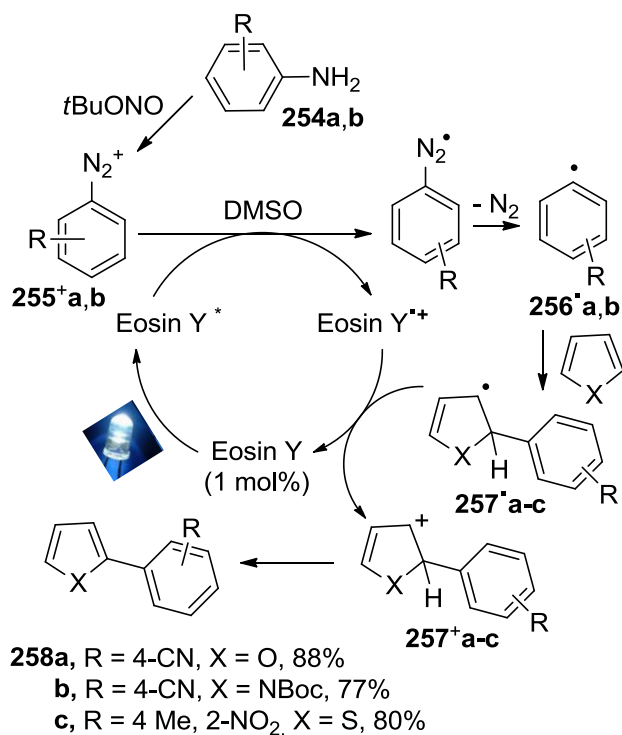
Photoarylation of five-membered heteroaromatic rings has been also performed in ethanol by using inexpensive TiO$_2$ as the photocatalyst. TiO$_2$ catalyzed the formation of aryldiazoethers **259a-c** that underwent photochemical reduction by photoexcited TiO$_2$ to form aryl radicals **260˙a-c** that were in turn trapped by an electron-rich heteroaromatic.[201] Oxidation of radical intermediates **261˙a-c** and deprotonation afforded the desired biaryls **262a-c** (Scheme 81). The chemical adsorption of arenediazonium salts on the photocatalyst surface and the ensuing formation of visible light absorbing TiO$_2$-azoethers allowed the use of a CFL lamp as the light source to promote the process.

Scheme 81. Visible Light Arylation of Heteroarenes under Heterogeneous Catalysis

262a, R = 4-F, 96%
   b, R = 3-OMe, 80%
   c, R = 2-CN, 83%
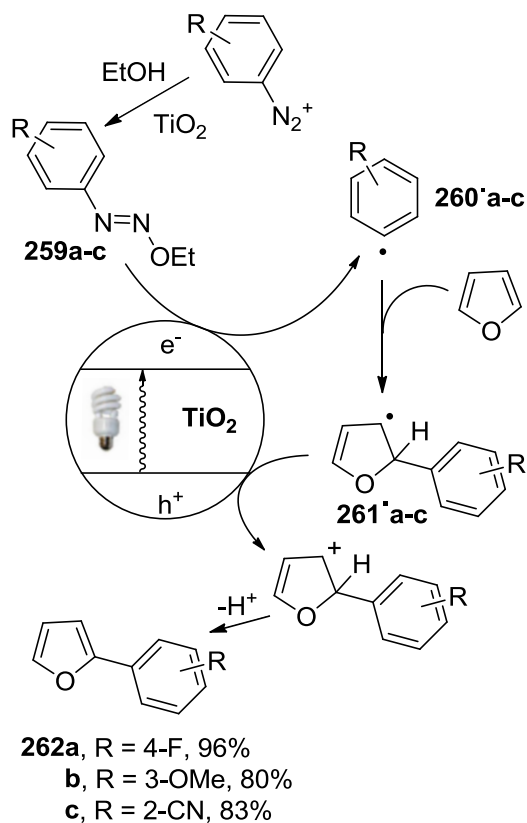
The arylation of protonated *N*-heteroarenes (e.g. pyridine, pyrazine, and pyridazine) was likewise accomplished starting from arene diazonium salts (under Ru[II] photocatalysis)[202] and diaryliodonium salts (under Ir[III] photocatalysis).[203]

Notably, the regioselective photoarylation of isoquinolines (**263**) has been applied as a key step in the synthetic route to alkaloid menisporphine, having potential application as antiangiogenic agent (Scheme 82).[204]

Scheme 82. Photocatalytic Arylation of Isoquinoline 263 as the Key Step in the Synthesis of Menisporphine
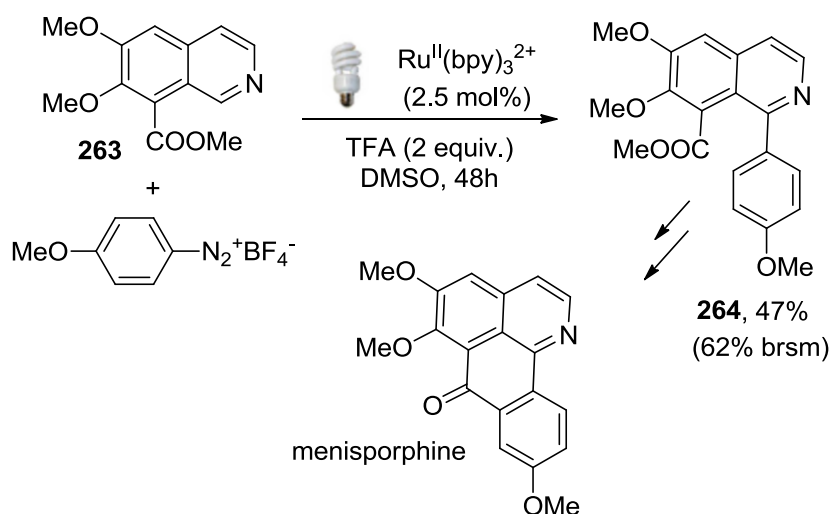
Ruthenium photocatalyzed arylation of methyl substituted aromatics by arenediazonium salts has been also described, though a complete selectivity was achieved only when using symmetric benzene and *p*-xylene.[205]

Alkenes (especially, styrenes) or alkynes were widely used as reaction partners for aryl radicals and several photocatalytic variants of the classical Meerwein reaction have been developed. The intermolecular coupling of onium salts with, respectively, alkenes, alkynes, and enones can be photocatalyzed by ruthenium and iridium complexes, as well as organic dyes, and mostly involved a three-component reaction. As an example, the consecutive Ar-C and C-O bond formation across the double bond of styrenes was obtained by using diaryl iodonium salts as substrates (Scheme 83a).[206] The reaction was initiated by the reduction of these salts (e.g. Ph_2I^+) by excited iridium complex $Ir^{III}(ppy)_3$ and involved the subsequent generation of a phenyl radical upon loss of neutral iodobenzene. Addition of the phenyl radical onto the C=C double bond of **265a-c** afforded radical adducts **266·a-c**. Ensuing oxidation of **266·a-c** to benzyl cations **266⁺a-c** yielded the desired phenethyl ethers **267a-c** upon addition of the alcoholic solvent (Scheme 83a). When the process

was carried out in acetonitrile/water or water/DMF mixture, an overall aminoarylation[206] or formyloxyarylation (compounds **268a-c**, Scheme 83b)[207] process took place, respectively.

In a related application, benzyl aryl ketones were prepared by irradiation of arenediazonium salts in the presence of styrenes in oxygen-saturated methanol.[208] The three-component oxyarylation of simple alkenes has been likewise carried out by using a dual gold and photoredox catalytic system.[209] Indeed, organic dyes, such as Fluorescein and Eosin Y, were used as the photocatalyst in the reaction involving arenediazonium salts, whereas less reducible diaryl iodonium derivatives required more reductant iridium complexes.[209]

Scheme 83. a) Oxyarylation and b) Formyloxyarylation of Styrenes by Photoredox Meerwein Reaction

a)

267a, R = H, 70%,
b, R = 4-CF$_3$, 66%
c, R = 3-Cl, 83%

b)

268a, R =H, 76%
b, R = Me, 61%
c, R = Cl, 74%
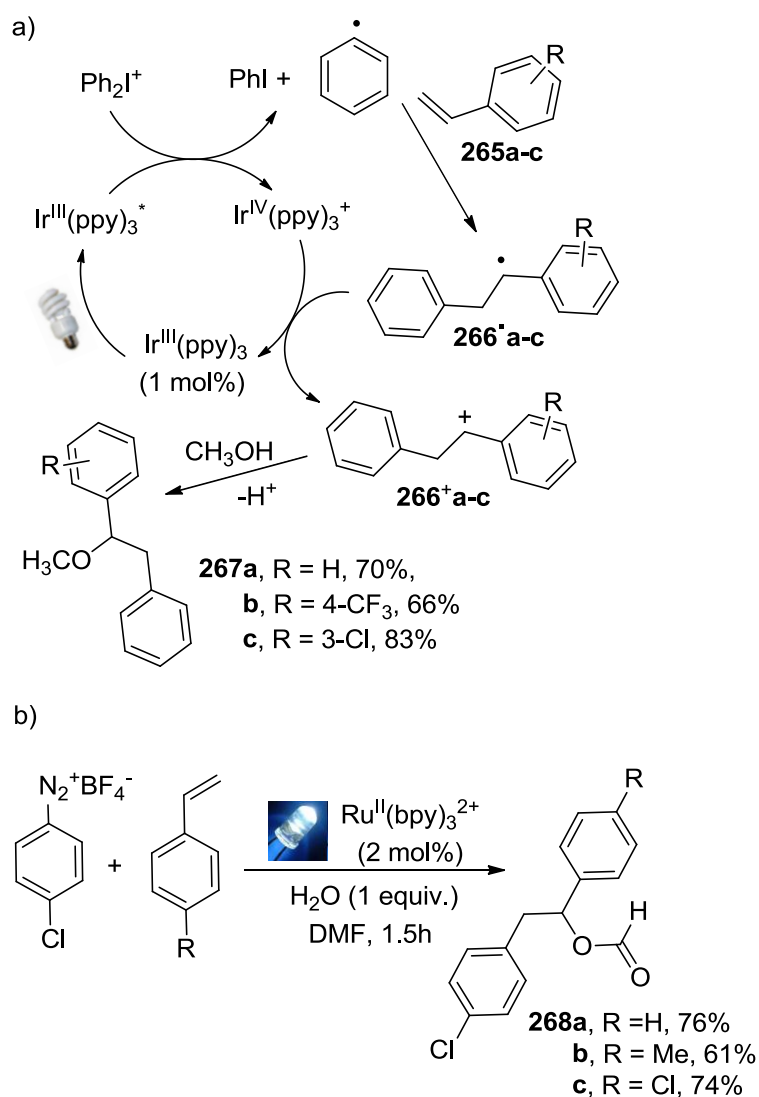
In rare instances, arylsulfonium salts **269$^+$a-c** were used as the aryl radical source. An example deals with the synthesis of triarylethanes **270a-c** through the photocatalytic arylation of diphenylethylene in the presence of iPr$_2$NEt as reductive quencher (Scheme 84).[210] The same substrates have been also employed in radical allylation processes.[210]

Scheme 84. Photoredox Catalyzed Synthesis of Triarylethanes from Arylsulfonium Salts

270a, Ar = C_6H_5, 70%
b, Ar = 4-$CH_3C_6H_4$, 70%
c, Ar = 4-FC_6H_4, 58%
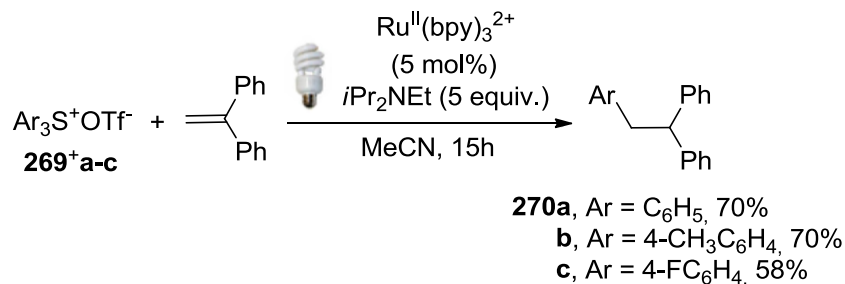
The photocatalytic generation of aryl radicals from aryl iodonium salts in the presence of $Cu^I(dpp)_2^+$ as the photocatalyst has been described. The process was found to involve the generation of an iodanyl radical ($Ar_2I^{\bullet}$), that fragmented to iodobenzene and an aryl radical. Trapping of the generated intermediate by allylsulfones as radical acceptors resulted in the construction of an Ar-allyl motif (e.g. **271a,b**, Scheme 85).[211]

Scheme 85. Copper(I) Photocatalyzed Synthesis of Allyl Arenes

271a, Ar = 4-MeC_6H_4, 71%
b, Ar = 4-$tBuC_6H_4$, 67%
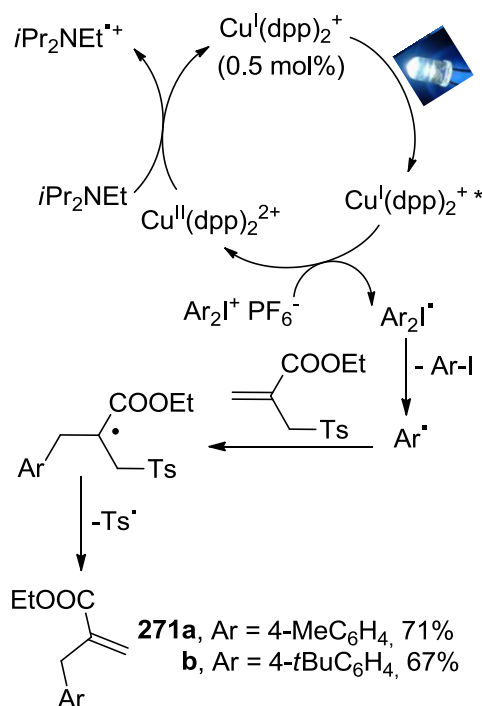
Aryl radicals are known to react with CO to form the corresponding acyl radicals. Thus, irradiation of a solution of the chosen diazonium salt, containing benzene, CO (70 atm) and Eosin Y as the

photocatalyst, resulted in a three-component synthesis of aromatic ketones **272**,[212] as shown in Scheme 86 (right part). Analogously, benzoic esters **273** were prepared from the photocatalyzed coupling of arenediazonium salts, CO and an alcohol,[213,214] the latter acting as both reactant and solvent (Scheme 86, left). In the latter case, the SET oxidation of the benzoyl radical intermediate to the corresponding benzoyl cation was responsible for the formation of the desired ester.

Scheme 86. Photocatalyzed Multicomponent Route to Aromatic Ketones (right part) and Esters (left part)
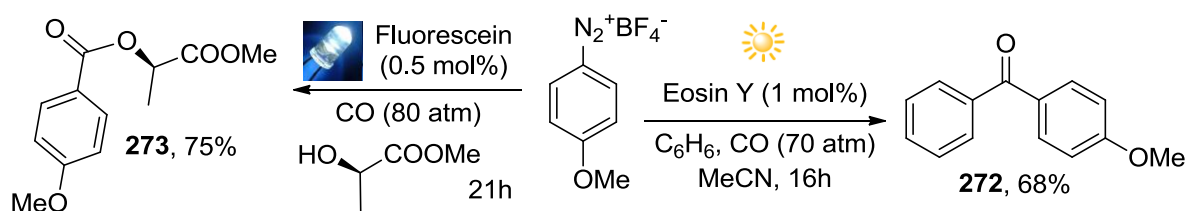
4.2. by Ipso-substitution of a Halogen

In this case the strategy is based on the formation of an aryl radical or an aryl cation. Aryl radicals can be generated through the photohomolysis of Ar-halide bonds.[3,215] A versatile route to biaryls and heterobiaryls involved the irradiation of heterocyclic halides bearing an aldehyde or a nitro group in position C-2 (**274**), in the presence of (hetero)aromatics.[215,216] Simple aromatics such as thiophene and benzene were often used in a large excess, thus playing the dual role of reactant and solvent (or, at least, co-solvent; Scheme 87a). A radical intermediate was also invoked in the cyanoborohydride promoted photochemical coupling of aryl iodides with benzene (Scheme 87b).[217]

Scheme 87. Synthesis of a) Heterobiaryls and b) Biaryls via Photochemically Generated Aryl Radicals

a)

276, 94%　　　　　　　　　　**274**　　　　　　　　**275**, 98%

b)

277a, R = 4-OMe, 78%
b, R = 4-COOEt, 68%
c, R = 3-OMe, 79%
d, R = 2-COOEt, 70%
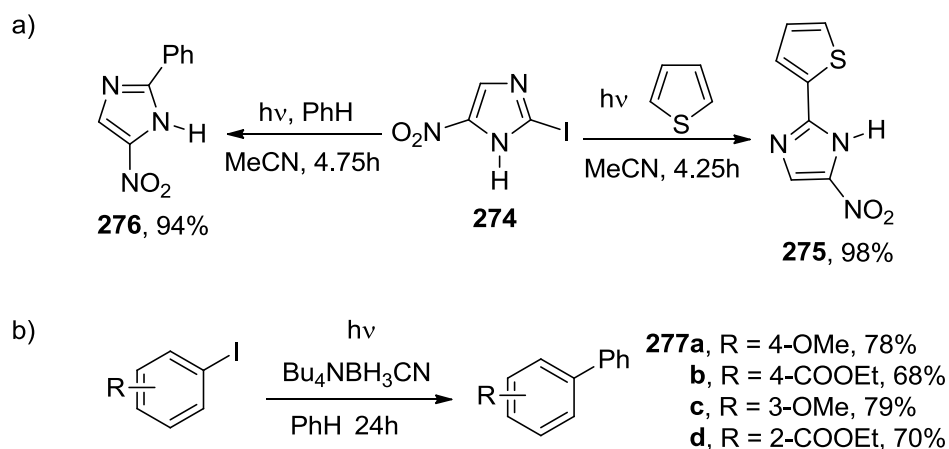
An $S_{RN}1$ process has been recently exploited in a protocol for the synthesis of differently substituted stilbenes **279a-d**[218] via a transition-metal-free Mizoroki-Heck-type reaction. Thus, an aryl radical arising from irradiation of aryl halides (ArI) was efficiently trapped by styrene, and the resulting benzyl radicals **278˙a-d** underwent deprotonation by tBuO⁻K⁺ to form stilbene radical anions **279˙⁻a-d**, which were oxidized to the desired products via electron transfer to the starting substrate (Scheme 88). 18-Crown-6 ether was employed to coordinate the potassium ion in tBuO⁻K⁺ salt, thus enhancing the properties of tBuO⁻ as an electron donor.

Scheme 88. Photoinduced Transition-Metal-Free Synthesis of Stilbenes

279a, R = OMe, 87%
b, R = Ph, 79%
c, R = Me, 64%

279d, 54%
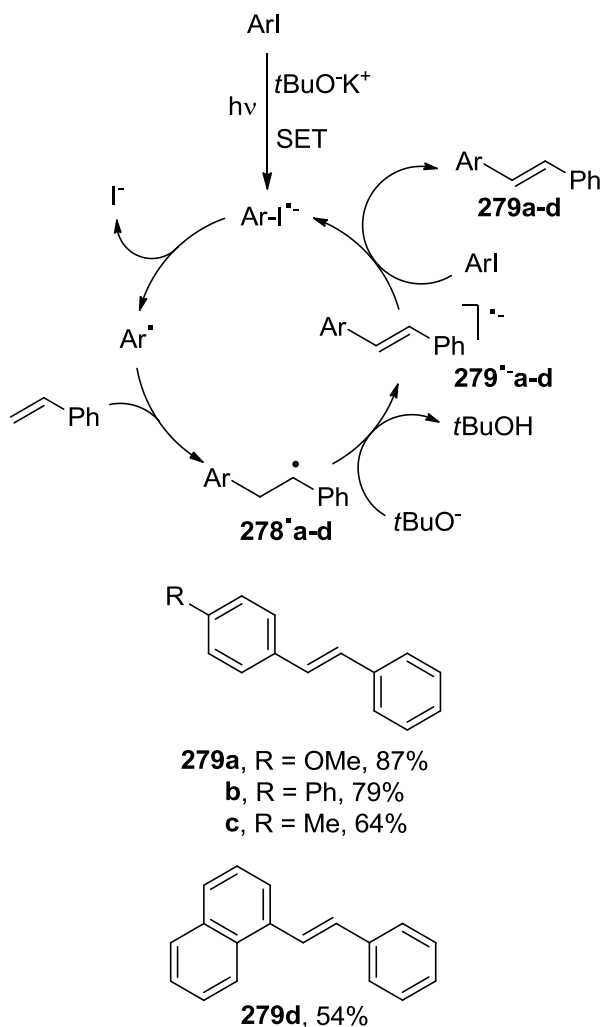
Recently, a two photon approach for the dehalogenation/arylation of electron-poor aromatic halides has been reported and was based on the use of perylene bisimide **281** as the photocatalyst. Excited **281*** was initialy reduced via a PET reaction with triethylamine to its stable and colored radical anion **281**·⁻ (Scheme 89). Ensuing excitation of **281**·⁻ to **281**·⁻ * allowed to reduce aryl chlorides **280**, thanks to the strong reducing power of **281**·⁻ *. The generated radical anion **280**·⁻ gave a phenyl radical **283**· (upon chloride anion loss) that was trapped by furans or pyrroles to give biaryls **282**.[219]

Scheme 89. Two Photon Photocatalyzed Arylation of Aryl Chlorides
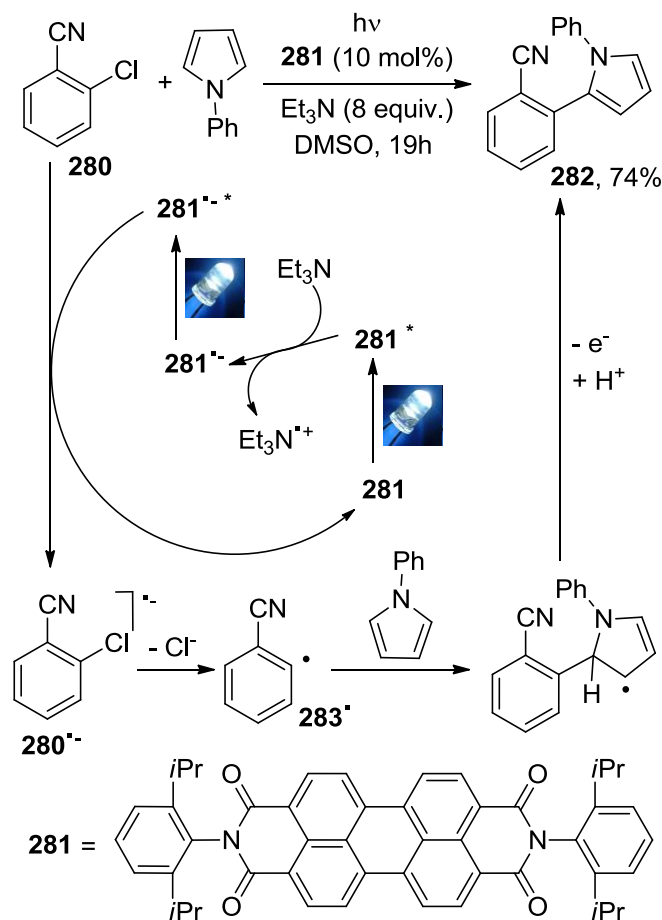
The synergistic combination of photoredox catalysis and transition metal (Ni⁰-based) catalysis has been exploited the formation of Aryl-C(sp³) bonds by reaction of aminoacids with aryl halides. In the photocatalytic step, irradiation of an Ir^{III} photocatalyst resulted in the formation of a long-lived photoexcited Ir^{III*} state that oxidized mono-electronically N-Boc protected α-amino acid **284**. The resulting radical underwent loss of CO_2 to generated α-amido radical **285·** (Scheme 90). At the same time, oxidative addition of the Ni⁰ complex onto the Ar-halogen bond in **286a-d** generated the Ni^{II} intermediates **287a-d**. This Ni^{II}-aryl species intercepted the α-amido radical, thus forming the organometallic Ni^{III} adducts **288a-d**. Subsequent reductive elimination resulted in Ar-C bond formation, expelling the Ni^{I} intermediate **290** and the desired benzylamines **289a-d**. Last, a SET process between the Ir^{II} species and the Ni^{I} species **290** allowed the regeneration of the starting

catalysts.[220] Interestingly, *N,N*-dimethylaniline could be likewise used as substrate (instead of **284**).
More recently, the same approach has been exploited in the synthesis of aromatic ketones by using
pyruvic acids as precursors of the corresponding acyl radicals.[221]

**Scheme 90. Decarboxylative Cross-coupling of *N*-Protected Aminoacids with Aryl Halides via
Merged Nickel/Photoredox Catalysis**

Ir^{III} = $Ir^{III}(dF(CF_3)ppy)_2(dtbbpy)^+$
dtbbpy = di-*tert*-butylbipyridine
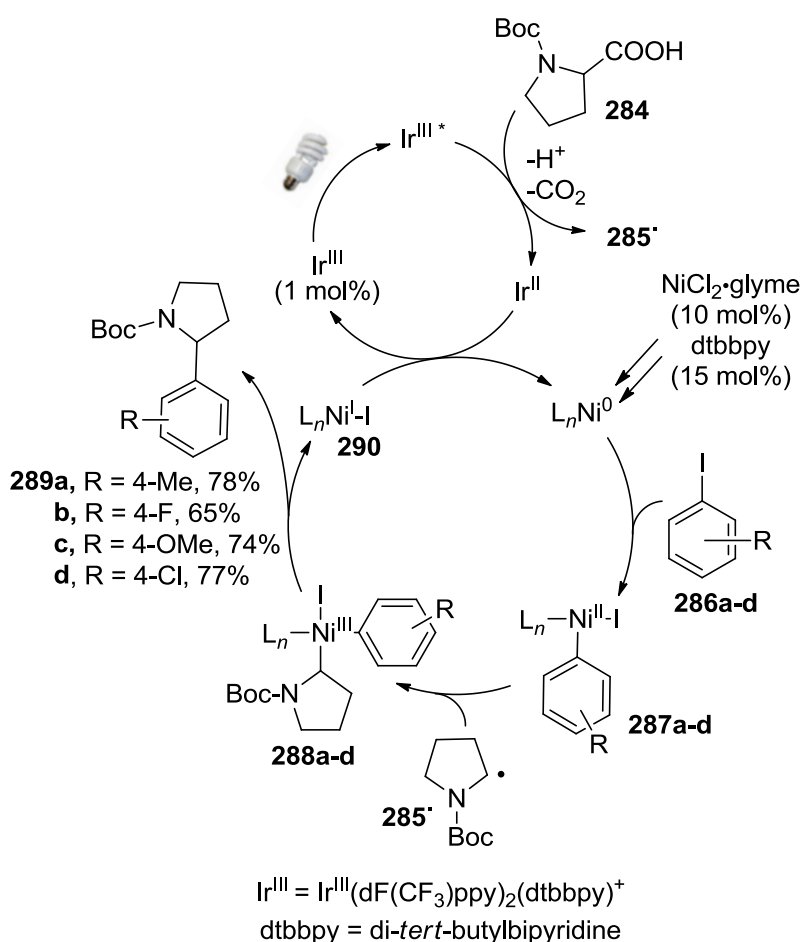
At the same time, a photoredox/Nickel dual catalytic route for Ar-C(sp^3) bond formation starting
from organoboron derivatives (e.g, **291**) has been developed (Scheme 91). Indeed, while the above
mentioned approach was limited to easily oxidizable substrates, such as α-aminoacids and *N,N*-
dialkylanilines, the introduction of a -BF$_3^-$K$^+$ moiety as electroauxiliary group[222] in the reagents
allowed for the generation of a wide range of radicals, including benzyl (Scheme 91),[223]
alkoxyalkyl[224] and even secondary alkyl radicals.[225]

Scheme 91. Cross-Coupling of Benzyl Trifluoroborates and Aryl Bromides via a Dual Photoredox/Nickel Catalytic System
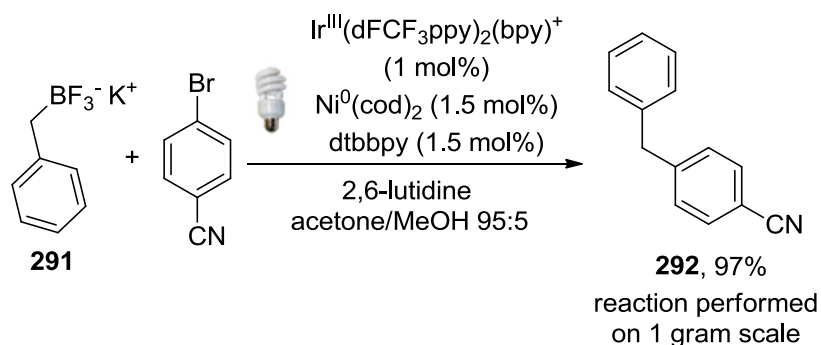
The generation of strong but selective electrophiles such as (triplet) aryl cations has been reported from a wide range of aryl chlorides bearing either electron-donating (such as amino, alkoxy and alkyl substituents) or weakly electron-withdrawing (acetals, esters) groups in protic solvents.[226] Due to the biradicalic nature of these intermediates, photoreduction via hydrogen abstraction is the main phenomenon observed in neat solvents.[227] However, when a π-bond nucleophile (whether an alkyne, an alkene or an (hetero)aromatic) is present in excess with respect to the starting aromatic (from 4 up to 20 equiv.), triplet cations are selectively trapped and formation of Ar-C bonds is the main or the exclusive process observed.[38] As an example, the addition of triplet phenyl cations ^{3}**293**$^+$ onto a double bond led to distonic diradical adduct ^{3}**294**$^+$ that, upon ISC, afforded a singlet phenethyl cation **295**$^+$ and/or a σ-bridged intermediate **296**$^+$, termed "phenonium ion" (Scheme 92a).[228,229] Once formed, phenonium ions can follow different pathways, depending on the nature of the substrates and on the reaction conditions. In any case, the process can be engineered in order to make one path predominant over the others and different arylations were thus performed.[3] As an example, trapping of aryl cations by ethyl vinyl ether afforded cation adducts **297**$^+$**a-d** in which the positive charge was mainly localized in the α-position with respect to the alkoxy group. Addition of the nucleophilic solvent resulted in a three-component process, where acetals of α-arylaldehydes or ketones **298a-d** were obtained in good isolated yields (Scheme 92b).[230] The corresponding aryl

aldehydes or ketones were easily formed by adding small amounts of acid to the photolyzed solution, thus resulting in a one pot preparation of α-aryl aldehydes or ketones.[231]

Scheme 92. a) Reactivity of Triplet Aryl Cations with Alkenes. b) Photochemical Multicomponent Route to 3-Arylacetals

298a, R = OCH$_3$, 70%
b, R = OH, 70%,
c, R = NMe$_2$, 62%
d, R = nBu, 56%
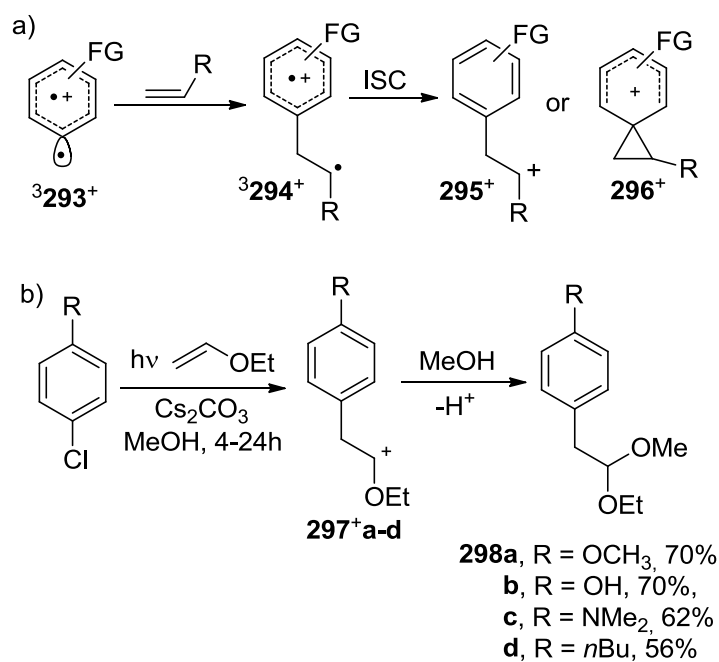
Reaction of aryl cations with alkynes led to ring-closed vinylenephenonium ions **300$^+$a,b** that in turn gave the corresponding arylalkynes **301$^+$a,b** after deprotonation. This photochemical, metal-free analogue of the Sonogashira reaction is particularly efficient when applied to electron-rich aromatics such as anisole and thioanisole derivatives (**299a,b**, Scheme 93).[232]

Scheme 93. Metal-free Sonogashira Coupling of Aryl Chlorides and Alkynes

301a, R = OMe, 71%
b, R = SMe, 58%
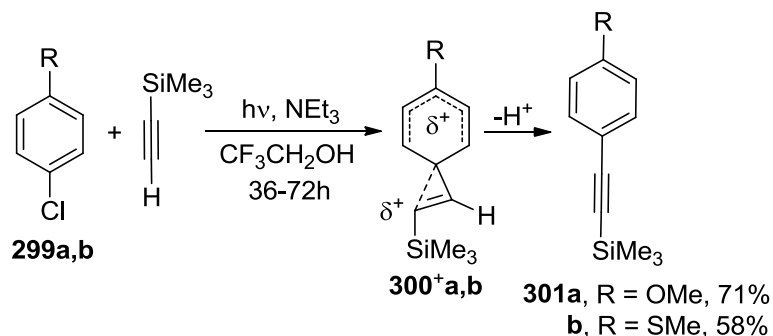
Triplet aryl cations also efficiently reacted with symmetric aromatics such as benzene, *p*-xylene, mesitylene and durene, forming mono- and poly-substituted biaryls via Wheland intermediates **302⁺a,b** (Scheme 94). Interestingly, asymmetric or crowded derivatives, a key structural feature in many pharmaceutically and biologically active compounds, as well as in several BINOL ligands, have been easily accessed through this approach. Since the use of aggressive intermediates such as phenyl cations is not affected by steric hindrance of the nucleophile, biphenyls with two, three or even four substituents in *ortho-* to the axial bond (e.g. compounds **303a,b** in Scheme 94) were easily prepared.[233]

Scheme 94. Photochemical Metal-Free Synthesis of Crowded Biaryls

303a, R = Me, 84%
b, R = SiMe₂*t*Bu, 77%
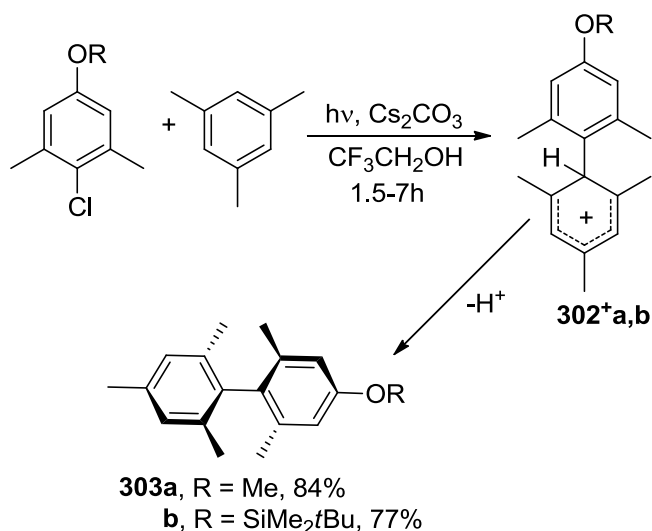
Triplet phenyl cations are also efficiently trapped by cyanide anions. Thus, irradiation of aryl halides **304a-d** (chlorides and even fluorides) in a water/acetonitrile solution of KCN, afforded a wide range of electron-rich benzonitriles (**305a-d**) in satisfactory yields (Scheme 95).[234]

Scheme 95. Photochemical Synthesis of Benzonitriles

304a-d

305a, X = F, R = 4-NH$_2$, 71%
    b, X = F, R = 4-OH, 69%
    c, X = Cl, R = 3,4-OCH$_2$O, 77%
    d, X = Cl, R = 4-SMe, 53%
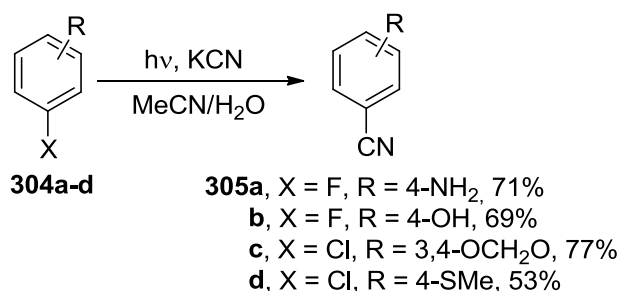
4.3. by Ipso-substitution of a CN Group

As previously mentioned, the formation of the radical anion of an aryl halide can lead to the liberation of a stable anion with the concomitant generation of a phenyl radical, in turn responsible for valuable arylation processes. On the contrary, the radical anion of electron-poor arenes not bearing good leaving groups can be a persistent species.[235] Typical is the case of aromatic nitriles (e.g. *o*-DCB) being the corresponding radical anions (*o*-DCB$^{\bullet-}$) a rather persistent, non basic and non nucleophilic species.[19,235]

On the other hand, excited benzonitriles are strong oxidants (Chart 1) and easily undergo electron transfer reactions with suitable electron-donors. Indeed, photoinduced electron transfer reactions involving cyanoarenes were investigated by several research groups in the nineties[19] and recently rediscovered. An historical example concerned with the photochemical benzylation of *o*-DCB, in the presence of either benzyltrimethylsilane (75% yield)[236] or benzyltributylstannane (81%)[237] (Scheme 96). In details, a radical ion couple *o*-DCB$^{\bullet-}$/**306**$^{\bullet+}$**a,b** was formed and fragmentation of the organometallic radical cations (by losing an electrofugal group, EG$^+$) gave a benzyl radical intermediate that added to *o*-DCB$^{\bullet-}$ forming anion **307**$^-$. The latter mainly underwent

rearomatization (by cyanide anion detachment) or, in the presence of a proton donor, led to a dihydroaromatic. In the first case, an ipso substitution of the cyano group occurred with the formation of an Ar-C bond at the expense of another Ar-C bond.[238]

Scheme 96. Benzylation of *o*-Dicyanobenzene via PET

EG = SiMe$_3$, 75%
EG = SnBu$_3$, 81%
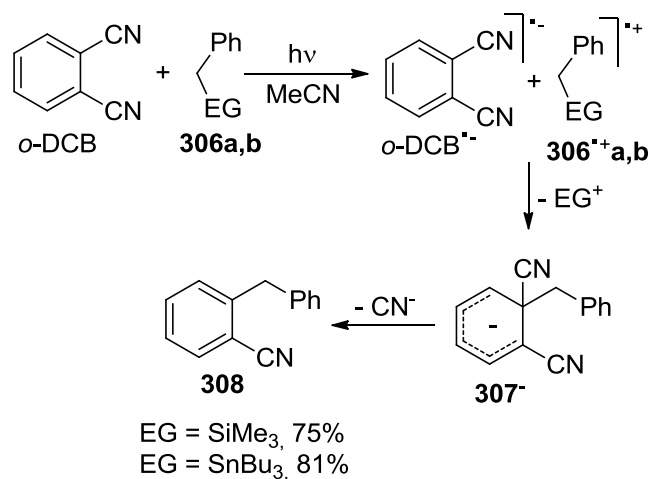
Other electron donors have been successfully employed, including amides and lactams (such as *N*-methylpyrrolidone **311**),[239] ethers,[240] silylethers[241] and even alkanes,[242,243] albeit a strong oxidant in the excited state such as 1,2,4,5-benzenetetracarbonitrile (TCB) had to be used (some examples in Scheme 97).

Scheme 97. Photoinduced Ipso-Substitution of a CN Group in TCB
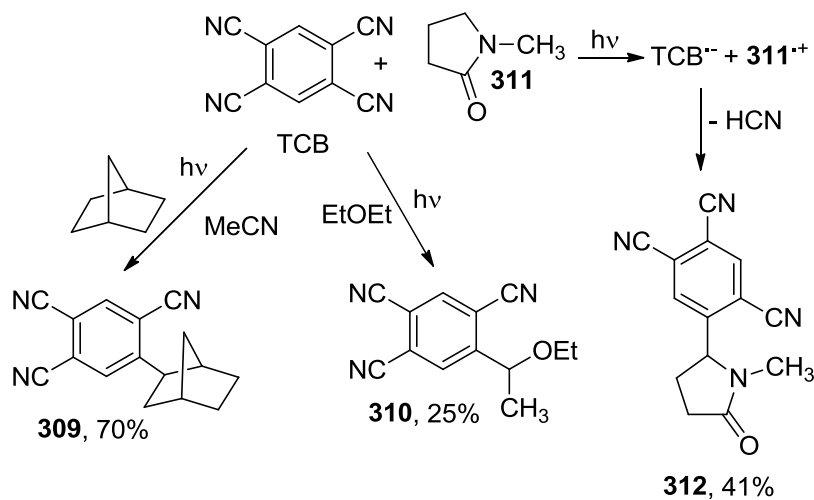
On the other hand, when the radical cation is not fragmentable, it can couple with a nucleophile (e.g. a carbon nucleophile or a nucleophilic solvent) and the resulting intermediate can combine with the radical anion of the cyanoaromatic. Again, loss of CN⁻ affords the corresponding three-component product and the overall process is known as Nucleophile Olefin Combination Aromatic Substitution (NOCAS, Scheme 98).[244,245] As an example, TCB reacted with an aromatic alkene (the electron donor) and a 1,3-dicarbonyl derivative **313** (partially in the enolic form, acting as the nucleophile) to give the three-component adduct **315** (Scheme 98, path a).[246] Notice that loss of a -COMe group occurred during the work-up, probably via an acid-catalyzed decomposition of **314** upon chromatographic separation on silica gel. Analogously, compound **316** was obtained in 65% yield[247] by irradiation of TCB in the presence of styrene and *N*-Boc protected pyrrole (Scheme 98, path b).

Scheme 98. Three-Component Reaction via Nucleophile Olefin Combination Aromatic Substitution (NOCAS)
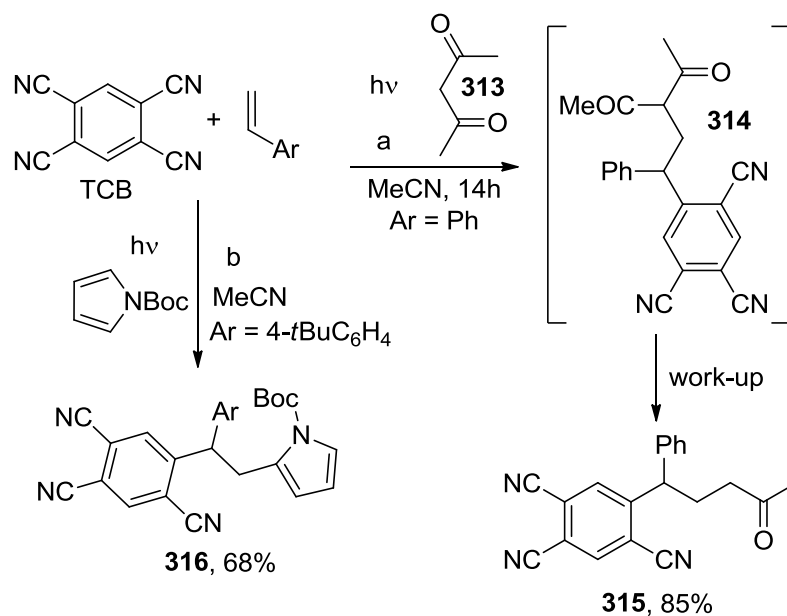
As seen above, the radical anion of cyanoarenes can be formed by UV light irradiation in the presence of an electron donor. A photocatalytic access to these intermediates, however, took place via oxidative quenching of excited Ir^{III}(ppy)$_3$ by 4-cyanopiridine **317**, that was converted into the corresponding (persistent) radical anion **317$^{•-}$** (Scheme 99). An organocatalyst (a thiol RS-H) was in turn oxidized by the Ir^{IV} complex and the corresponding thiyl radical RS$^{•}$ was achieved upon deprotonation. The latter abstracted a labile allylic hydrogen atom from cycloalkene **318** to provide an allyl radical **319$^{•}$**. Thus, intermolecular radical-radical anion coupling was responsible for the formation of a new Ar-C bond and resulted in the synthesis of pyridine **320** in a good yield.[248] Interestingly, the same procedure has also been extended to the benzylation of cyanoarenes by benzyl ethers.[249] Substituted benzylamines have been obtained from a photocatalytic decarboxylative coupling between α-aminoacids and cyano(hetero)arenes.[250] α-Amino arylation of cyano(hetero)arenes by tertiary amines was also achieved under catalytic conditions (Ir^{III}(ppy)$_3$ as the photoredox photocatalyst) in the presence of a base.[251]

Scheme 99. Ir^{III} Photocatalyzed Synthesis of Allylated Pyridines
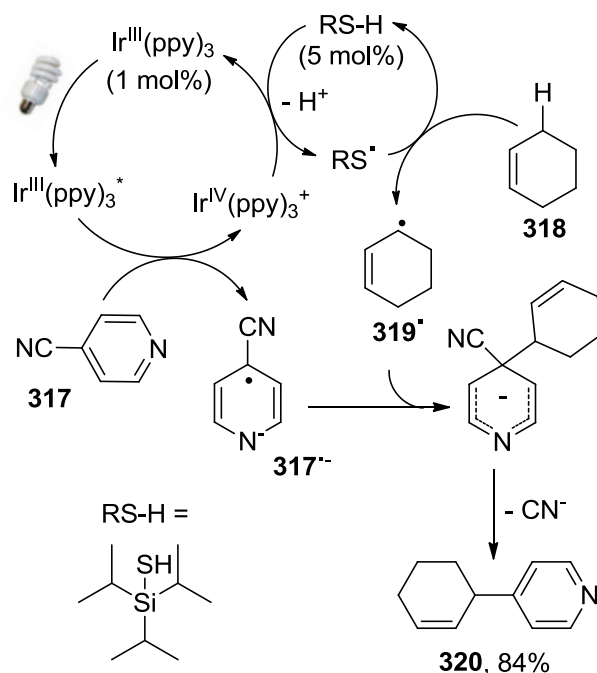
4.4. by Ar-H Activation

Aryl-C bond has been formed also via the introduction of a carbon based substituent on the aromatic ring in place of a hydrogen. This goal has been achieved via radical attack onto an aromatic ring (usually of an heteroaromatic base) or via a photo-Fries rearrangement. In most cases, photo-Fries rearrangements were the elective choice to form selectively an Ar-C bond through Ar-H activation.[13] As an example, irradiation of phenyl esters (or *N*-phenyl substituted amides) generated a phenoxy (or an aminyl) radical along with an acyl radical (Scheme 3a). Radical recombination gave a mixture of the *ortho-* and *para-* substituted ketones, but clear cut processes were also described. Substituted anilides were recently exploited as substrates in the preparation of 3,5-disubstituted 1,4-benzodiazepines via photo-Fries rearrangement (Scheme 100). Thus, *para-* substituted anilides **321a,b** underwent a photoinduced acyl migration and the resulting *ortho-* aminoacylbenzene derivatives **322a,b** were first derivatized with a protected naturally-occurring aminoacid and then cyclized to the desired benzodiazepines **323a,b**.[252] Treatment of the *o*-amino

ketones **322a,b** with Michael acceptors, such as dimethyl acetylenedicarboxylate, afforded 6,4-disubstituted quinoline 2,3-dicarboxylates that upon further elaboration gave various naphthyridine derivatives.[253]

Scheme 100. Synthesis of 1,4-Benzodiazepines via Photo-Fries Rearrangement of Anilides

321a,b   **322a**, R = CH$_2$Ph, R^1 = H, 60%
  b, R = CH$_2$Ph, R^1 = OMe, 56%
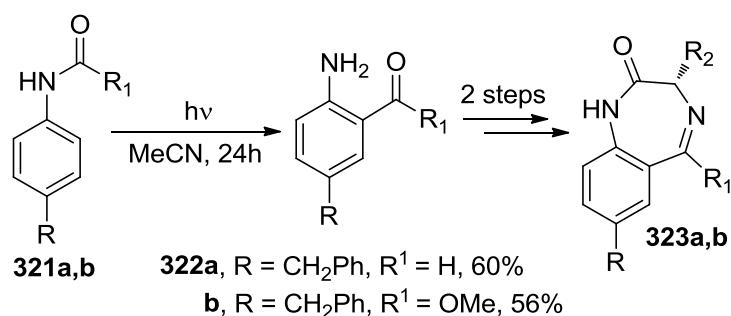
As hinted in Section 1.1, Barton esters, obtained via coupling of carboxylic acids with thiohydroxamic acid, are considered as convenient radical precursors exploiting the photolability of the N-O bond.[7] Thus, photogenerated 1-adamantyl radical was trapped by protonated lepidine **324**$^+$ to afford, after deprotonation, the corresponding 2-substituted lepidine **325** (Scheme 101).[254]

Scheme 101. Photochemical Alkylation of Lepidine by a Barton Ester

325, 97%
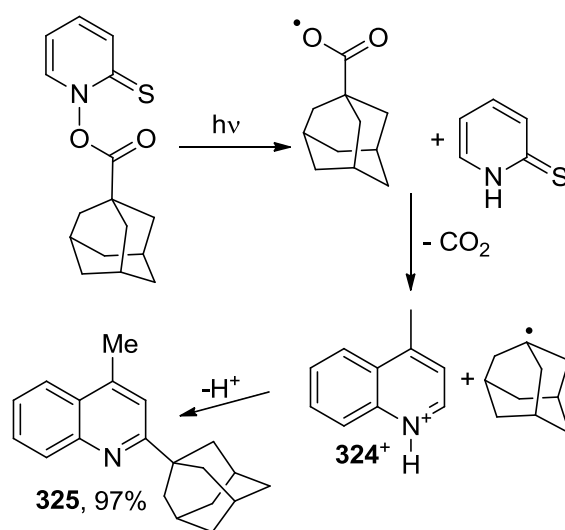
In some instances, carbon-centered radical deriving from decarboxylation maintained the stereochemistry of the carbon bearing the COOH group. As an example, new *C*-nucleosides (e.g. **328**) were obtained in a high yield and with complete stereocontrol through the treatment of sugar derived acid **326** with PhI(OAc)$_2$ and ensuing irradiation of the resulting (diacyl-oxyiodo)arenes **327** in the presence of lepidine (Scheme 102).[255]

Scheme 102. Ar-H Activation in Heteroaromatics
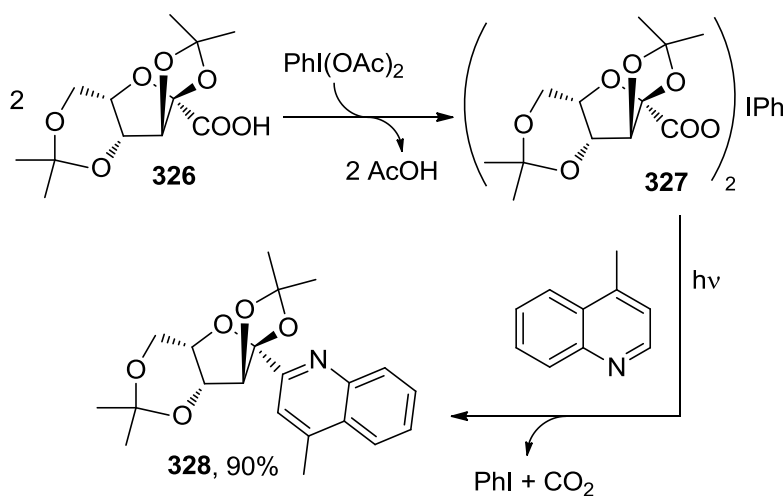
The photocatalyzed generation of radicals from amides was early reported in the sixties,[6,256] (see further Section 5.1.1.). Formamide was the most investigated radical precursor for the generation of carbamoyl radicals, albeit it was often used both as the reagent and as the reaction solvent (or co-solvent). Protonated heterocycles, such as lepidine and quinoline, were the elective radical traps and were conveniently functionalized under sunlight irradiation in a TiO$_2$ suspension of the amide, in the presence of H$_2$O$_2$ as an oxidant (Scheme 103).[257,258]

Scheme 103. Sunlight Driven Functionalization of Quinoline and Lepidine

329a, R = H, 90%
b, R = CH$_3$, 69%
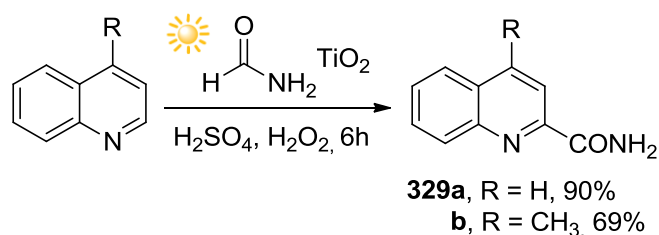
The photocatalytic alkylation of heterocycles was also exploited as a key step in the synthesis of drugs. Thus, the selective aminoalkylation of pyridazine **330** was successfully adopted for the synthesis of JAK2 inhibitor LY2784544 and other analogues, that were obtained in high purity via simple crystallization (Scheme 104).[259]

Scheme 104. Photoredox Catalyzed Aminoalkylation of Pyridazine 330

331, 56%
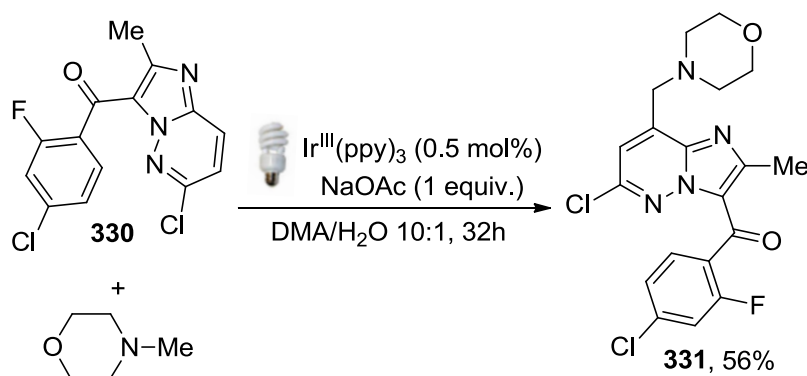
The introduction of small alkyl groups (e.g a methyl group) in complex molecules often requires the use of aggressive oxidants and high temperatures. Very recently, methylation approaches exploiting photoredox catalysis have been reported in the literature. In one case, a methyl radical was generated from the oxidative quenching of photoexcited Ir^{III} complex with protonated t-butyl peroxyacetate ester **332**$^+$ and trapped by a nitrogen-based six-membered heterocycle under acidic conditions. Thus, selective methylation of medicinal and agrochemical agents, such as camptothecin and fasudil (**333**$^+$), was obtained in 77% and 43% yield, respectively (Scheme 105).[260] Efficient

ethylation and cyclopropanation processes have been likewise carried out having recourse to the same approach.

Scheme 105. Regioselective Methylation of Fasudil (333[+])

Ir[III] = Ir[III](dF(CF$_3$)ppy)$_2$(dtbbpy)[+] (2 mol%)
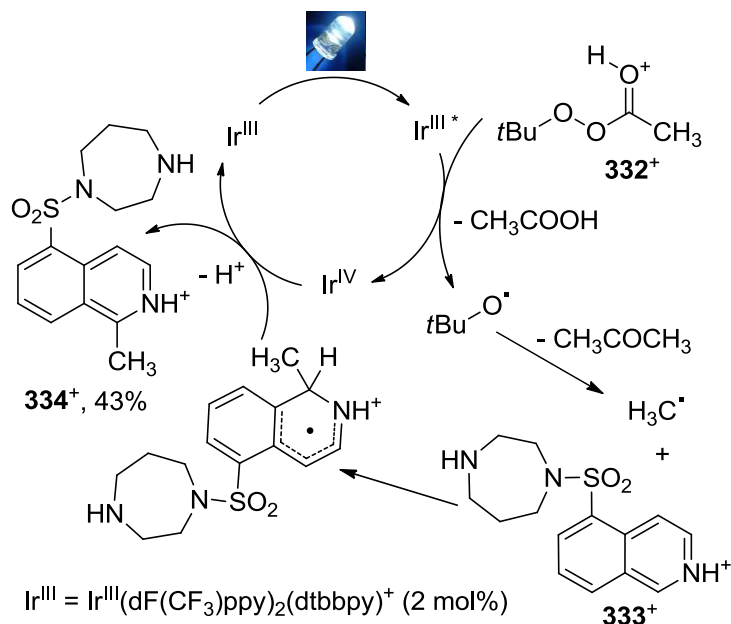
Another elegant approach based on the use of simple alcohols (such as methanol) as alkylating agents has been reported. The process involved the use of Ir[III](ppy)$_2$(dtbbpy)[+] as photoredox catalyst and thiol **335** as co-catalyst. Thiyl radical **336·** arising from the photocatalytic cycle was responsible for the generation of an α-hydroxyalkyl radical, that was trapped by a protonated heteroarene to form radical cations **337·+a-c**. Upon deprotonation and dehydration, also involving a spin-center shift, benzyl radicals **338·a-c** were obtained. Single electron transfer between photoexcited Ir[III] complex and **338·a-c** closed the catalytic cycle, affording the desired products **339a-c** (Scheme 106).[261]

Scheme 106. Photocatalyzed Methylation of Nitrogen Based Heterocycles with Methanol
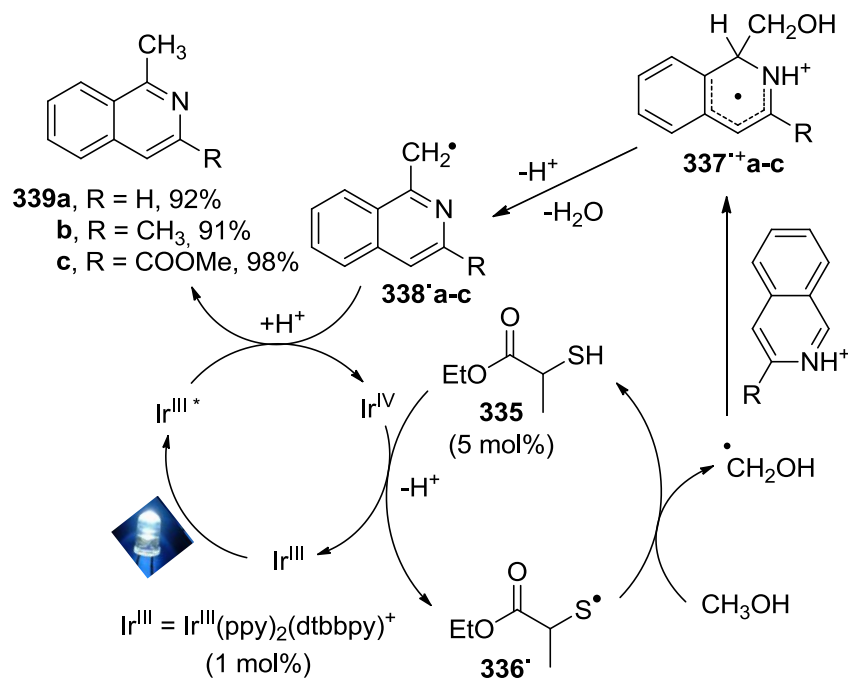
The incorporation of a trifluoromethyl group into drug candidates often enhances their efficacy by improving permeability to cellular membrane and increases resistance to oxidative metabolism. Accordingly, several efforts have been devoted to the direct trifluoromethylation of arenes and heteroarenes by means of photoredox catalysis.[186,187] An early photochemical strategy for the radical trifluoromethylation of simple aromatics and heteroaromatics involved the use of $Ru^{II}(phen)_3^{2+}$ or $Ir^{III}(Fppy)_3$, trifluoromethanesulfonylchloride (as source of the $F_3C^{\bullet}$ radical) and a household light bulb.[262] The protocol has been applied to the synthesis of pharmaceutical agents, such as anti-Alzheimer CF_3-Aricept precursor **340** (Scheme 107). By using a similar approach, *ortho*-trifluoromethylation of anilines has been obtained in the presence of $Ir^{III}(ppy)_3$ and Togni's Reagent as trifluoromethylating agent.[263] The $Ru^{II}(bpy)_3^{2+}$ photocatalyzed perfluoroalkylation of five membered heterocycles, such as pyrroles, indoles, (benzo)furans and thiophenes, has been optimized under flow conditions, thus allowing a significant acceleration of the process (from hours in batch to minutes in flow).[264] The heterogeneous mesoporous graphitic carbon nitride (mpg-C_3N_4) catalyst has been likewise successfully used.[265]

Scheme 107. Photoredox Catalyzed Trifluoromethylation of Arenes

340, 94%
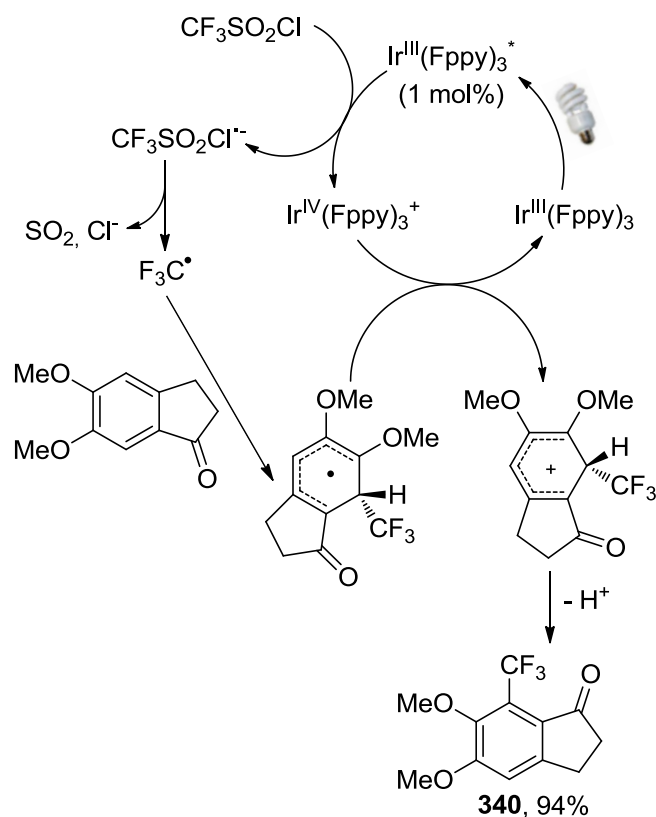
The aromatic ring of α-cyano arylacetates was selectively perfluoroalkylated in the presence of a base via visible light irradiation of a colored EDA complex formed between the carbanion of **341a-c** and a perfluoroalkyliodide (e.g. $C_6F_{13}I$, an example in Scheme 108).[266]

Scheme 108. Selective *ortho*-Perfluoroalkylation of α-Cyano Arylacetates

341a-c

TMG = 1,1,3,3-tetramethyl guanidine

342a, R = OMe, 76%
b, R = SiMe$_3$, 86%
c, R = Cl, 36%
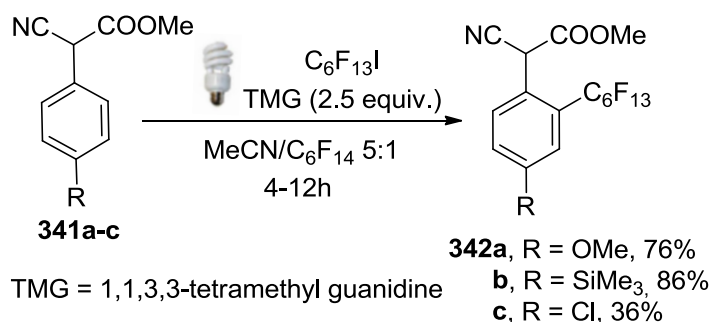
Bromodifluoroacetamides (e.g. **343**) were used in the difluoroacetamidation of arenes and heteroarenes via visible-light photoredox catalysis by using *fac*-Ir^{III}(ppy)$_3$ (Scheme 109). Indeed,

the intermediacy of a substituted difluoromethyl radical arising from photoinduced reduction of the corresponding bromoderivative has been confirmed by spin trapping experiments.[267] In a similar manner, α-aryl-α,α-difluoroacetate esters[268] and α-aryl-α,α-difluoromethyl phenylsulfones[269] were obtained. In both cases, the resulting compounds could be easily reduced to give the corresponding α,α-difluoromethylarenes.

Scheme 109. Difluoroacetamidation of Unactivated Arenes and Heteroarenes
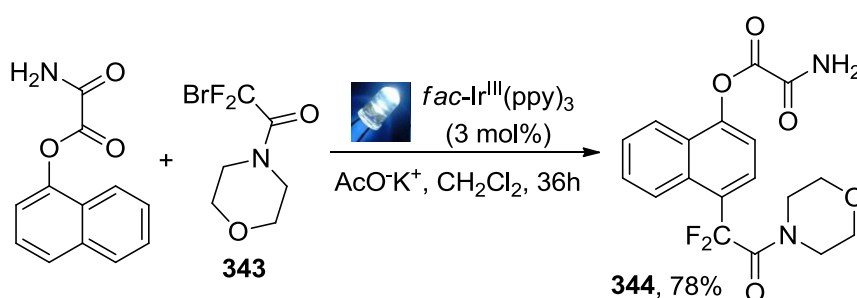
5. ADDITION ONTO C=X BOND

Most of the reactions pertaining to this section involve the addition of a photogenerated radical (whether formed by hydrogen atom or by electron transfer) onto the double bond.

5.1 Addition onto C=C bond

5.1.1 Addition of H-C. In this process a carbon-centered radical typically adds to a double bond and the desired compound is then formed via final hydrogen atom donation to the resulting radical adduct. The election choice is the homolytic cleavage of a C-H bond with incorporation of both the C-radical and the hydrogen atom in the final compound. Since in most cases a nucleophilic radical is generated, electron-poor olefins are the ideal partners of the reaction. The generation of the desired radical, however, is not an easy task, particularly when simple alkyl radicals are involved due to the strength of the bond to be broken and to the fact that hydrocarbons do not absorb at a convenient wavelength (typically in the far UV, < 200 nm), in turn causing a non selective reaction

upon excitation. A milder approach for the C-H bond cleavage is photocatalysis (Scheme 1). However, application of photoredox processes on benzyl and phenacyl halides, carboxylic acids, organoborates and others allows for a more convenient radical generation in a predictable and easy way. In the latter case, the incorporation of hydrogen usually arises from reduction of the adduct radical followed by proton addition.

As for those reactions involving a hydrogen atom transfer step, the feasibility of the process depends on the strength of the C-H bond to be cleaved. As for oxygenated derivatives, (substituted) dioxolanes, ethers and alcohols have been used for the generation of α,α-dioxyalkyl- and α-oxyalkyl radicals, respectively. This approach has long been known and the first examples dealing with the addition of (di)oxyalkyl radicals onto olefins have been reported in the 1960s.[6] These processes were promoted by ketones and, interestingly, both electron-rich and electron-poor olefins could be used as coupling partners, although the latter consistently gave higher yields.[270,271] More recently, the activation of the methylene hydrogens in the 2-position of 1,3-dioxolane was achieved via photocatalyzed (by (substituted) benzophenones) generation of the corresponding dioxolan-2-yl radical. This offered the opportunity to introduce a masked aldehyde function in the final product.[272] Interestingly, an asymmetric variant made use of olefins bearing bis-oxazolidine chiral auxiliaries.[273] In a related example, the 1,3-dioxolanyl group introduced was further elaborated for the synthesis of a *bis*-tetrahydrofuranyl ligand for the synthesis of HIV protease inhibitor UIC-94017. Thus, benzyl-protected 5(*S*)-hydroxymethyl-2(*5H*)-furanone **345** gave dioxolanyl derivative **346** in 82% yield and with a high degree of stereoselectivity (anti/syn = 96:4; Scheme 110a). The reaction was carried out in neat 1,3-dioxolane, but the photocatalyst (benzophenone) was used here only in a 10 mol% amount.[274] The presence of (long) alkyl chains in 2-substituted-1,3-dioxolanes did not hinder the hydrogen abstraction process, as demonstrated in the preparation of (−)-tetrahydrolipstatin (a potent pancreatic lipase inhibitor), where the key step was based on the photochemical addition of 2-undecyl-1,3-dioxolane onto diketene.[275]

Scheme 110. Photocatalytic Generation of (di)Oxyalkyl Radicals and Addition to Electron-Poor Olefins
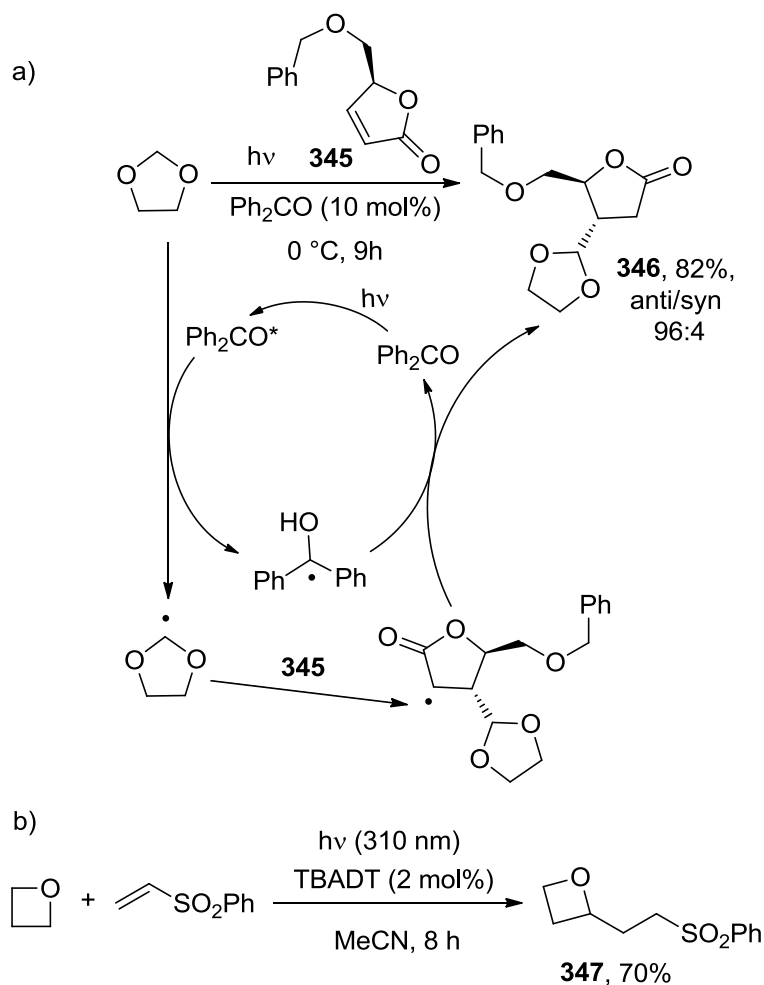
Related 1,3-benzodioxole derivatives were likewise recently considered as substrates, also due to the presence of this moiety in a number of compounds endowed with biological activity. Thus, the smooth activation of the methylene hydrogens has been obtained by using TBADT (2 mol%) as the photocatalyst, leading to the formation of 2-substituted-1,3-benzodioxoles in good yields.[276]

TBADT likewise promoted the challenging activation of the C-H bonds in oxetane derivatives and allowed the addition of the resulting radicals onto electron-poor olefins. As an example, parent oxetane was photoadded to phenyl vinyl sulfone in the presence of 2 mol% TBADT to give derivative **347** in 70% isolated yield (Scheme 110b).[277] Interestingly, the reaction on 2-substituted

derivatives occurred with some selectivity that was explained on the basis of a competition between addition onto the double bond and back-hydrogen atom transfer.[277]

In some instances, trialkylorthoformates have been likewise used as radical precursors. Thus, in the functionalization of a hex-2-enopyranosid-4-ulose, the introduced -C(OAlk)$_3$ group was not stable upon chromatographic purification and was converted into a -COOAlk group.[278]

Turning to alcohols, the most widely employed method for the activation of the C-H bonds in the α-position with respect to the OH group is hydrogen abstraction by excited aromatic ketones.[6] Thus, with the aim of synthesizing building blocks useful for the preparation of analogues of glutamate and kainoids (e.g. kainic acid), methanol has been photoadded to chiral 5(*S*)-5-triisopropylsiloxymethyl-*N*-boc-dihydropyrrole-2(5*H*)-one in the presence of benzophenone in the role of the photocatalyst. The adduct was stereochemically pure, although it was formed only in a modest yield (51%).[279]

Recently, excited 4,4'-dimethoxybenzophenone (20 mol%) promoted the addition of isopropanol (used as the solvent) to furanone **348** to give **349** (Scheme 111).[280] Noteworthy, the reaction was carried out in a LED-driven microchip reactor and reached completion in only 5 min. Different reaction setups have been applied to the same reaction with the final aim of devising more environmental-friendly procedures (e.g. characterized by a lower energy consumption).[281-283]

Scheme 111. Aromatic Ketones Photocatalyzed Addition of Alcohols to Furanones
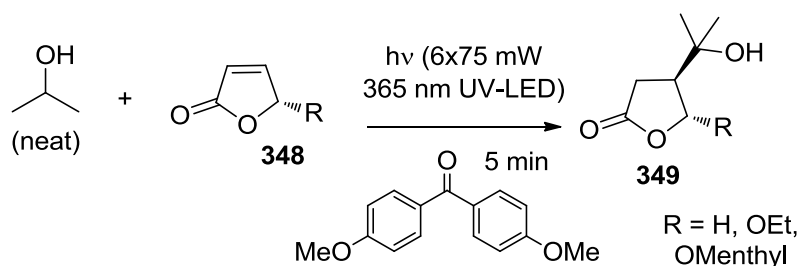
Acyl radicals are important intermediates in organic synthesis and a breakthrough in their generation is starting directly from aldehydes via photoactivation of the formyl C(=O)-H bond. Indeed, this approach met some success, particularly when exploiting a photocatalytic strategy. Aromatic ketones were first used in the role of photocatalysts,[284] and the acyl radicals formed were exploited in the photoacylation of quinones to form the corresponding acylated hydroquinones in good yields.[285,286]

TBADT has been likewise applied as photocatalyst for the generation of acyl radicals from both aliphatic[287] and aromatic[288] aldehydes under UV irradiation, but solar light irradiation was shown to be a viable alternative.[289] One of the drawbacks of this reaction is the competitive decarbonylation of acyl radicals deriving from secondary or tertiary aldehydes. However, this limitation can be alleviated by lowering the reaction temperature. Thus, when the reaction was carried out at -20 °C, the acyl radical **351·** deriving from cyclohexanecarboxaldehyde **350** efficiently added to cyclopentenone to give diketone **352** in 46% yield along with small amounts of the decarbonylated product (Scheme 112, path a).[287] Noteworthy, **351·** was likewise obtained under TBADT-photocatalyzed conditions via carbonylation of cyclohexyl radical under CO atmosphere (80 atm) to form the same diketone **352** in a higher isolated yield (62%, Scheme 112, path b).[290] Recently, a catalytic approach based on the use of a hypervalent iodine(III) derivative **353** working under visible light irradiation was reported.[291] The proposed mechanism involved a radical chain reaction promoted by homolysis of an I-O bond in the catalyst upon irradiation. Indeed, a iodanyl radical was postulated as the key intermediate, prone to abstract a hydrogen atom from the formyl group of the aldehyde and giving the desired acyl radical. The present process allowed to obtain product **352** in 78% yield, avoiding decarbonylation of the secondary acyl radical even at room temperature (Scheme 112, path c).[291]

Scheme 112. Acyl Radical Generation and Ensuing Addition to C=C Double Bonds
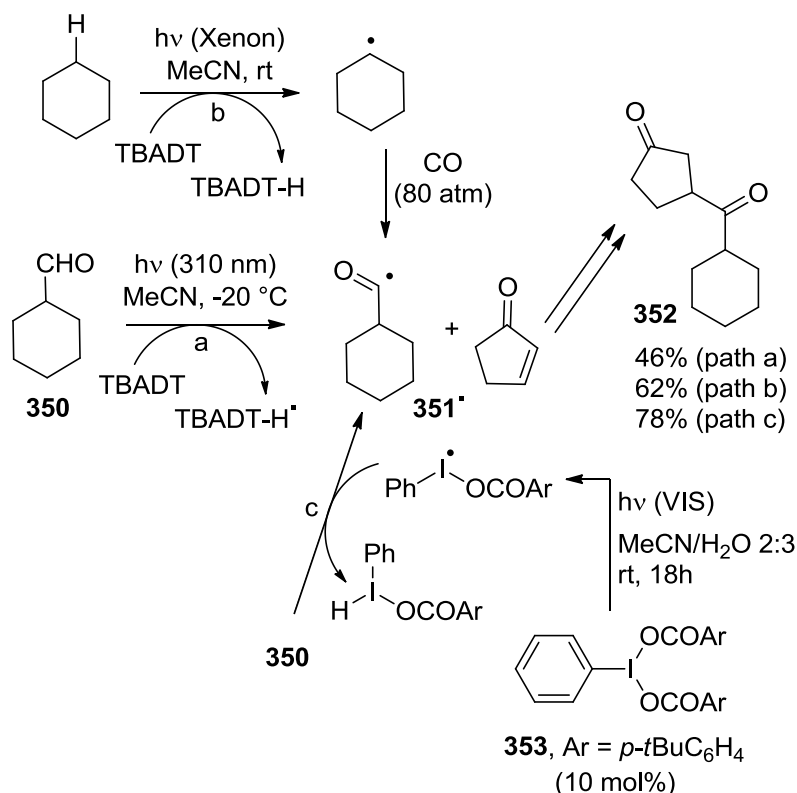
Apart from aldehydes, the C(=O)-H moiety is present in other derivatives, such as formate esters and formamides. However, photocatalysis was demonstrated to be a robust methodology for the activation of this C-H bond only in the latter substrates, allowing for the generation of carbamoyl radicals. The formyl hydrogen in parent formamide was photochemically cleaved by using benzophenone in the role of the photocatalyst (see Scheme 113a). The reaction of excess formamide (actually the reaction medium was HCONH$_2$/tBuOH 6:1) with diethyl maleate to give the amidation product **354** took place in an excellent yield (90%) and was conveniently carried out under sunlight irradiation, although a large excess of the aromatic ketone (18 equiv.) was required, in turn generating benzopinacol as a byproduct.[292] A greener process that allowed to use a lower amount both of the amide (a four-fold excess) and of the photocatalyst (TBADT, 2 mol%) has been developed.[293] As an example, N-methyl formamide was photoadded to unsaturated sulfone **355** to give norbornane derivative **356** in 64% yield in a highly diastereoselective way (see Scheme 113b).

Noteworthy, the process was also completely regioselective and no competitive activation of the methyl hydrogens was observed.[293,294]

Scheme 113. Carbamoylation Reactions Photocatalyzed by a) Aromatic Ketones and b) TBADT
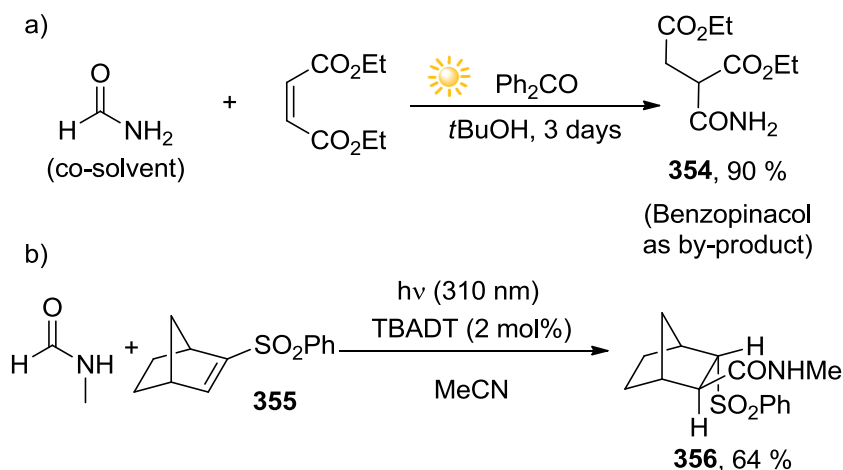
Apart from carbamoyl radicals, amides, or at least those characterized by some substitution patterns, were also useful for the generation of α-amidoalkyl radicals. The latter were generated by direct TBADT-photocatalyzed chemoselective hydrogen abstraction from tertiary amides, with no competitive cleavage of other C-H bonds (see above). TBADT was excited under solar light irradiation and *N,N*-dimethylformamide (4 equiv.) photoadded onto dimethyl maleate **357** (0.1 M in MeCN) to give succinate derivative **358** in 64% yield after 5 days illumination (see Scheme 114, conditions *i*).[289,293] Interestingly, the same reaction was carried out in a flow photoreactor consisting in coils of UV-transparent FEP tubing (Fluorinated Ethylene Propylene; i.d.: 2.1 mm; reactor volume: 50 mL) wrapped around a traditional water-cooled 500 W medium pressure Hg vapor lamp. Indeed, the adoption of flow conditions resulted in a better yield of **358** (81% isolated yield) and allowed to increase the concentration of the limiting reagent up to 0.2 M, while reducing the reaction time to *ca.* 2h (a 0.4 mL min^{-1} flow rate was adopted; Scheme 114, conditions *ii*).[295] Analogous results were reported when using carbamates as hydrogen donors.[293]

Scheme 114. Photocatalyzed Amidoalkylation of Electron-Poor Olefins

Conditions:
i) TBADT (2 mol%), **357** 0.1 M, ☀ (5 days), batch
ii) TBADT (1 mol%), **357** 0.2 M, Hg-lamp (500 W), flow (4 mL min^{-1})
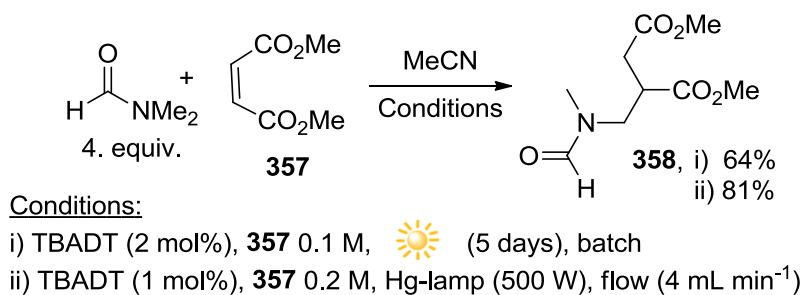
The potentiality of photocatalyzed HAT reactions is apparent in the challenging generation of alkyl radicals by the cleavage of unactivated C-H bonds. Thus, these radicals have been most often generated from (low-boiling point) cycloalkanes in order to avoid selectivity issues (Scheme 115) by using either organic and inorganic photocatalysts. In the former case, aromatic ketones (e.g. benzophenone) have been largely used, although these are effective only when used in a high, often equimolar, amount. Accordingly, β-cycloalkyl dinitrile **360** was smoothly synthesized in 66% isolated yield starting from cyclohexylidene malononitrile **359** and cyclohexane (see Scheme 115, path a).[296] In a related case, ketene thioacetal *S,S*-dioxides, a class of captodative olefins, were likewise successfully used as radical traps.[297]

Scheme 115. Cyclohexane as Radical Precursor Under Photocatalyzed Conditions
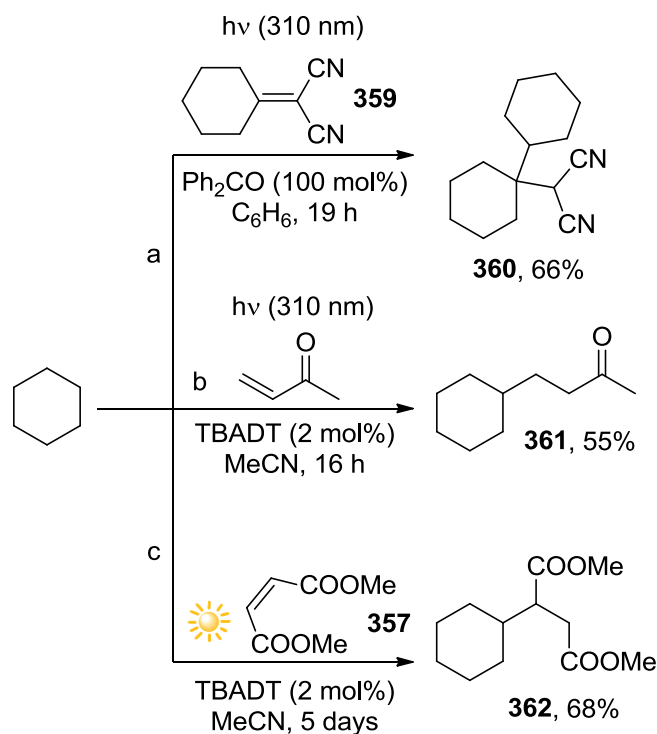
By contrast, TBADT offers some advantages with respect to benzophenone in the photocatalytic activation of alkanes since it can be used in catalytic amounts and is easily separated from the desired product.[298,299] Thus, the photochemical alkylation of a range of electron-poor olefins by cyclic alkanes was obtained by using only 2 mol% of TBADT. In the case of the reaction of cyclohexane with methyl vinyl ketone, the desired adduct **361** was obtained in 55% yield after 16 h of irradiation (Scheme 115, path b).[300] The alkylation of α,β-unsaturated esters, ketones and nitriles was conveniently carried out by simply exposing the reaction vessel on a window ledge. As an example, dimethyl maleate **357** was smoothly alkylated by cyclohexane (5 equiv.) to give compound **362** (68% isolated yield) in the presence of 2 mol% TBADT. The irradiation was carried out on 100 mL starting solution and allowed to obtain **362** on a gram scale (1.55 g) after a few sunny days (5 days; 8 h per day; Scheme 115, path c).[289]

Noteworthy, apart the usual reactivity trend in HAT reactions (CH > CH$_2$ > CH$_3$), TBADT showed a marked preference for nucleophilic rather than electrophilic sites in the hydrogen abstraction step.

This was rationalized through the intervention of a radical polar effect in the transition state. This behaviour has been recently exploited for the regioselective alkylation of aliphatic nitriles by electron-deficient alkenes.[301] As an example, the methine hydrogen in 4-methylvaleronitrile **363** was selectively activated and the resulting radical added to dimethyl maleate **357** to give adduct **364** in 62% isolated yield upon sunlight irradiation for 7 days (Scheme 116).[301]

Scheme 116. Regioselective Alkylation of Aliphatic Nitriles with Electron-Poor Olefins
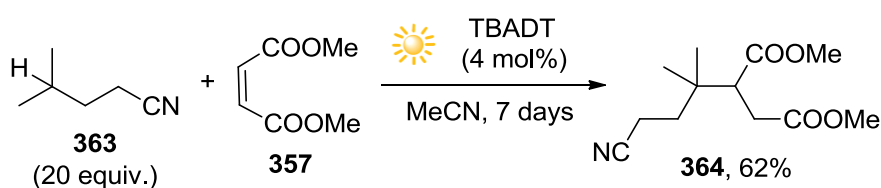
Another interesting way to generate alkyl radicals is through photoredox catalysis by oxidation of an organic molecule followed by loss of a good electrofugal group (e.g. H^+, TMS^+; see also Section 1.1.3). A typical case is the generation of α-aminoalkyl radicals mostly generated by photoinduced mono-electronic oxidation of the corresponding amines and ensuing deprotonation from the α-position (see Scheme 117 below). The first step is fast, given the low oxidation potential of these compounds, but fragmentation has to compete with efficient back-electron transfer. As an example, when using aromatic ketones as photocatalysts, SET quenching by amines was fast, but the production of trappable radicals was inefficient and accompanied by extensive decomposition of the ketone. This was thus used in a high (stoichiometric) amount, making the work up procedure difficult. Nevertheless, ketones bearing electron-donating substituents, such as 4,4'-dimethoxybenzophenone or Michler's ketone (4,4'-bis(*N,N*-dimethylamino)benzophenone) exhibited a higher efficiency.[302]

Heterogeneous photocatalysis has been likewise applied for the generation of α-aminoalkyl radicals by using either TiO_2 or ZnS.[303,304] In this case, a large excess of the amine (preferably used as the

solvent) was required to obtain a satisfactory product yield, presumably because only the molecules adsorbed at the surface of the semiconductor particle were involved in the SET step. Acyclic amines gave no alkylation under the above conditions, except when a thiocarbonyl or xanthate derivative (e.g. *S*-methyl-*N*,*N*-diethyldithiocarbamate, 5 mol%) was present, apparently because the aminoalkyl radicals were stabilized by a reversible trapping by the thiocarbonyl species, thus facilitating the addition to alkenes.[305]

Recently, visible light photoredox catalysis has been applied to the generation of α-aminoalkyl radicals (this is a quite uncommon case, much more common is the generation of the corresponding iminium ions, see for example Section 7.5) and the ensuing addition to electron-poor C=C double bonds.[306,307] Ru[II] [306,307] and Ir[III] [306,307] complexes, as well as organic dyes[307] (although the latter gave a poor performance) were chosen as photocatalysts. As an example, the redox potential of excited Ru[II](bpy)$_3^{2+}$ was sufficient to oxidize *N*-Aryl THIQ **228b** to the corresponding radical cation **228b**$^{\bullet+}$. Deprotonation and addition of the resulting radical **366**$^{\bullet}$ onto electron-poor olefins (e.g. methyl vinyl ketone) gave substituted *N*-aryl THIQs (such as **365**) in good yields, while the Ru[II] complex was regenerated (see Scheme 117).[306]

Scheme 117. Photoredox Catalyzed Generation of α-Amino Radicals
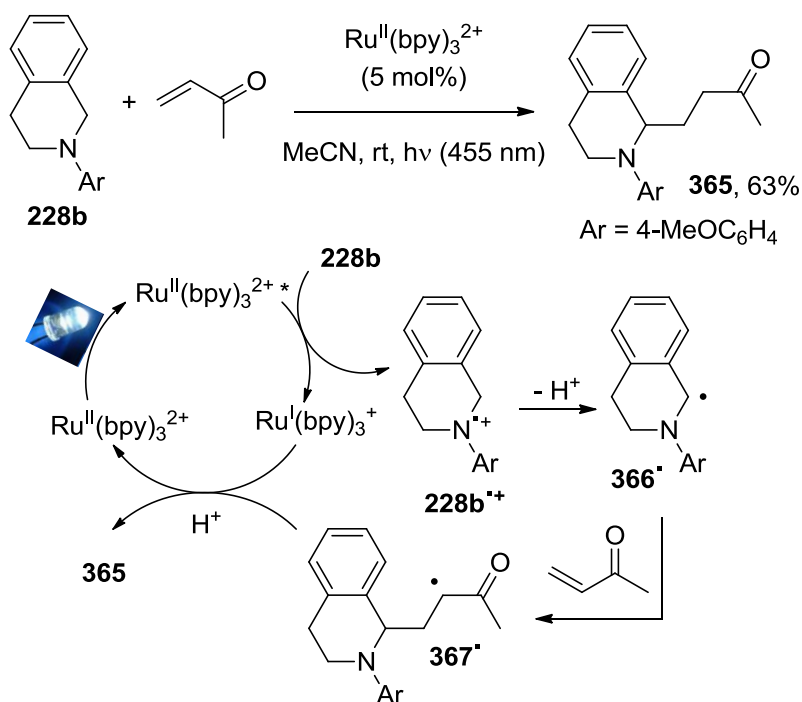
The above photocatalytic strategy was also used on α-silylamines. These compounds are characterized by an oxidation potential lower than that of the corresponding amines and the obtained radical cations undergo cleavage of the stable Me_3Si^+ cation, thus making the generation of the desired α-alkylamino radical predictable. Typically, cyanoarenes[6] or, in recent years, Ru^{II}- and Ir^{III}-based complexes have been chosen in the role of photocatalysts for the aminoalkylation of electron-poor olefins.[308] An enantioselective version of this reaction has been more recently developed.[309] This is based on a cooperative dual catalytic approach, based on a photoredox catalyst (Ru^{II} in Scheme 118) and a chiral Lewis acid (Sc^{III}). Thus, the former was excited by irradiation (a 23 W compact fluorescent light bulb has been used) and caused the mono-electronic oxidation of **368** leading to the generation of the desired radical **372·**. The chiral Sc^{III}-pybox (pyridine bis-oxazoline; see (*S,S*)-**370**) complex coordinated the electron-poor olefin **369**, thus directing the attack of the α-amino radical on the C=C double bond. The resulting addition products (e.g. **371**) have been obtained in high yields and with excellent enantiomeric excess (Scheme 118).[309]

Scheme 118. Enantioselective Conjugate Radical Addition of α-Aminoalkyl Radicals via a Dual Catalytic Approach
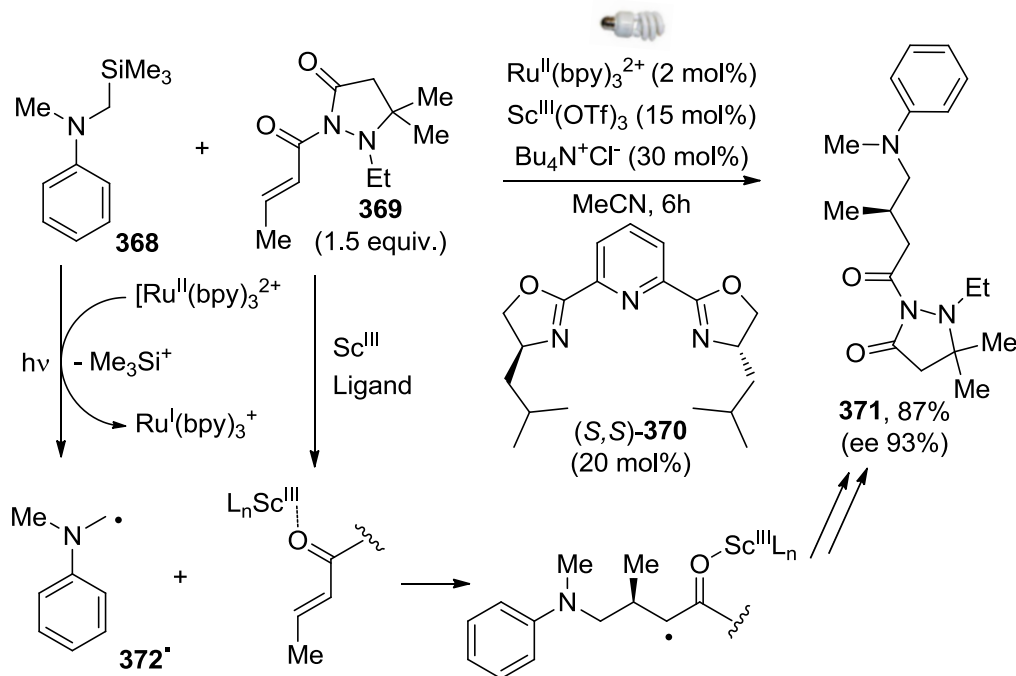
Another interesting alternative for the generation of α-aminoalkyl- or α-amidoalkyl radicals is starting from substituted α-aminoacids through a decarboxylation reaction via the intermediacy of a carboxyl radical. Thus, irradiation of *N*-Boc protected glycine under basic conditions (to form the corresponding carboxylate salt **373⁻**, a better electron donor) in the presence of an Ir-based complex, caused the oxidation of **373⁻** to the corresponding carboxyl radical. The latter then underwent CO_2 loss and the resulting radical added to dimethyl alkylidene malonate **374** to give adduct **375** in a high yield (96%; see Scheme 119). Interestingly, **375** could be further elaborated to give (±)-pregabalin, an anticonvulsant drug, in two further steps.[310]

Scheme 119. Synthesis of (±)-Pregabalin through a Photoredox Catalyzed Approach
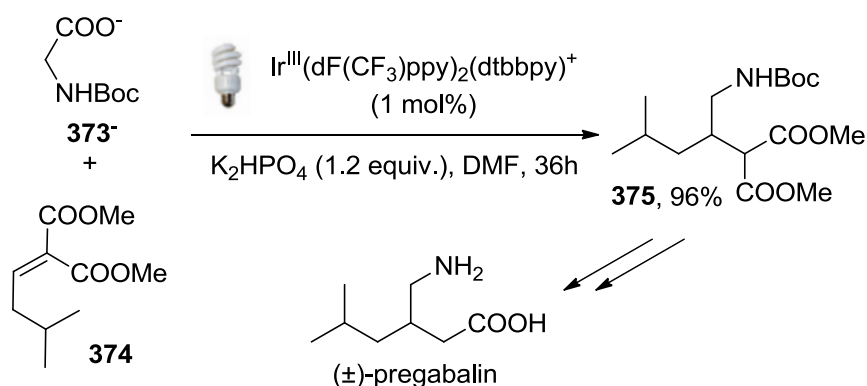
α-Amidoalkyl radicals were recently obtained through the use of protected (e.g. with a Boc group) aminomethyltrifluoroborates, such as **376**, and used in the photocatalytic hydroaminomethylation of olefins. These salts underwent mono-electronic oxidation by an excited Ir^{III}-based complex causing a deboronation to give the desired radical. Noteworthy, this reaction could also be carried out under sunlight for 4h (Scheme 120) and, when applied to unsaturated esters, gave access to a series of γ-aminobutyric acid (GABA) derivatives (e.g. **377**, obtained in 70% yield).[311]

Scheme 120. Photoredox Catalyzed α-Aminomethylation of Electron-Poor Olefins
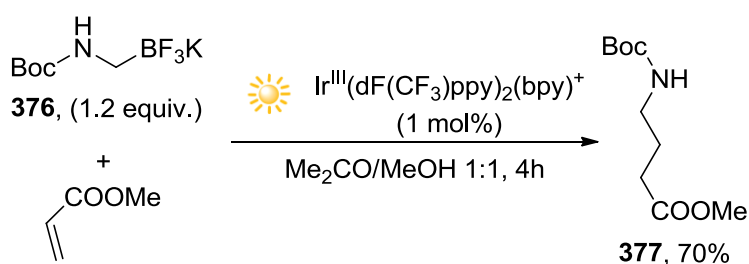
A similar photocatalytic strategy was recently extended to related α-thioalkyl radicals starting from thioalkyltrifluoroborates (e.g. **378**). This procedure represents a new approach for the solar light induced synthesis of alkyl sulphides (Scheme 121).[312]

Scheme 121. Alkylation of Unsaturated Nitriles via Photogenerated α-Thioalkyl Radicals

378 + CN → (Ir^{III}(dF(CF$_3$)ppy)$_2$(bpy)$^+$ (2 mol%), Me$_2$CO/MeOH 1:1, 8h) → **379**, 75%
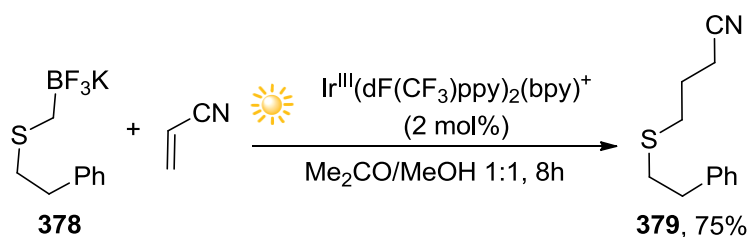
Generating alkyl radicals from the corresponding alkanes through a SET process is a demanding task due to high oxidation potential of hydrocarbons (Figure 1). The reaction met some success, however, in the case of adamantane, which was found to add to isopropylidene malononitrile in the presence of titania (TiO$_2$).[313] By contrast, tetraalkylstannanes showed to be much more effective as radical precursors. With asymmetric derivatives, the most stable alkyl radical was selectively generated upon mono-electronic oxidation and ensuing fragmentation. Thus, a butyl or a *tert*-butyl radical was generated by SET oxidation of tetrabutylstannane or *tert*-butyltrimethylstannane, respectively, under photocatalysis by aromatic nitriles (e.g. by TCB). The presence of a convenient co-catalyst, e.g. biphenyl, limited the occurrence of the undesired *ipso*-substitution of the cyano group in TCB (see Section 4.3.).[314] An analogous TCB photocatalyzed *t*-butylation of dimethyl maleate with *n*-C$_8$H$_{17}$OSiMe$_2$-*t*Bu has been reported.[314]

A quite unusual class of radical precursors is that of 2,2-disubstituted-1,3-dioxolanes, that upon mono-electronic oxidation, give a radical cation that fragments to give an alkyl radical and a stabilized carbocation. Particularly interesting is the case of 2-alkyl-2-phenyl-1,3-dioxolanes, since the presence of the aromatic ring lowered the oxidation potential of the substrate and led to a selective fragmentation. Thus, upon oxidation of **380** in the presence of TCB (*ca.* 6 mol%), dimethyl maleate **357** was alkylated to give **381** in 64% yield (Scheme 122a). Recently, organoborates (e.g. compound **382**) have been likewise used as alkyl radical precursors. As an example, diethyl ethylidenemalonate **383** was alkylated in the presence of 2 mol% Mes-Acr$^+$ClO$_4^-$

in the role of the photocatalyst. Trapping of the photogenerated alkyl radical by the electron-poor olefin and mono-electronic reduction of the resulting adduct radical followed by protonation, gave **384** (Scheme 122b).[315] Noteworthy, the same strategy was be applied to carboxylic acids.[315]

Scheme 122. Alkylation of Electron-Poor Olefins by Using a) 1,3-Dioxolanes and b) Organoborates as Radical Precursors
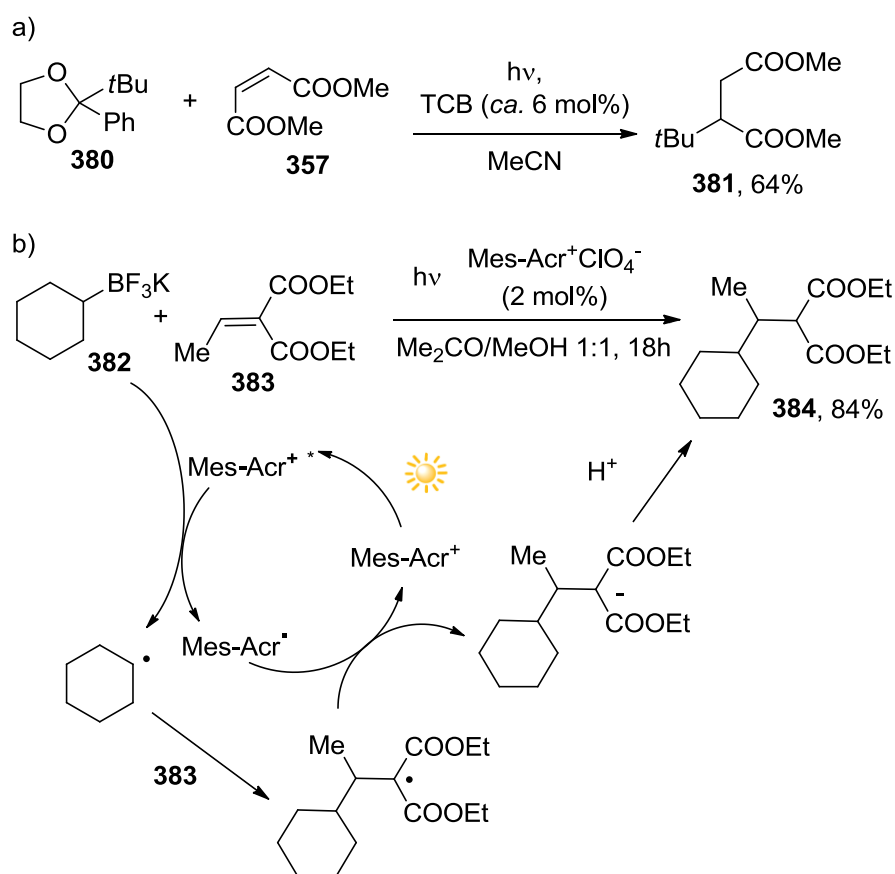
A particular case is that of persistent benzyl radicals. Mesomeric stabilization makes access to these radicals easier, particularly through a PET step. Trapping of these relatively stable species by an added alkene has to compete with several other paths, including coupling with the reduced catalyst (when a cyano arene is used) or dimerization. In any case, when an alcohol is used as co-solvent the desired alkylation takes place selectively. As an example, dimethyl maleate **357** was benzylated by toluene under DCN photocatalysis in the presence of *t*BuOH as co-solvent.[316]

Both the use of more easily cleaved precursors (involving a C-Si rather than a C-H bond) and of heterogeneous rather than homogeneous conditions (in order to minimize ion pairing and thus both back-electron transfer processes and coupling) led to higher alkylation yields. Thus, a satisfactory benzylation of conjugated acids, esters and carbonyls was obtained by using TiO_2 as heterogeneous photocatalyst and benzyltrimethylsilanes or, with a lower efficiency, phenylacetic acids as precursors of benzyl radicals.[317-319] The results could be further improved when the heterogeneous catalyst was loaded with a small amount of Pt (which facilitates ET)[318] or when adding an inorganic oxidant (e.g. Ag_2SO_4).[319] The sunlight driven TiO_2 catalyzed monobenzylation of maleic anhydride was carried out on a multi-gram scale by using benzylsilanes as starting substrates.[320]

Recently, the same reaction was carried out by using TBADT in the role of photoredox catalyst and gave the desired products in good yields. Also in this case the best performance was obtained in a highly nucleophilic solvent (a 0.5 M $LiClO_4$ $MeCN/H_2O$ 5:1 mixture). Indeed, both benzyl silanes (**385a**, X = $SiMe_3$)[321] and alkyl aromatics (**385b**, X = H)[322] were used as substrates, while the electron-poor olefins played the double role of radical traps and electron acceptors. As an example, benzylation of *N*-phenyl maleimide to give **386** occurred in 68 and 55% isolated yield, when starting from **385a** and **385b**, respectively (Scheme 123).[321,322]

Scheme 123. Decatungstate Photocatalyzed Benzylation of Electron-Poor Olefins

386, 68% from **385a**
55% from **385b**
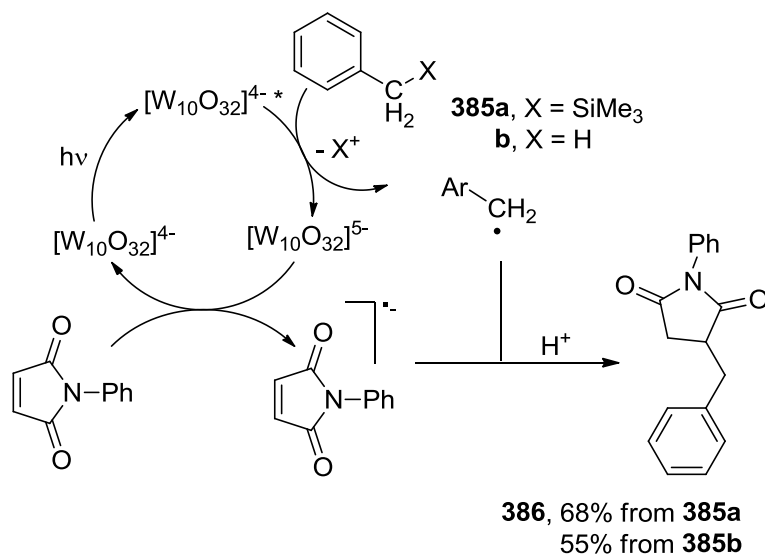
3-Bromo pyrroindolines **387** and furoindolines underwent mono-electronic reduction and loss of bromide ion, to form the corresponding benzyl radicals. These were conveniently trapped by α,β-unsaturated enone **388** in good yields (see Scheme 124). Noteworthy, this strategy could also be exploited for the synthesis of a collection of structurally complex alkaloid-terpenoid hybrids such as **389** of potential biological interest.[323]

Scheme 124. Photoredox Catalyzed Addition of Pyrroloindolines to Enones

387

388
(2 equiv.)

$Ir^{III}(ppy)_2(dtbbpy)PF_6$
(2.5 mol%)

Et_3N (2 equiv.), DMF

389, 90%
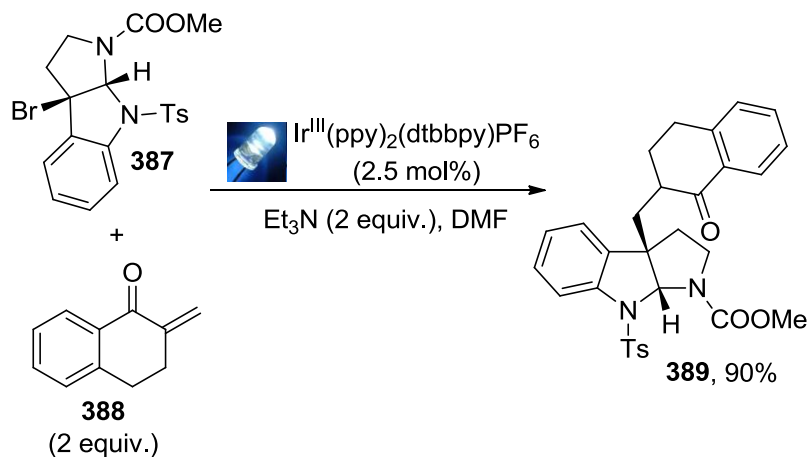
In one instance, a photoredox approach was exploited for the generation of α-acetyl radicals and the ensuing addition onto electron-rich olefins. Thus, α-halo (mainly chloro) amides were used as the substrates and underwent mono-electronic reduction followed by chloride anion loss in the presence of an Ir^{III} complex and a reductive quencher (Bu$_3$N) under irradiation with blue LEDs. As an example, propanamide **390** was added to 1,1-diphenylethylene in an anti-Markovnikov fashion to give product **391** in 77% isolated yield (Scheme 125).[324]

Scheme 125. Visible Light Photoredox-catalyzed Addition of α-Halo Amides to Olefins
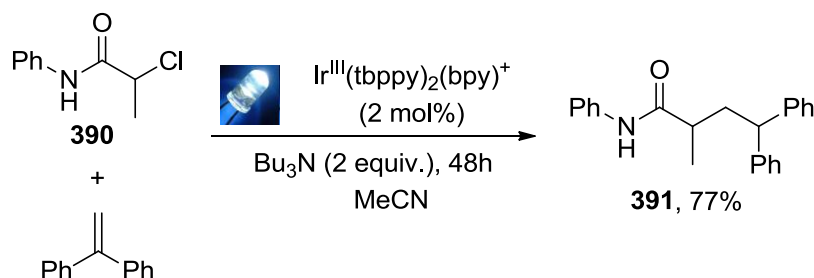
5.1.2. Addition of Y-C (Y ≠ H). The vicinal functionalization of alkenes, that is the addition of two groups across a C=C bond is not an easily achieved task, but a number of methods involving photogenerated intermediates have been proposed.

The reaction between radicals photogenerated from Barton esters (e.g. **392**) with methanesulfonyl or *p*-toluenesulfonyl cyanide in the presence of an (electron-rich) alkene represents a smooth entry for the preparation of β-cyanosulfone **393** in high yields. The process is initiated by addition of the sulfonyl radical onto the double bond, thus starting a radical chain reaction (Scheme 126).[325]

Scheme 126. Preparation of β-Cyanosulfones
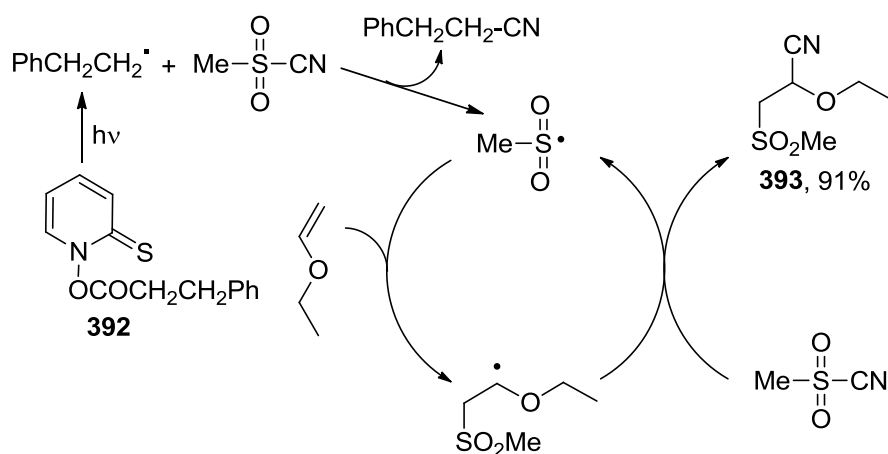
α-Oxy radicals were likewise obtained via photolysis of the corresponding Barton esters. These were in turn prepared from uronic acids and irradiated in the presence of an electron-poor olefin. A double functionalization of the C=C double bond occurred, since the thiopyridyl group resulting from Barton esters cleavage was incorporated in the final product.[326-328]

Analogously, the carboxylic group of α-aminoacids was protected as thiopyridone ester and the desired α-aminoalkyl radical was photogenerated. Thus, the side-chain decarboxylation of protected glutamic and aspartic acids allowed the preparation of α-aminoadipic and α-aminopimelic acid derivatives.[329]

Apart from the use of Barton esters, the generation of radicals can be carried out via photolysis of substrates containing labile bonds. This is the case of bisphenyl carbodiazone that upon irradiation liberated a phenyl radical by cleavage of a C(=O)-N bond. These intermediates have then been applied to the carbo-oxygenation of electron-poor olefins in a three-component process comprising TEMPO radical. Thus, irradiation of diazo derivative **394** in dichloromethane generated the desired phenyl radical upon nitrogen loss. Subsequent trapping by ethyl acrylate and coupling of the adduct radical with TEMPO led to the final product **395** (Scheme 127a).[330] With other olefins, however, a

significant amount of a byproduct was likewise formed, arising by trapping of the photogenerated acyl radical by TEMPO.[330]

Another class of substrates prone to undergo homolysis upon irradiation is represented by organic selenides, where the C-Se bond can be easily cleaved. This approach was exploited to introduce a masked carbonyl functionality through the addition of a 1,3-dithian-2-yl radical onto an electron-poor olefin. Thus, irradiation of 2-phenylseleno-1,3-dithiane **396** in the presence of butyl acrylate caused homolysis of the C-Se bond and radical addition led to adduct **397** in 75% yield (Scheme 127b). When the reaction was applied to highly substituted electrophilic olefins or to simple alkenes, however, poor results were obtained.[331]

Scheme 127. Double Functionalization of Olefins Starting from Substrates Containing Labile Bonds
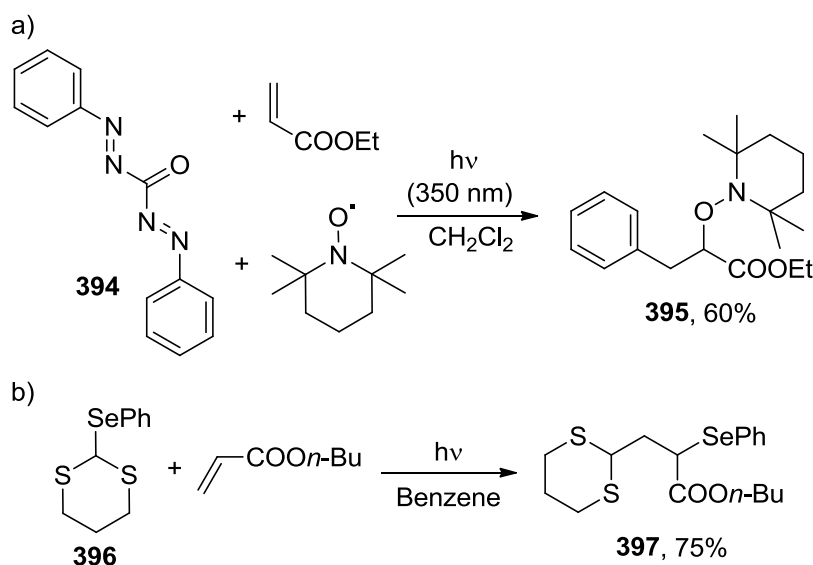
Electrophilic radicals were likewise conveniently photogenerated starting from diethyl 2-phenylselenomalonate and trapped by a nucleophilic olefin (e.g. terminal alkenes or vinyl ethers) to form the corresponding adducts in good yields, with incorporation of the PhSe group. The reaction, however, required an excess either of the starting diester or of the olefin.[332,333]

A class of reactions that is being increasingly studied for the double functionalization of alkenes involves the use of a visible light absorbing photocatalyst.[334] Most of them concerns with the generation of electrophilic radicals (efficiently trapped by electron-rich olefins) and some representative examples have been reported in the following.

ATRA (Atom Transfer Radical Addition) reactions consist in the addition of a halocarbon derivative across a double bond, where new C-C and C-Halogen bonds are formed. In the last few years, this process has been widely investigated under photoredox catalyzed conditions, and mono-electronic reduction of the halocarbon is usually involved as the activation key step. Several alternatives have been considered in the role of the photocatalyst, including Ru^{II}-[335] Ir^{III}-[335,336] and, more recently, Cu^I-based complexes.[337] Thus, excited $Cu^I(dap)_2^+$, a slightly stronger reducing agent (-1.43 V vs SCE, Figure 2) with respect to the well known Ru^{II}- and Ir^{III}- complexes, was able to reduce diethyl bromomalonate (**217**) to the corresponding radical anion. Bromide loss and trapping of the resulting radical **218**[•] by Boc-protected allylamine **398** ensued and gave alkylated compound **399** as the end product (Scheme 128).[337] In view of its peculiar redox properties, this photocatalyst could be succesfully applied also on benzyl halides, that were added onto styrenes and enol silyl ethers. When starting from *o*-nitrobenzyl derivatives, the corresponding ATRA-products were in turn easily converted to the corresponding tetrahydroquinolines.[338]

Scheme 128. Copper Photocatalyzed Functionalization of Olefins via an ATRA Process
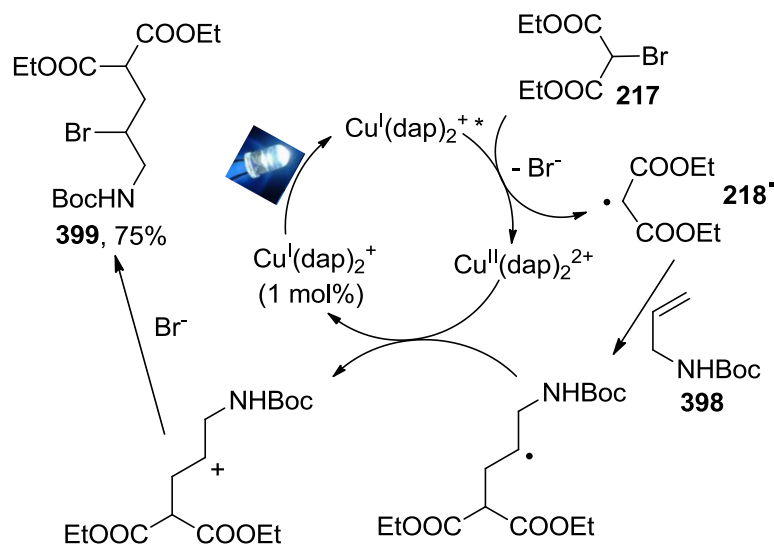
Recently, a different photocatalytic approach has been proposed for performing ATRA reactions. This is based on the use of an aromatic aldehyde (e.g. *p*-anisaldehyde) in the role of light-absorbing species. This excited photocatalyst, however, transferred energy to the the halocarbon rather than promoting the transfer of an electron and homolysis of the formed excited halocarbon finally led to the desired ATRA product.[339]

The introduction of (per)flouroalkyl groups (e.g. trifluoromethyl) in organic derivatives was achieved via a slightly modified versions of ATRA reactions. Thus, fluoroalkylsulfonyl chlorides have been used as substrates and activated through a mono-electronic reduction step. SO$_2$ extrusion then occurred, finally leading to the double-functionalized chloro(fluoroalkyl) derivatives **400** (Scheme 129, left part). Interestingly, this approach could be applied to both electron-rich[340] and electron-poor[341] olefins (e.g. acrylamides) under photoredox catalytic conditions mediated by Ru- and Cu- complexes, respectively.

Trifluoromethylsulfonyl chloride has been widely investigated and it has been demonstrated that SO$_2$ loss could be avoided under particular conditions involving the Cu^I(dap)$_2{}^+$ photoredox catalyst, thus leading to the trifluoromethylchlorosulfonylation of double bonds (e.g. **401**). This behaviour

has been rationalized by an inner sphere mechanism, where the metal center is believed to bind SO$_2$Cl, thus preventing SO$_2$ loss (Scheme 129, right part).[342]

Scheme 129. Different Pathways in the Double Functionalization of Olefins with Trifluoromethylsulfonyl Chloride
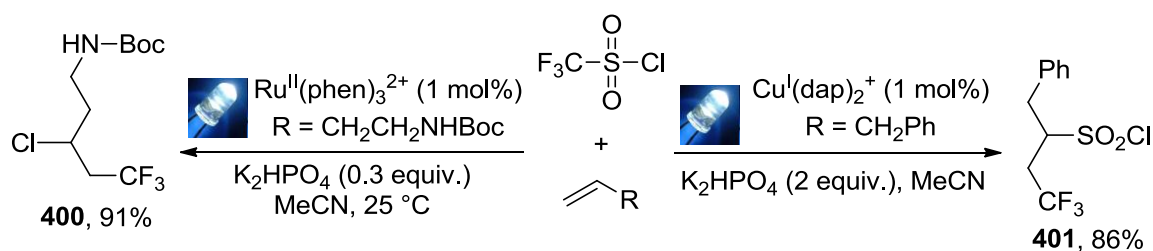
The conditions reported above for ATRA reactions can also lead to different products, depending on the actual substrates and the additives used. As an example, enamides could be alkylated in a three-component reaction, involving a halocarbon (e.g. diethyl bromomalonate) and an alcohol, thus resulting in the functionalization of the double bond by formation of a C-C and a C-O bonds.[343] Here the process was initiated by absorption of visible light by an Ir^{III}-based complex. The resulting radical adduct was then oxidized to the corresponding iminium ion and trapped by the nucleophilic solvent (EtOH). As a result, β-alkylated α-carbamido ethers (actually a stable imine equivalent) were obtained under very mild conditions and in good to excellent yields.[343]

In a different multi-component approach, Umemoto's reagent **402**$^+$ was used to generate a trifluoromethyl radical upon mono-electronic reduction in the presence of a suitable photoredox catalyst (a Ru^{II}- or Ir^{III}-complex). Trapping of F$_3$C$^•$ by both aromatic and aliphatic alkenes was followed by oxidation to a benzyl cation with the concomitant regeneration of the catalyst. Interception of the cation with a nucleophile ensued, causing the azidotrifluoromethylation,[344] aminotrifluoromethylation[344] or oxytrifluoromethylation[345] of the C=C bond upon reaction with trimethylsilylazide, amines or alcohols, respectively (Scheme 130). In a related application,

enecarbamates were subjected to the same procedure and reacted with different O-, N- and C-nucleophiles.[346]

Scheme 130. Photocatalyzed Three-component Reactions for the Difunctionalization of Alkenes
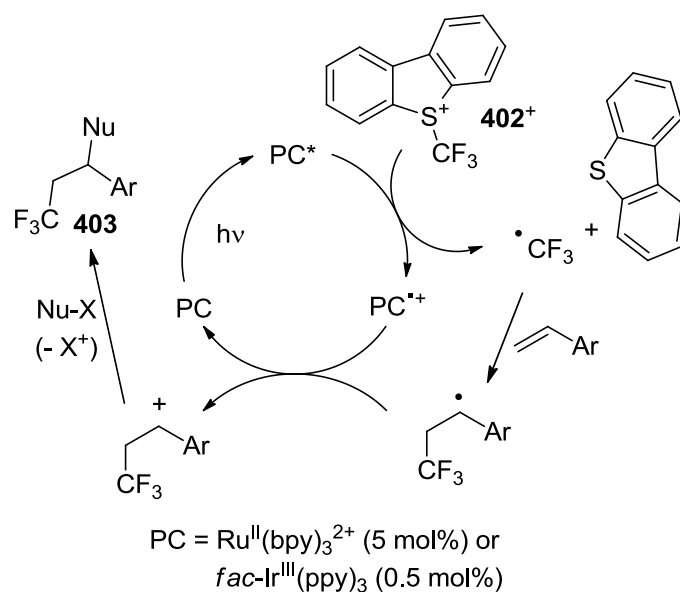
PC = Ru^{II}(bpy)$_3$$^{2+}$ (5 mol%) or
fac-Ir^{III}(ppy)$_3$ (0.5 mol%)

A further radical precursor is bromoacetonitrile that gave the cyanomethyl radical upon mono-electronic reduction. This electrophilic radical added to styrene derivatives to give, after oxidation and addition of an alcohol, a γ-alkoxynitrile. As an example, product **404** was obtained in 87% yield from styrene, bromoacetonitrile and methanol (Scheme 131).[347]

Scheme 131. Photocatalyzed Synthesis of γ-Alkoxynitriles

5.1.3. Other Reactions. This Section gathers reactions where the original structure of the double bond has been modified during the reaction course. One example deals with the direct irradiation of a mixture of acetylpyridines and silyl ketene acetals, resulting in an intermolecular PET between the two reagents followed by radical-radical coupling, that afforded the corresponding β-piridyl-β-hydroxyesters in high yields.[348] Enol acetates gave α-trifuoromethylated ketones under photocatalytic conditions, where one of the C-atoms involved in the double bond became the C-atom of the carbonyl moiety. In the process, CF_3SO_2Cl released the trifuoromethyl radical upon chloride anion and SO_2 loss, in a process triggered by a mono-electronic reduction. Addition of the radical onto the acetate, oxidation and loss of an acetyl cation ensued to give the final product (e.g. **405**, Scheme 132).[349] α-Trifluoromethyl ketones could be likewise synthesized in another photocatalytic procedure, involving styrenes, 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (Togni's Reagent) and DMSO (in the role of oxidant).[350] Related procedures were applied to the synthesis of β-ketosulfoxides[351] and γ-ketoesters.[352]

Scheme 132. Synthesis of α-Trifluoromethylated Ketones

5.2. Addition onto C=N Bond

The addition of radicals onto C=N double bonds (in imines or iso(thio)cyanates) opens the way to the synthesis of interesting *N*-containing derivatives, including functionalized amines. In some

instances, however, the original C=N moiety is retained in the final product. This is the case of sulfonyl derivative **407**, that underwent a radical addition process accompanied by loss of the sulfonyl group, while maintaining the oxime ether moiety in product **408**. Thus, open chain thiohydroxamate esters (e.g. **406**) were used as radical precursors and activated upon irradiation to give the desired radical upon decarboxylation (Scheme 133).[353] However, the presence of a COOMe group in the place of a hydrogen directly linked to the oxime carbon decreased to some extent the radical addition yield.[353]

Scheme 133. Functionalization of Oxime Ethers Exploiting Thiohydroxamate Esters as Radical Precursors

Similarly, the C=N bond of a ketoxime ether underwent addition of a photogenerated alkyl radical (obtained from an alcohol) and gave access to a β-oxygenated quaternary α-amino acid derivative. Importantly, this methodology was adopted as a key step in the preparation of the immunosuppressant (+)-myriocin.[354]

Apart from their use as radical traps, C=N-containing derivatives (particularly when conjugated) can also be exploited as electron-acceptors. As an example, this strategy was adopted in the CdS (on a ZnS carrier) photocatalyzed addition of cyclic olefins (e.g. cyclopentene) to some phenylcyano-*N*-benzoylimines (**409**). The photocatalyst promoted both the mono-electronic oxidation and reduction of the alkene and the imine, respectively, to give the corresponding radical ions. Proton exchange ensued and a chemoselective heterocoupling led to the formation of adducts such as **410** (81% yield; Scheme 134).[355] *N*-adamantylimines were also used, affording homoallyladamantylamines in

modest to excellent yields. In this case, CdS grafted onto alumina was adopted as the photocatalyst under visible light irradiation.[356]

Scheme 134. Addition of Photogenerated Radicals onto Imines

More recently, imines were used as electron-acceptors in the synthesis of β-amino ethers. These imines (e.g. **411**) were coupled with benzyl ethers in the presence of a thiol organocatalyst (methyl thioglycolate **412**) and an Ir-based photoredox catalyst. Thus, the excited complex reacted with the thiol to give a thiyl radical through a concerted PCET. In turn, the reduced photocatalyst gave the *N*-aryl imine radical anion **411·⁻** through a mono-electronic reduction, while the thiyl radical abstracted a hydrogen atom from the benzyl ether. Radical-radical anion coupling, followed by protonation, afforded the desired aminoether (e.g. **413**, 77% yield; Scheme 135).[357]

Scheme 135. Dual Catalytic Approach for the Synthesis of β-Amino Ethers

Apart from imines, another interesting class of radical traps is represented by (aryl) isocyanates or isothiocyanates. Mono-electronic oxidation/deprotonation of aromatic tertiary amines (e.g. *N,N*-dimethylaniline) by an Ir^{III}-based complex gave the corresponding α-amino radical **414˙**. The latter was then trapped by the isocyanate to give a radical adduct **415˙**, finally leading to the desired α-amino amide (e.g. **416**) in good yields.[358] Interestingly, the success of the process was based on the high reductive potential of the employed catalyst (FIr^{III}pic, containing one picolinate ligand), capable to reduce radical **415˙** (see Scheme 136). Analogously, pentafluorophenyl isocyanate was used as the radical trap in the carbamoylation of ethers via the photoinduced functionalization of ethereal α-C-H bonds in the presence of benzophenone as the photocatalyst.[359]

Scheme 136. Synthesis of α-Amino Amides

5.3. Addition onto C=O Bond

The reactivity of the C=O moiety towards photogenerated intermediates is quite low. Indeed, photoaddition reactions at the carbonyl (or carboxyl) group are feasible only when this moiety functions as the acceptor in a PET step. Typical are the PET reactions between phthalimides (or maleimides) and good electron donors (e.g. carboxylates). Thus, irradiation led to the photodecarboxylative addition to phthalimides in what was considered a versatile alternative to the use of Grignard reagents. As an example, the potassium salts of several phenylacetic acids were used for the benzylation of *N*-methyl phthalimide **417**, to give **418**) in good yields (Scheme 137, upper part).[360] Interestingly, in favourable cases α-keto carboxylates could be likewise used, finally leading to the acylation of **417** to give **419** (Scheme 137, lower part).[361]

Scheme 137. Radical Addition to CO Bonds in Phthalimides

When starting from ω-arylpropanoic acids, a series of 3-(alkyl and aryl)methyleneisoindolin-1-one derivatives were conveniently accessed by dehydration/deprotection of the resulting photoproducts. This is a class of compounds having potential biological activity.[362] As mentioned in Section 2.5, the intramolecular version of the same reactions allowed for the easy synthesis of medium- and large-size rings.[363]

6. SYNTHESIS OF ALKYNES

This section includes processes involving the construction of a new C-C(sp) bond. With a few exceptions, the synthesis of alkynes through photogenerated intermediates involves the displacement of a good radicofugal group from one of the C(sp)-atoms of the triple bond. The use of aromatic ketones in the role of the photocatalyst allowed the alkynylation of a variety of C(sp^3)-H bonds in (protected) amines, ethers, alcohols and even alkanes. The reaction proceeded through hydrogen atom transfer from the substrate to the excited carbonyl to give the corresponding radical, then trapped by 1-tosyl-2-(trimethylsilyl)acetylene (**420** in Scheme 138) to yield the final

alkynylated derivative with the concomitant release of a tosyl radical.[364] Notably, this approach has also been adopted as a key step in the synthesis of (+)-lactacystin (see Scheme 138).[55]

Scheme 138. Synthesis of (+)-Lactacystin through a Radical Alkynylation Step

Another possibility for the generation of radicals is through a photoredox catalyzed approach. Thus, the activation of *N*-acyloxyphthalimides was obtained by using a Ru^{II}-based complex. The mono-electronic reduction of these substrates caused the release of the phthalimide group and afforded the desired C-centered radical after decarboxylation. A variety of alkynes have been screened as radical traps, but those bearing a phenylsulfone moiety were found to give the best performance.[365] Noteworthy, this procedure occurred under very mild conditions, offering a wide functional groups tolerance and also demonstrating a compatibility with biomolecules.[365]

As mentioned in Sections 4.2 and 5.1.1, alkyl trifluoroborates are excellent radical precursors. As an example, irradiation of Ru^{II}(bpy)$_3$$^{2+}$ in the presence of alkyl trifluoroborate **423** led to the formation of the corresponding alkyl radical upon deboronation. This was then trapped by alkynyl benziodoxole **424** to give a radical adduct and the desired alkyne **425** upon loss of a benziodoxole radical BI$^•$ (Scheme 139). The reaction required the addition of the mild oxidant
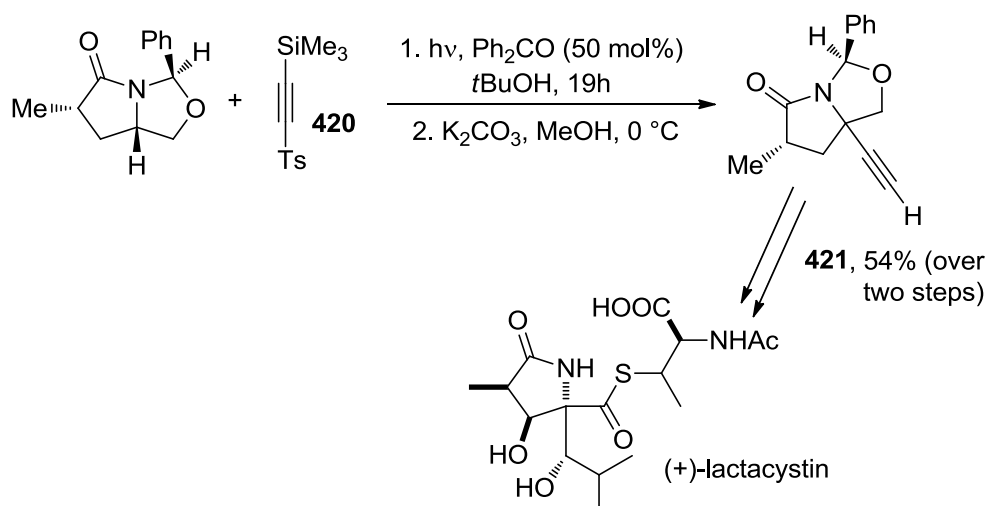
hydroxybenziodoxole **422** and of a base (Na₂CO₃), probably involved in the initiation step and in suppressing undesired side reactions.[366]

Scheme 139. Photoredox Catalyzed Synthesis of Alkynes
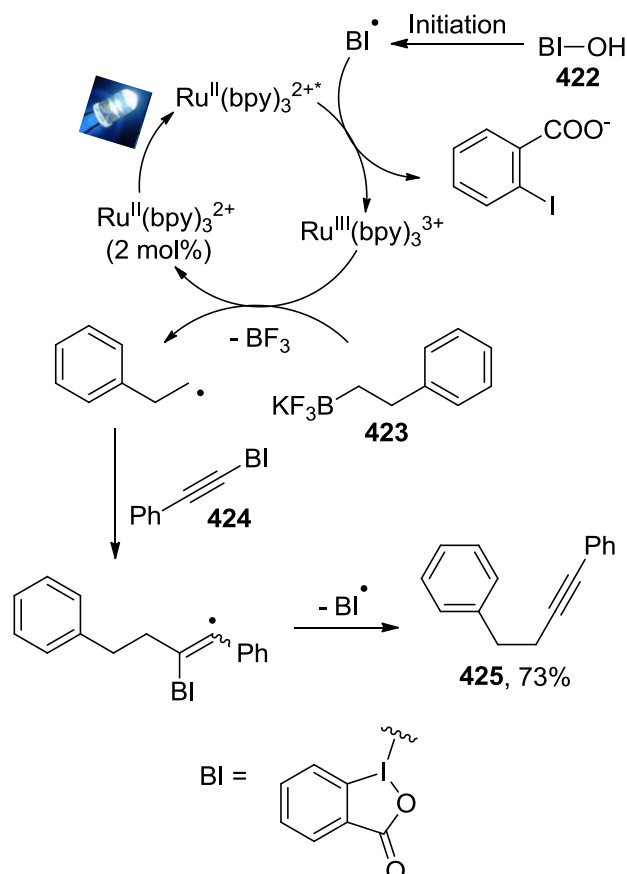
Similarly, the reaction between tertiary aliphatic amines and 1-iodoalkynes was carried out under photoredox catalyzed conditions in the presence of a dimeric gold(I) complex. The reaction was satisfactory under sunlight irradiation (also on a gram scale) and led to the synthesis of α-alkynyl amines in good yields.[367] The same products were formed by exploiting a dual catalytic approach, where the photoredox catalyst was coupled with a thermal Cu-based catalyst. Notably, in this case, non-activated alkynes could be used as the substrates.[368,369]

Irradiation with sunlight likewise promoted the synthesis of ynones in the presence of a catalytic amount of hydroxybenziodoxole **422** (30 mol%). The reaction was performed on α-ketoacids (e.g.

426) that coupled with bromoacetylenes (such as **427**) after decarboxylation and afforded the desired ketones (**428**, Scheme 140).[370]

Scheme 140. Sunlight Induced Synthesis of Ynones
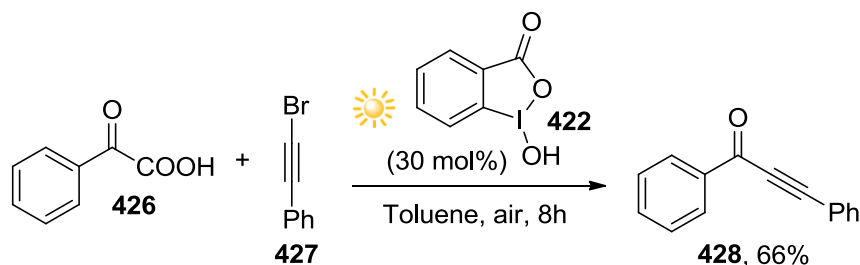
Ynones were smoothly formed as well by a three-component reaction starting from iodoalkanes and 1-alkynes under CO pressure (45 atm) in the presence of $Pd^{II}Cl_2(PPh_3)_2$ (5 mol%). An alkyl radical was formed by a photoinduced C-I cleavage with the help of a Pd(0) species. Carbonylation of the radical followed by coupling with $Pd^{I}I$ and the alkyne gave the hoped for alkyl alkynyl ketone in a satisfying yield.[371]

7. OTHER C-C BOND FORMATION

7.1. Cyanation

Cyanation reactions involving photogenerated intermediates follow either of two paths, a radical process or the nucleophilic addition of the cyanide anion onto electrophilic derivatives (iminium ions). As for the first approach, the benzophenone photomediated generation of carbon-centered radicals from ethers was applied to the smooth synthesis of α-cyanoethers via a direct C-H cyanation process.[372] The radical formed via hydrogen atom transfer from the substrate to the excited ketone was trapped by tosyl cyanide **429** to form the corresponding nitrile **430**. Cyclic

ethers (including crown ethers, Scheme 141) were particularly suitable for the reaction, although alcohols, substituted amides and alkanes could be likewise functionalized.[372]

Scheme 141. Photocatalyzed Synthesis of α-Cyanoethers
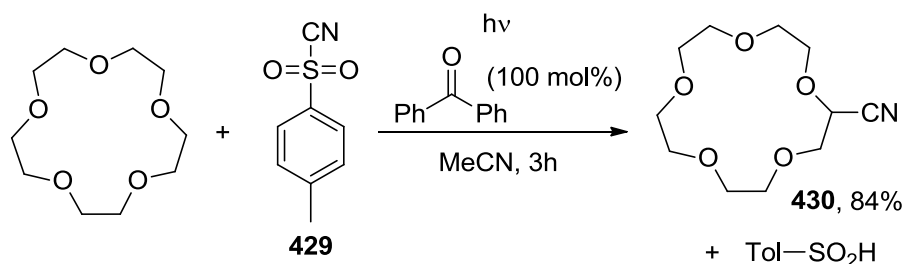
Turning to the second approach, the generation of iminium ions from tertiary amines under photoredox catalyzed conditions is a long known approach, where two main pathways are possible. The first one involves three steps, namely a mono-electronic oxidation of the amine, the loss of a cation (usually a proton) from the α-position, and a second mono-electronic oxidation of the resulting α-amino radical.[6] In the second mechanism, the first oxidative step is followed by hydrogen atom abstraction (usually by a highly reactive oxygen-based species), leading directly to the desired iminium ion.

According to this strategy, several α-cyanoamines[369,373-376] (including valuable intermediates for the synthesis of indole alkaloids)[373-375] were synthesized. Interestingly, visible light could be conveniently adopted when using photocatalysts such as *N,N'*-dimethyl-2,7-diazapyrenium bis(tetrafluoroborate) [DAP^{2+}(BF$_4^-$)$_2$]. As an example, a series of alkaloids, including atropine, was photocyanated by using this visible light absorbing sensitizer and Me$_3$SiCN as the cyanide source. The success of the reaction was in part attributed to the stability of the radical cation generated by monoelectronic reduction of the diazapyrenium salt.[375]

Recently, rose bengal was reported to photocatalyze the cyanation of THIQs in the presence of Me$_3$SiCN as the nucleophile. The dye (5 mol%) was used here in combination with graphene

oxide.[377] An interesting variation of this procedure involved the cyanation of allyl amines (in turn resulting from a preliminary aza-Baylis-Hillman process). Thus, when subjected to irradiation in the presence of a catalytic amount of a Ru^{II}-complex (the photocatalyst) and of Me$_3$SiCN, these substrates underwent cyanation in the γ-position, with a shift of the double bond to give an enamine.[378]

Notably, the generation of iminium ions under photocatalyzed conditions has been applied to the functionalization of complex natural products, *viz.* (+)-catharanthine (**431**). Thus, irradiation of **431** in the presence of a polyfluorinated Ir^{III}-based catalyst led to rearranged α-cyano amine **432**, arising from fragmentation of the radical cation formed. Noteworthy, **432** was used as the intermediate in the synthesis of three different naturally-occurring derivatives, namely (−)-pseudotabersonine, (−)-pseudovincadifformine, and (+)-coronaridine (Scheme 142).[379]

Scheme 142. Synthesis of Naturally-occurring Derivatives via Photocyanation/Fragmentation of (+)-Catharanthine
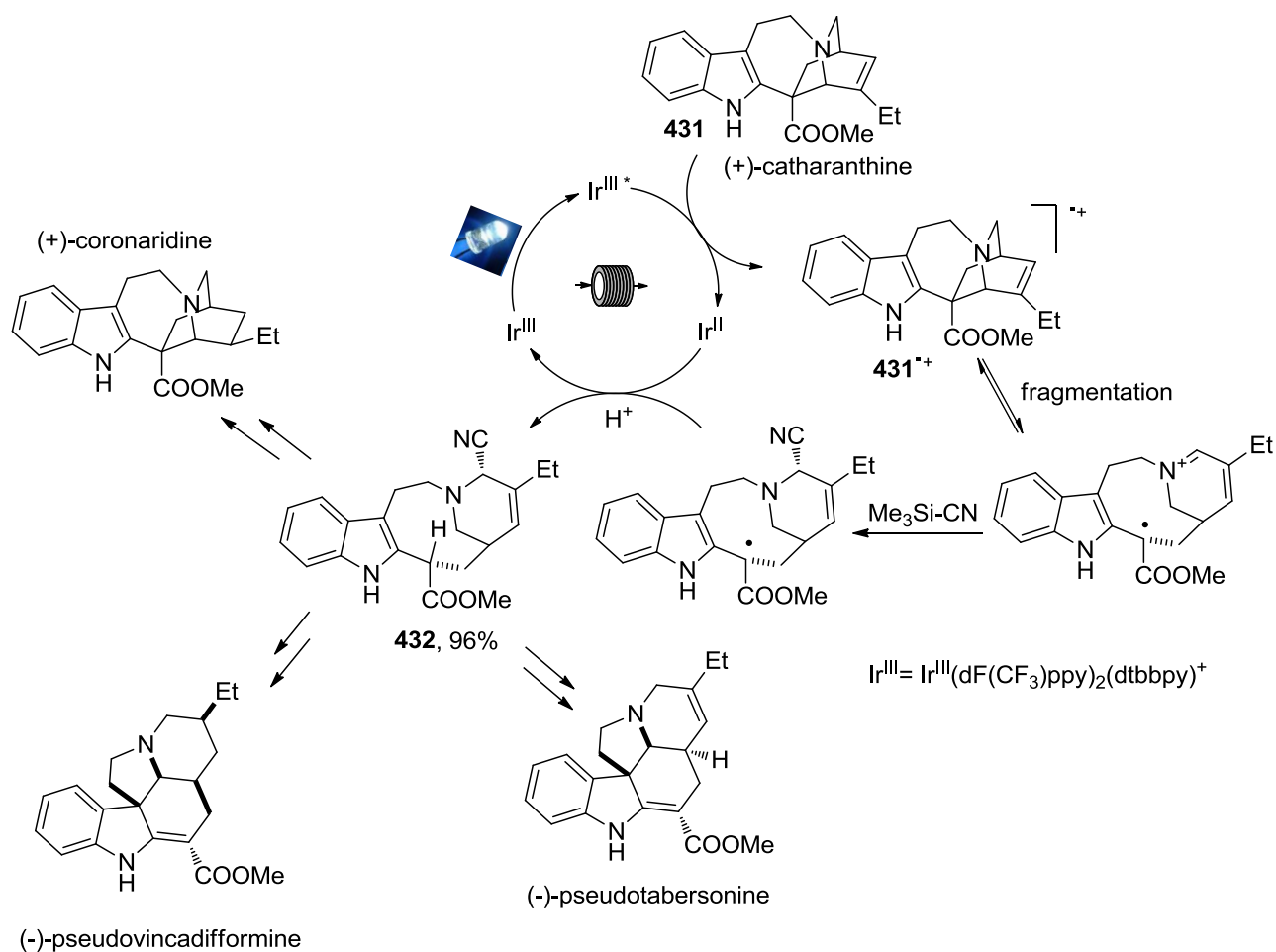
7.2. Carbonylation

Carbon monoxide is an important building block in organic synthesis due to its ability to form two new chemical bonds at the C-terminus, upon reaction with radical species. Depending on the actual reaction conditions, a wide variety of carboxyl derivatives (such as amides and esters), carbonyls (particularly, ketones) and alcohols (under reductive conditions) can be accessed by having recourse to carbon monoxide. As an example, the synthesis of esters was carried out by reaction between an in situ formed acyl iodide and the desired alcohol. In turn, an elegant way to prepare the acyl iodide was found in the Atom Transfer Carbonylation (ATC) where alkyl radicals (generated by photolysis of a suitable alkyl iodide **433**) underwent a carbonylation, as illustrated in Scheme 143. The

reaction of the acyl radical with the starting alkyl iodide **433** gave an acyl iodide **434** that in turn reacted under basic conditions with an alcohol (e.g. benzyl alcohol) to give the corresponding ester **435**.[380] A larger reaction scope could be obtained in the presence of a catalytic amount of Pd^0(PPh$_3$)$_4$.[381] Interestingly, the same protocol was also applied to the synthesis of amides[382] and of alcohols,[383] when the reaction was carried out in the presence of a (secondary) amine or a suitable reducing agent (e.g. Bu$_4$N$^+$BH$_4^-$), respectively. Alkyl selenides (in place of alkyl halides) were likewise converted to the corresponding acyl selenides upon incorporation of CO.[384]

Scheme 143. Photoinduced Atom Transfer Carbonylation (ATC)
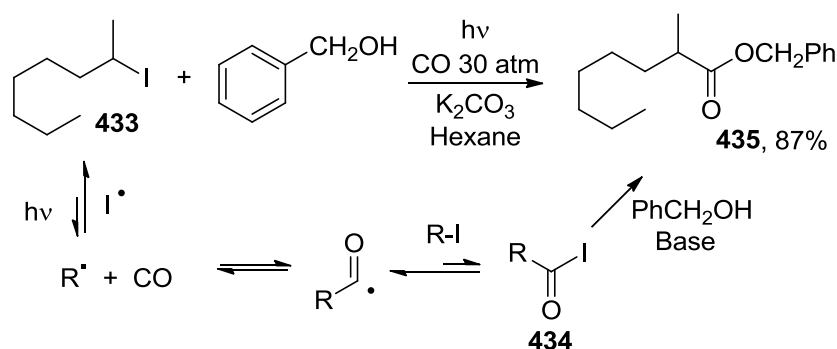
The synthesis of acyl hydrazides was recently obtained via a TBADT photocatalyzed multi-component process starting from cycloalkanes, CO and diisopropyl azodicarboxylate. The mechanism involved generation of an alkyl radical (via C-H bond activation in the cycloalkane) that was subsequently trapped by CO and then by the azo-derivative.[385]

7.3. Vinylation

This Section gathers those reactions occurring either through a radical addition onto a triple bond or through the substitution of one group on a pre-formed double bond. As reported in Section 5.1.2, the direct irradiation of substrates containing labile bonds (e.g. C-Se) can be exploited for the double functionalization of unsaturated derivatives. Indeed, this approach has been found convenient also for the preparation of vinyl selenides by addition onto alkynes.[333]

Electron-poor alkynes can be conveniently functionalized under photocatalyzed conditions in the presence of aromatic ketones. The absorption of aromatic ketones extends up to the UV-A region, with some superimposition with the solar spectrum. Indeed, solar irradiation turned out to be a viable choice for carrying out the photochemical addition of cyclopentane onto methyl propiolate **48** to give alkylated derivative **436** in 77% yield as a diastereoisomeric mixture, with a slight preference for the *E*-isomer (Scheme 144). The cycloalkane plays the dual role of solvent and reactant and no polyalkylated derivative was detected in the crude mixture. Alkynes were successfully alkylated also by using recyclable polymer-bound photocatalysts, such as benzophenone bound to Merrifield resin or to a silica gel surface through an aminopropyl tether.[386] The same approach was adopted in the addition of oxygenated radicals (e.g. dioxolanyl radicals) onto alkyl propiolates or dialkyl acetylendicarboxylates.[387]

Scheme 144. Sunlight Photocatalyzed Vinylation of Cyclopentane
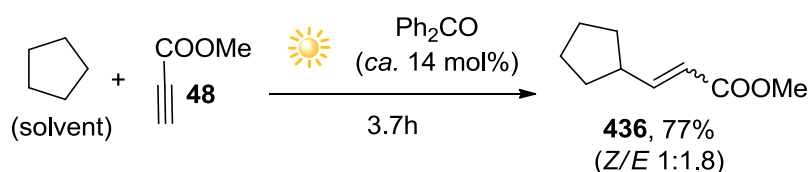
Recently, a related photocatalytic approach was applied to the same reaction, leading to the vinylation of THF-derivatives with alkynes. The reaction was based on the use of Eosin Y and *tert*-butyl hydroperoxide. Thus, the excited photocatalyst promoted an energy transfer to the peroxide, that underwent homolysis to give a couple of *O*-centered radicals. These were in turn capable to abstract a hydrogen atom from the 2-position of THF, giving the corresponding α-oxy radical. Trapping by the triple bond gave a vinyl radical that reacted with THF, starting a chain reaction.[388]

Recently, Ru^{II}-complexes photocatalyzed ATRA processes (see Section 5.1.2) were used to promote the synthesis of trifluoromethyl alkenyl iodides starting from perfluoroalkyl iodides and alkynes.[335,389] In one case, the excited Ru^{II}-complex was reduced by TMEDA, giving a highly

reducing Ru^I species. This was prone to activate CF_3I through an additional electron transfer step causing the generation of a trifluoromethyl radical. Attack onto the alkyne (e.g. phenylacetylene) ensued and gave a vinyl radical **437·** that abstracted iodine from starting CF_3I in a chain process, finally leading to the desired alkenyl iodide **438** with a marked preference for the *E*-isomer (Scheme 145).[389] Notably, a fine control of the reaction conditions (the base used was found to play a key role) allowed to divert the reaction course, leading to the synthesis of trifluoromethylated alkenes or alkynes.[389]

Scheme 145. Visible-Light Photoredox Catalyzed Trifluoromethylation of Alkynes

TMEDA = *N,N,N',N'*-tetramethylethylenediamine
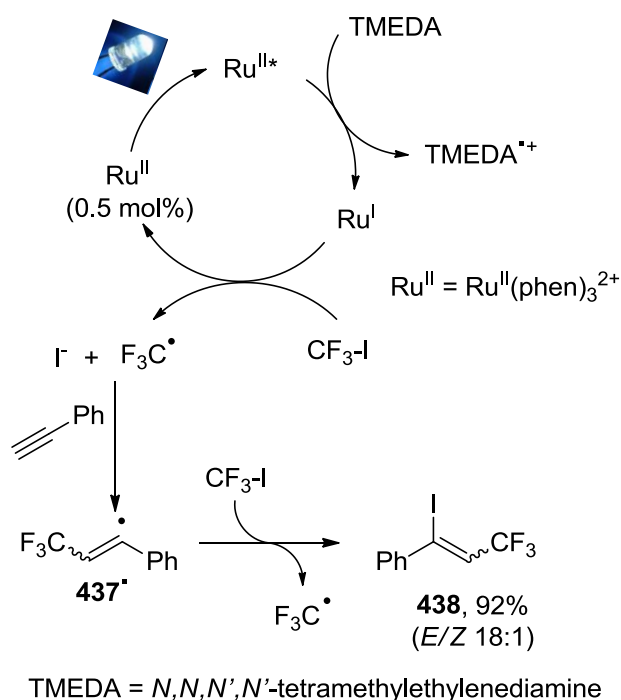
As mentioned, alternative vinylations could be accomplished by introducing a new substituent onto an already formed C=C double bond. Most of the available alternatives for this target involve the use of photocatalysts. There is, however, a recent example where the direct UV irradiation of (non-activated) alkyl iodides in basic water in the presence of styrene led to the corresponding coupling products in a transition metal-free Heck-type reaction.[390]

Sparse examples deal with the generation of alkyl radicals by irradiation of organometallic compounds, e.g. alkylcobalt complexes, where the reaction is accompanied by a rearrangement in the coordination sphere of the metal. The use of air-stable alkyl-Cobalt complex (e.g. **174**; Scheme 146, see further Scheme 62) has emerged as a convenient method for the generation of C-centered radicals from the corresponding alkyl iodides (see further Section 2.5). Thus, irradiation of a mixture containing an alkene, an alkyl iodide and a trialkyl amine in the presence of a catalytic amount of **174** allowed for a base-mediated alkyl Heck-type coupling, as reported in Scheme 146.[155] A related photohomolysis of alkyl-Co^{III} species was applied to amino acid derivatives for the synthesis of (−)-α-kainic and (+)-allokainic acid.[391]

Scheme 146. Synthesis of Alkenes via Alkylcobalt Complexes
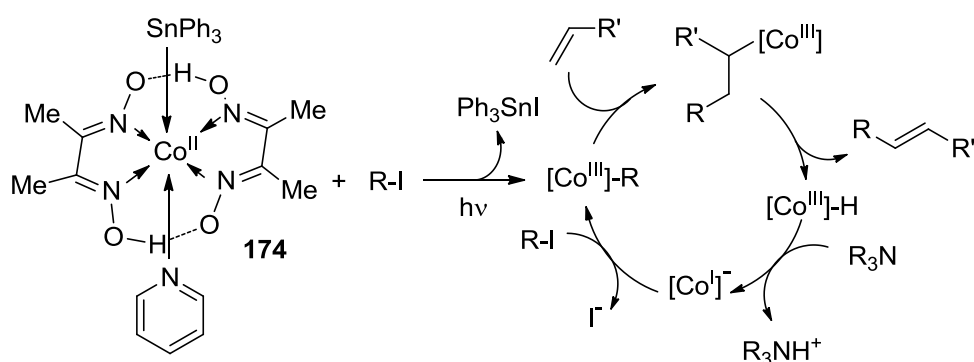
More recently, several photoredox catalyzed approaches have been devised for performing vinylation reactions. As for the first case, the trifluoromethylation of alkenes by CF$_3$I to give the corresponding trifluoromethyl-substituted olefins has been achieved by irradiation of a Pt^{II}-complex in the presence of a base. Thus, CF$_3$I underwent mono-electronic reduction promoted by excited Pt^{II}* and afforded the trifluoromethyl radical. This was trapped by the alkene to give a radical adduct that was in turn oxidized by the deactivated catalyst to give the corresponding cation **440$^+$**. Addition of iodide ensued to give an alkyl iodide that underwent a base promoted elimination reaction, restoring the original double bond. As an example, 1-dodecene **439** gave product **441** in 97% yield with a marked preference for the *E*-isomer (Scheme 147).[392] In a related process, a

catalytic amount of a Ru^{II}-based complex was coupled with Umemoto's reagent (402^+) in the role of "CF_3" source. Notably, this trifluoromethylation process was successful also with 1,1-di and tri-substituted alkenes, providing the corresponding multi-substituted trifluoromethylalkenes.[393] Furthermore, the stereochemistry of the final product could be controlled through an appropriate combination of the photoredox catalyst and of the CF_3-containing substrate.[394] Similarly, the difluoroalkylation of alkenes has been carried out in the presence of an Ir^{III}-complex starting from ethyl 2-bromo-2,2-difluoroacetate.[395]

Scheme 147. Photoredox Catalyzed Trifluoromethylation Mediated by a Cyclometalated Pt(II) Complex
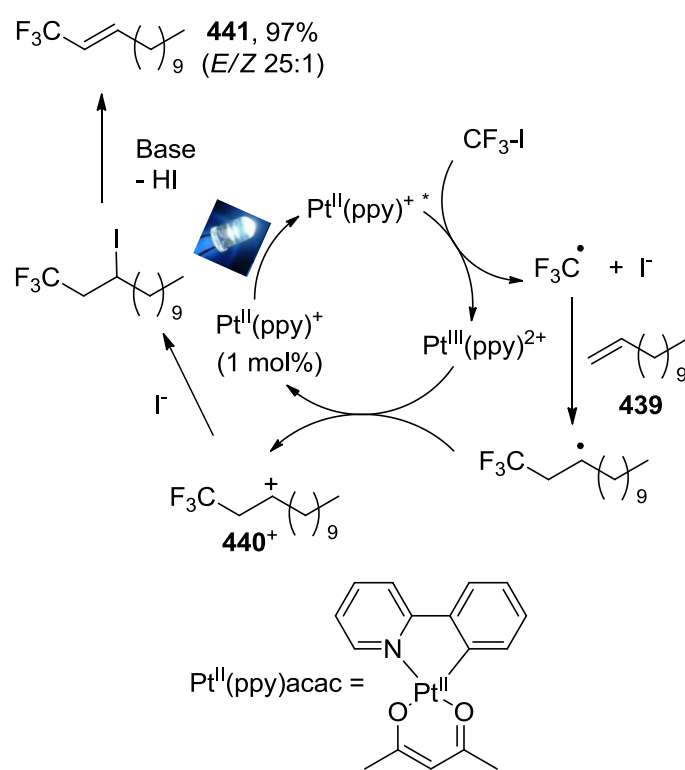
Other methodologies involve the use of alkenes bearing a substituent that is eliminated at the end of the reaction and directs the formation of the new C-C bond. α,β-Unsaturated acids,[396,397] vinyltrifluoroborates[398] and vinyl sulfones,[399] have been used in this approach. Alkyl trifluoroborate **442** functioned as radical precursor when irradiated in the presence of a Ru^{II}-complex and afforded

the corresponding C-centered radical upon mono-electronic oxidation followed by deboronation. Meanwhile, α,β-unsaturated acid **443** reacted in situ with acetoxybenziodoxole **444** to give a vinyl carboxylic acid complex **445**, prone to trap the generated radical at the α-carbon. The so formed radical adduct gives the final alkene (**446** in 69% yield) with the concomitant loss of CO_2 and of the benziodoxole radical BI$^\bullet$ (Scheme 148).[396]

Scheme 148. Photoredox Catalyzed Vinylation of Radicals via Decarboxylation of α,β-Unsaturated Acids
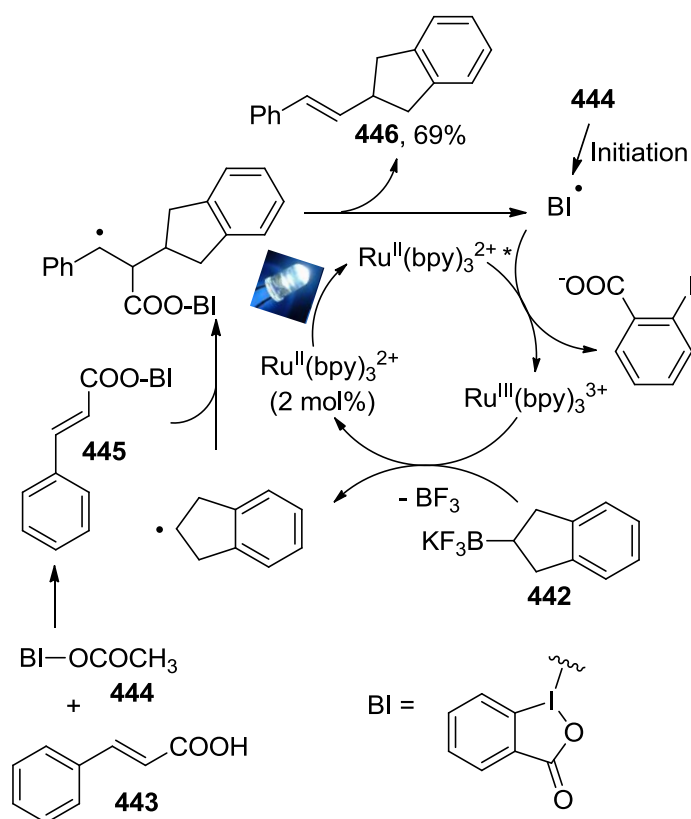
More recently, dual catalytic systems have appeared, where a photocatalytic (more specifically, photoredox) cycle has been merged with a thermal catalytic cycle. A sequential catalytic approach involving a photoredox step and nucleophilic catalysis (by a tertiary amine, e.g. DABCO) was exploited to achieve the direct acroleination of THIQs. This methodology involved the photocatalytic generation of an iminium ion in the presence of an Ir^{III}-complex and of Cl_3CBr as the

oxidant. In turn, DABCO added to acrolein to give a nucleophile that efficiently trapped the iminium ion, in what can be considered a kind of aza-Baylis-Hillman reaction. Noteworthy, an asymmetric version of this reaction, employing a chiral amine as organocatalyst has been developed.[400]

Another example where two catalytic cycles are merged, involves the use of photoredox catalysis coupled with metal catalysis. This strategy, based on the use of a fluorinated Ir-complex photocatalyst and a Ni^0-based catalyst, allowed the decarboxylative coupling of carboxylic acids, including aliphatic α-oxy and α-amino acids, with vinyl halides (usually, iodides). Thus, the reaction was carried out under basic conditions and involved the in-situ formed carboxylate anion (e.g. **447⁻**, Scheme 149). In turn, this underwent mono-electronic oxidation by the excited Ir^{III}-complex and split CO_2 to give the corresponding C-centered radical **448˙**. A Ni^0 species was involved in the activation of the olefin derivative **449** and underwent oxidative addition to give a vinyl-Ni^{II} intermediate **450**. Interception of the C-radical generated a Ni^{III} organometallic species **451** that afforded the desired product (**452**) upon reductive elimination. The resulting Ni^{I} complex **453** then generated the photoredox catalyst by an additional SET, restoring the two catalysts and allowing them to start a new cycle (Scheme 149).[401]

Scheme 149. Dual Ni/Photoredox Catalytic Approach for the Vinylation of THF

Ir^{III} = Ir^{III}(dF(CF$_3$)ppy)$_2$(dtbbpy)$^+$
L$_n$Ni^0 = NiCl$_2$·dtbbpy
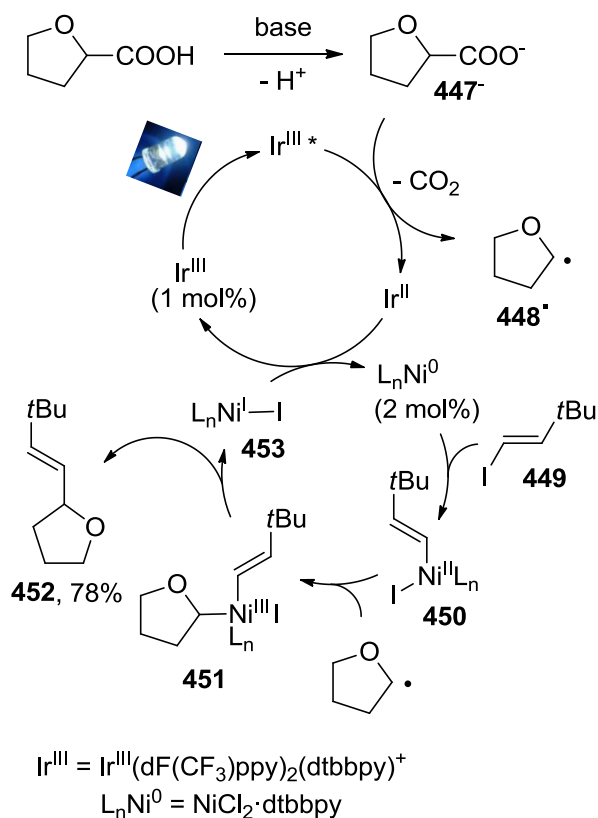
7.4. Allylation

Apart from thermal nucleophilic substitution reactions, allylation processes can be conveniently carried out by exploiting photogenerated radical intermediates. The generation of a radical by direct irradiation is viable, as in the case of modified Barton ester (**454**), that was chosen for the synthesis of pseudomonic acid C from L-lyxose (Scheme 150).[402] The α-oxy radical **455˙** generated by irradiation in toluene was trapped by allyltributyl stannane to give allylated derivative **456** in a good yield (80%), although a long irradiation time (65h) was required.

Scheme 150. Allylation via Barton Esters
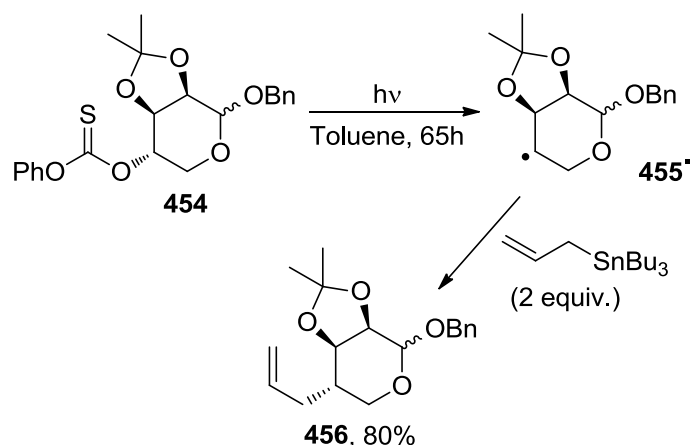
Indirect methods have been likewise applied. Photocatalysis by DCN in MeCN/water 4:1 mixture caused the oxidation of *N*-ethyl tetrahydroisoquinoline **457** to the corresponding iminium cation **459⁺** through an initial mono-electronic oxidation promoted by DCN* (methyl viologen **458²⁺** as cocatalyst). This was followed by deprotonation (assisted by the aqueous solvent) and further mono-electronic oxidation promoted by ground state DCN. The cation was finally trapped by allyltrimethylsilane and afforded allylated derivative **460** in 70% yield (Scheme 151).[403]

Scheme 151. DCN Photocatalyzed Allylation of *N*-Ethyl Tetrahydroisoquinolines
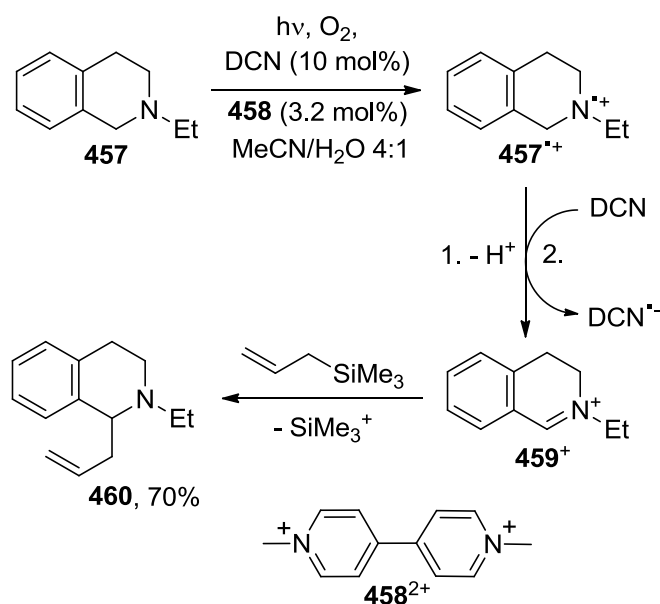
More recently, a Ru^{II}-complex[369] and a heterogeneous mesoporous graphitic carbon nitride (mpg-C$_3$N$_4$) catalyst[404] were likewise used in the allylation of THIQs. In the latter case, weak nucleophiles, such as allylstannanes, allylsilanes and allylboranes were employed as allylating agents.[404] The reducing power of a visible light photoredox catalyst was exploited in the generation of α-ketoradicals by ring opening of α-ketoepoxides (e.g. **461**). Both Ru- and Ir-based complexes have been used along with Hantzsch ester derivatives in the role of quenchers. Thus, reduction of **461** led to the corresponding radical anion, that underwent opening of the three-membered ring, and then reacted with allyl sulfone **462**. The final β-hydroxyketone **463** resulted upon loss of the sulfonyl group through an overall radical ring-opening/allylation tandem process occurring in a highly diastereoselective fashion (Scheme 152).[405]

Scheme 152. Photoreductive Allylation Procedure Starting from Epoxides
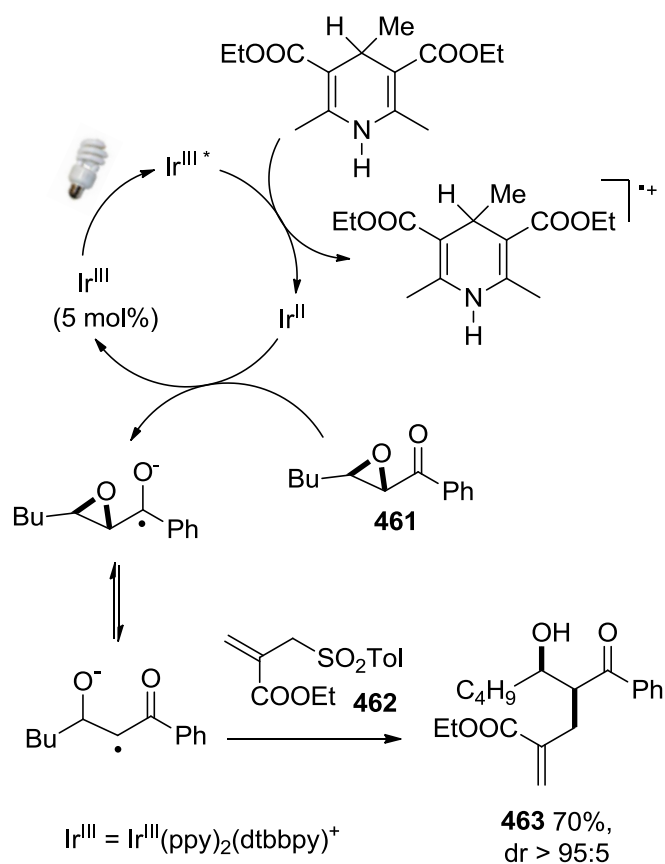
Another interesting possibility for carrying out allylation reaction is through the use of dual catalytic methods, where an Ir^{III}-centered complex was exploited for the generation of a radical species while a Pd^0-complex operated thermally and activated allyl esters (e.g. acetates and phosphates)[406] and allyl carbonates.[407] As an example, *N*-heteroaryl THIQ **464** was initially converted (by the excited Ir-complex) to the corresponding α-amino radical **465**· (Scheme 153). Meanwhile, a π-allylpalladium complex **467** was formed in situ by oxidative addition of the allyl ester (e.g. allyl diethyl phosphate **466**) onto the metal center. In the last step, a cross-coupling between the allyl radical (from reduction of the π-allylpalladium complex) and the α-amino radical led to the desired allylation product **468**. Interestingly, **468** could be further elaborated, giving access to a derivative belonging to the protoberberine family (**469**, Scheme 153).[406]

Scheme 153. Dual Pd/Ir Catalysis for the Synthesis of a Derivative Belonging to the Protoberberine Family
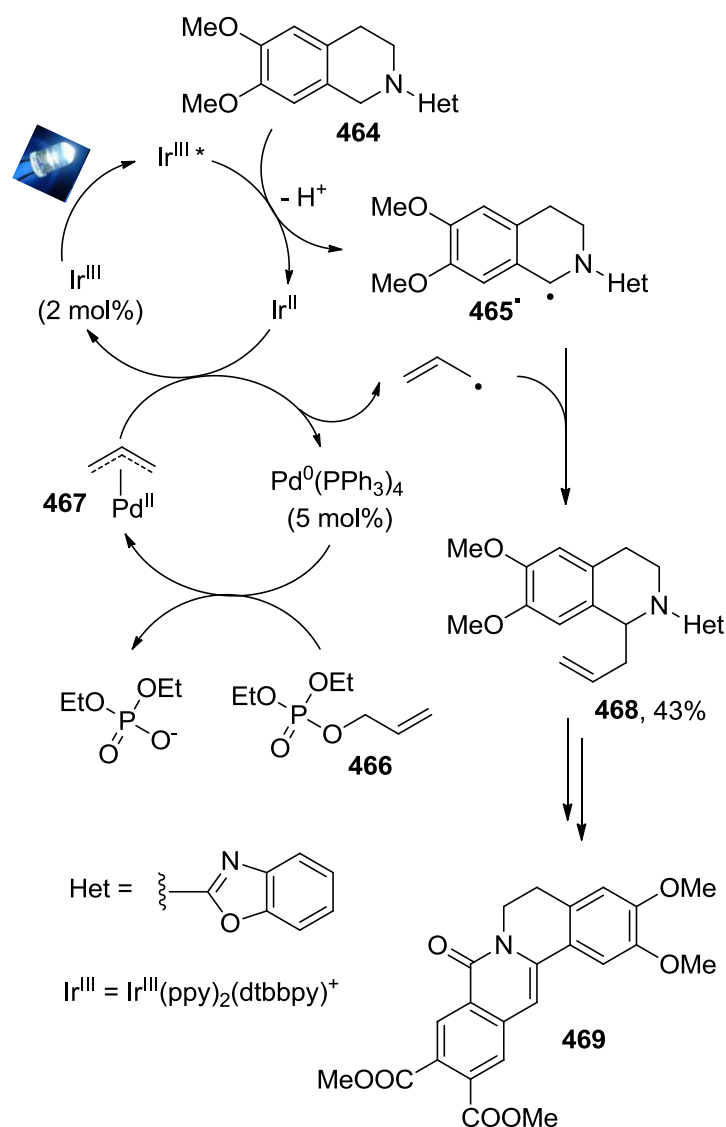
7.5. Benzylation

Benzylation reactions most often involve photocatalytic methodologies, although sparse examples of direct irradiation are known. Thus, benzyl substitution of the chlorine atom in heterocyclic derivative **470** was performed in DMSO in the presence of NaH and the chosen nucleophile (e.g. diethyl 2-methyl malonate **471**). As a result, the benzylation product **472** was obtained in a good yield (61%; Scheme 154) albeit the reaction was affected by the nucleophile nature and could also involve the bromine atom in the 8-position.[408]

Scheme 154. Benzylation of Diethyl 2-Methyl Malonate
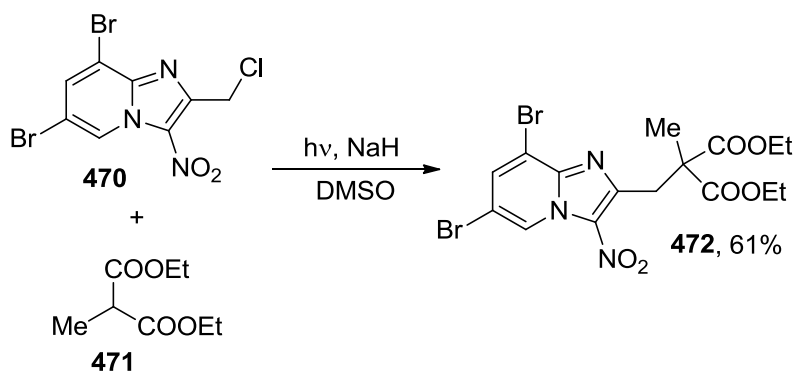
Recently, THIQs have been used as model substrates under photoredox catalyzed conditions for performing a plethora of C-C bond building processes, thanks to the predictable activation of the benzylic α-amino position to generate an iminium ion.

The α-functionalisation of tertiary amines via the Henry reaction is a typical example.[369,376,409-412] Thus, green light irradiation of a mixture of the chosen THIQ and nitromethane (or a different nitroalkane) gave the corresponding Henry coupled product **473** in a high yield, which was further improved when solar light was used.[409] Henry adducts from THIQs were likewise reported by using the tetrabutylammonium Eosin Y salt (2 mol%) as the photocatalyst. Interestingly, in the latter case the role of superoxide radical anion ($O_2^{\bullet-}$) was documented (Scheme 155, path a).[410]

The process was likewise applied for introducing fluorinated moieties in the benzylic position of the THIQ derivative, particularly for the difluoromethylation[413] and trifluoromethylation (product **474**)[377] (Scheme 155, path b) by using either difluoroenolates (generated in situ) or TMSCF$_3$ as the nucleophile, respectively.

Quite unusual nucleophiles can be likewise exploited for intercepting photogenerated iminium ions from THIQs[414,415] and *N,N*-dimethylanilines.[416] Thus, α-amino diazo compounds **475** were obtained in the reaction with α-diazo carbonyl derivatives[414] (Scheme 155, path c) whereas a Ugi-type, three-

component reaction gave α-amino amides[414] or imides **476**[415] (Scheme 155, path d) in the presence of an isonitrile[415,416] and a carboxylic acid.

Scheme 155. C-C Bond Formation via Photocatalytically Generated Iminium Ions
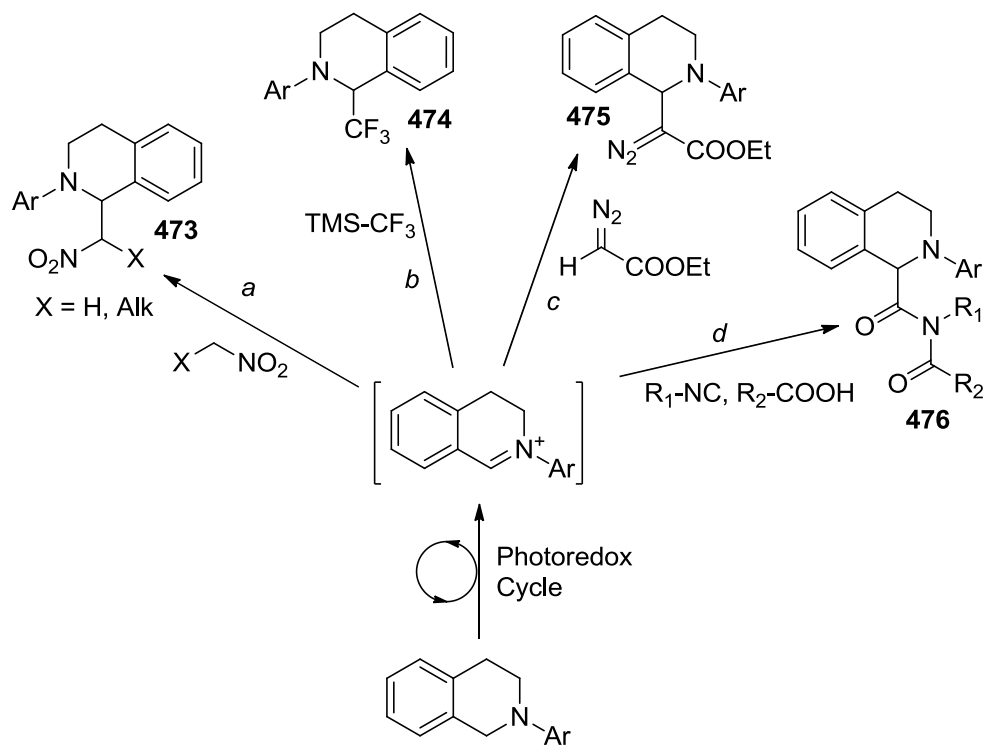
8. FUNCTIONALIZATION OF CARBON NANOSTRUCTURES

Carbon nanostructures, particularly nanotubes and fullerenes, represent an ideal platform for the synthesis of interesting nanomaterials with peculiar properties. Several approaches made use of photogenerated intermediates for the functionalization of carbon nanostructures via formation of new C-C bonds. Indeed, fullerenes (acting in the role of electron acceptors) were conveniently derivatized by having recourse to a PET process with suitable donors such as ketene silyl acetals,[417] allylstannanes[418] or α-silyl amines (Scheme 156, path a).[419] The Diels-Alder adducts of

[60]fullerene with 9-methyl anthracene were obtained selectively through a PET reaction in the solid state.[420]

Indirect methods, involving the use of a photocatalyst, have been likewise reported. Indeed, TBADT was used to functionalize [60]fullerene by activation of the C-H bonds in various substrates including toluene and anisole derivatives,[421] as well as alcohols (e.g. methanol, propargyl and benzyl alcohols)[422] and aldehydes.[423] Notably, the methylene hydrogens in crown ethers were likewise activated allowing the synthesis of [60]fullerene/crown ether conjugates **478** (Scheme 156, path b).[424] The versatility of TBADT as photocatalyst has also been exploited for the straightforward PEGylation of SWCNTs by photomediated addition of various PEGs (PEG200-600) onto the surface of carbon nanotubes, thus improving their dispersibility in water.[425] In a recent photoredox catalyzed approach, an Ir[III]-based complex was used as the photocatalyst in the addition of α-amino radicals on corannulene, a polycyclic aromatic hydrocarbon, using α-silyl amines as radical precursors.[426]

As recently reviewed,[427] photogenerated carbenes were successfully used as carbon-based intermediates for the functionalization of fullerenes. As an example, photolysis of 3-trifluoromethyl-3-phenyldiazirine afforded trifluoromethylphenylcarbene, that in turn reacted with [60]fullerene to give the corresponding photo-labeled C60 derivative **479** (Scheme 156, path c).[428]

Another strategy that can be exploited for [60]fullerene derivatization makes use of cycloaddition processes via photogenerated 1,3-dipoles or related radical ions. Adduct **483** was obtained by reaction of [60]fullerene either with an azomethine ylide **481** (photogenerated from 2,3-diphenyl-2*H*-azirine **480**, Scheme 156, path d) or with a 2-azaallenyl radical cation intermediate **482**[•+] (formed again from **480** under DCA photocatalyzed conditions, Scheme 156, path d').[429]

Scheme 156. Functionalization of Fullerenes
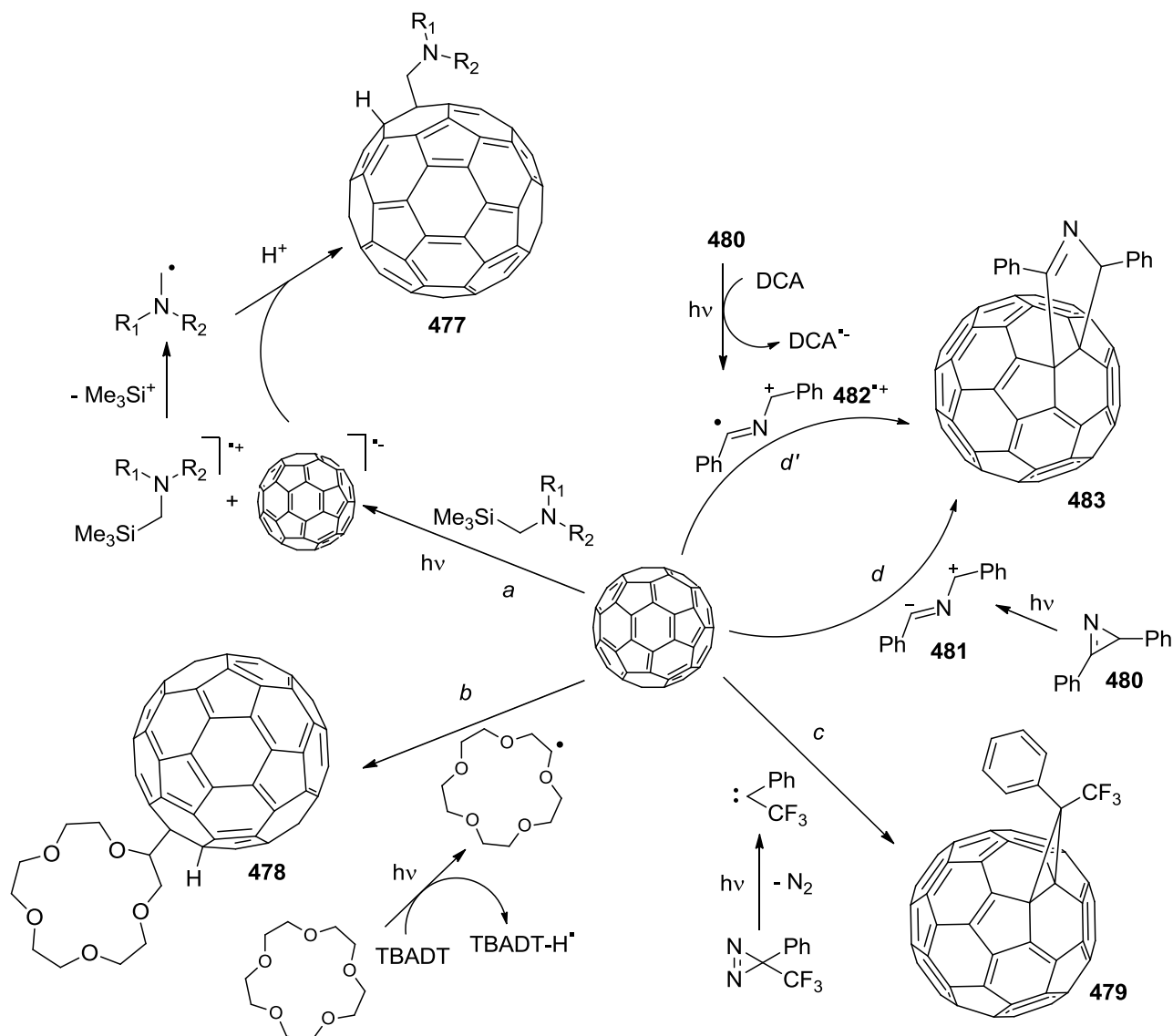
9. CONCLUSIONS AND OUTLOOK

Photochemical reactions involve the promotion of one of the components of the reaction mixture, whether the reagent or a photocatalyst, to its excited state by absorption of a photon. The energy of such states is comparable to the strength of most chemical bonds in organic molecules, which opens the path to the generation of reactive intermediates through a small energy barrier under otherwise unattainable mild conditions.

The scope of the photochemical approach has a varied breadth, depending on the intermediate involved. The generation of carbenes is practically limited to the direct irradiation of a few classes of compounds (mostly, α-diazoketones or diazirines), whereas biradicals and radical pairs are involved almost only in the Norrish-Yang cyclizations and in photo-Fries rearrangements, respectively. The direct generation of cations is in turn achieved via the photolysis of aryl and vinyl halides, while the photogeneration of anions is limited to a few decarboxylation processes.

Recently, the photocatalytic generation of radicals and radical ions has been the subject of increasing attention. Ten years ago colored derivatives, including Ru^{II} and Ir^{III} complexes, as well as organic dyes, started to be applied to long time known photoredox reactions. In most cases, the first step of the reaction is a photoinduced electron transfer (PET) process, with the generation of a radical ion. This intermediate reacts directly or acts as precursor of further intermediates, such as carbon-centered radicals or cations. On the other hand, radicals can also be generated via direct photocatalyzed hydrogen atom abstraction, although photocatalysts capable to perform this process are limited in number.

The recent dramatic development in the use of photogenerated intermediates gave access to several valuable synthetic targets (including naturally-occurring compounds) through the formation of both carbo- and heterocycles, of Ar-C bonds, the α- and β- functionalization of carbonyls and the addition to multiple bonds. The real breakthrough of this approach, however, is represented by the use of visible light or sunlight, that minimize the energetic expenditure of the process and make these synthetic methods really appealing. Indeed, the use of soft light sources such as household lamps, LEDs and obviously the sun, allows for the employment of (cheap) glassware commonly available in organic chemistry laboratories. These improvements recently allowed for the development of continuous flow photoreactors, resulting in the scale up of the synthesis of the desired targets to the multi-gram scale, with a concomitant minimization of the reaction time and of the amount of waste produced. Recent results show that multi-catalytic approaches are feasible,

where the combination of a photocatalytic cycle with other valuable methodologies, such as organo- and transition-metal based catalysis, allows for the building of very complex molecules, often with a high degree of chemo- and stereo-selection.

It would appear that photochemistry is going through an exciting period of advancement, comparable to what happened in the seventies for transition-metal catalyzed cross-coupling processes or fifteen years ago for organocatalysis. These periods of dramatic development left as an heritage a variety of robust and well established synthetic tools, nowadays routinely used. The same is expected to happen in the next few years also for photochemical reactions, long neglected in synthetic planning.

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Notes

The authors declare no competing financial interest

Biographies

Maurizio Fagnoni graduated in Pavia under the guidance of Prof. Angelo Albini. He is currently an Associate Professor of the Department of Chemistry at the University of Pavia. His research interests are mainly focused on the photoinduced or photocatalytic generation of reactive intermediates such as (bi)radicals, (phenyl) cations and radical ions and their application to eco-sustainable synthesis.

Davide Ravelli obtained his PhD in 2012 from the University of Pavia with a thesis on decatungstate photocatalyzed processes applied to organic synthesis (prof. A. Albini as the supervisor). Since November 2015, he is a fixed term researcher at the same University and his main research interests focus on the generation of radical intermediates through photocatalyzed Hydrogen Atom Transfer reactions and on the rationalization of organic reaction mechanisms by means of computational tools.

Stefano Protti studied Chemistry at the University of Pavia (Italy), where he graduated in 2003 and completed his PhD (supervisor: Prof. M. Fagnoni) in 2006, developing photochemical reactions via phenyl cations. He was post-doctoral fellow at the LASIR laboratory (Lille, France), at the iBitTec-S Laboratory (CEA Saclay, France), and at the PhotoGreen Lab (University of Pavia). Since December 2015, he is researcher at the same University. His research work is mainly focused on the development and the optimization of photochemical arylations procedures under metal-free conditions.

Acknowledgments

Abbreviations

ATC   Atom transfer carbonylation

ATRA   Atom transfer radical addition

bpm   2,2'-Bipyrimidine

bpy   2,2'-Bipyridine

bpz   2,2'-Bipyrazine

CFL	Compact fluorescent lamp
DABCO	1,4-Diazabicyclo[2.2.2]octane
dap	2,9-bis(*para*-Anisyl)-1,10-phenanthroline
DAP	*N*,*N*'-Dimethyl-2,7-diazapyrenium
DCA	9,10-Dicyanoanthracene
DCB	1,4-Dicyanobenzene
DCN	1,4-Dicyanonaphthalene
dF(CF$_3$)ppy	2-(2',4'-Difluorophenyl)-5-trifluoromethylpyridine
dpp	2,9-Diphenyl-1,10-phenanthroline
dppm	1,1-bis(Diphenylphosphino)methane
dtbbpy	di-*tert*-Butylbipyridine
FIr^{III}pic	bis-(2-(4,6-Difluorophenyl)pyridine)(picolinato)iridium
Mes-Acr$^+$	9-Mesityl-10-methylacridinium
mpg-C$_3$N$_4$	Mesoporous graphitic carbon nitride
PC	Photocatalyst
PCET	Proton-coupled electron transfer
PET	Photoinduced electron transfer

ppy   2,2'-Phenylpyridine

SET   Single electron transfer

TBADT   Tetrabutylammonium decatungstate

TCB   1,2,4,5-Tetracyanobenzene

TEMPO   2,2,6,6-Tetramethyl-1-piperidinyloxy radical

THIQ   Tetrahydroisoquinoline

TMEDA   Tetramethylethylenediamine

TPPBF$_4$ 2,4,6-Triphenylpyrylium tetrafluoroborate

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