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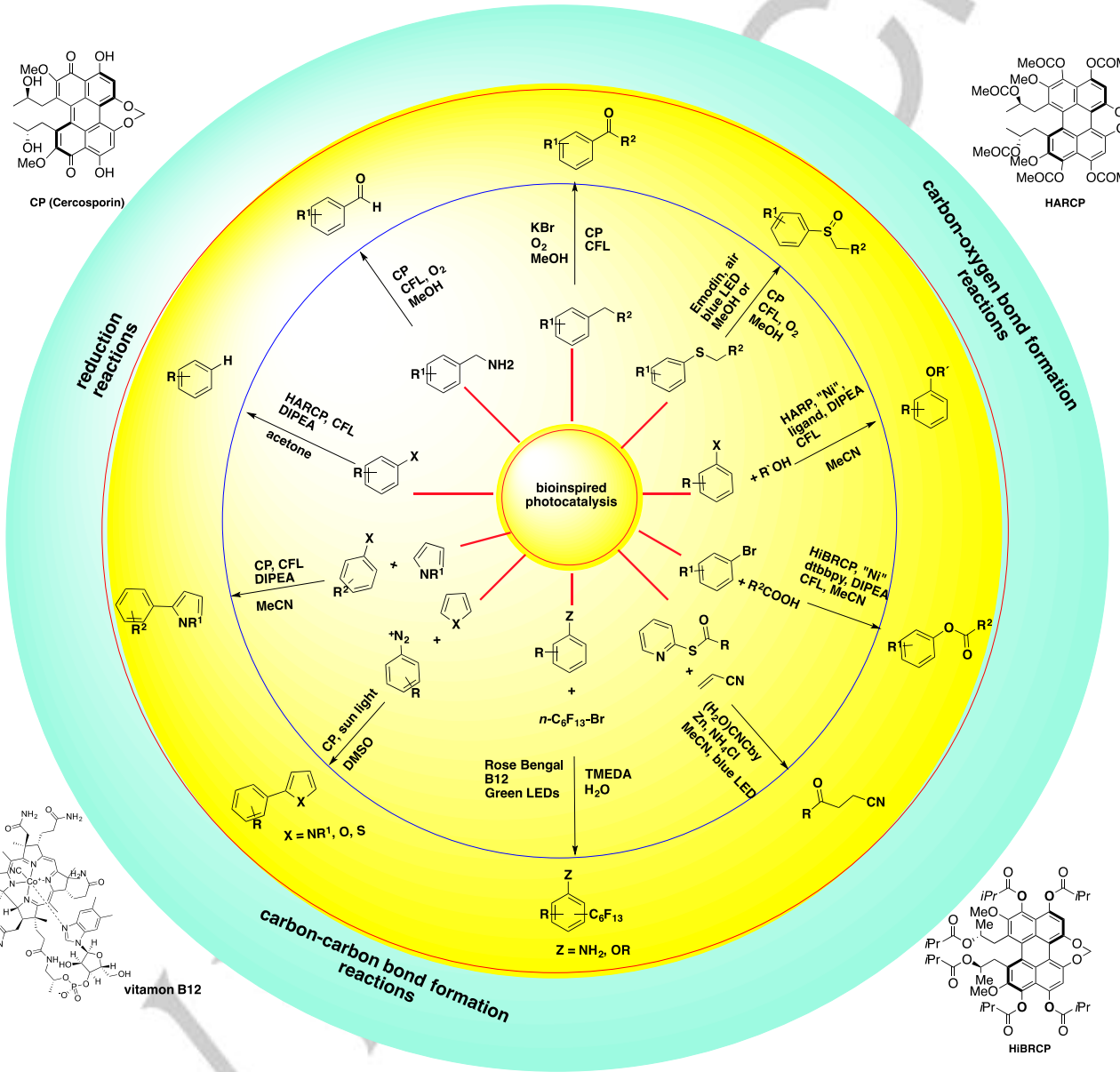
REVIEW

Bioinspired Photocatalyzed Organic Synthetic Transformations. The Use of Natural Pigments and Vitamins in Photocatalysis

Sebastián Barata-Vallejo,[a,b] Damian E. Yerien,[a] and Al Postigo *[a]



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Abstract: Due to the necessity for more environmentally benign processes in Synthetic Organic Chemistry, and in particular in Photocatalysis, a recourse to photocatalysts that are also found in Nature and mimic natural processes to accomplish organic transformations is very appealing. Synthetic useful reactions such as oxidations, reductions, carbon-oxygen, carbon-carbon and carbon-sulfur bond formation reactions, and *E-to-Z* geometrical isomerization reactions photocatalyzed by biological natural pigments, vitamins, cofactors, and compounds with antiviral activity will be discussed in this account. Interestingly, due to the remarkable redox properties and triplet energies of some of these catalysts that are found in Nature, both electron transfer (ET)- and energy transfer (EnT)-driven photocatalytic processes can be accomplished.

1. Introduction

To respond to the increasing need for eco-friendly catalytic processes in organic syntheses, visible light photocatalysis has occupied a paramount place. Visible light photocatalysts are aimed to produce highly reactive radical or radical ion species generated through electron or energy transfer paths in photocatalytic cyclic processes, which facilitate reactions otherwise difficult to take place or thermodynamically unfavorable to produce. In this regard, transition metal photocatalysts such as those derived from Ru or Ir polypyridyl complexes have been used in combination with conventional photocatalytic systems.[1–4] However, the cost of these polypyridyl complexes of Ru and Ir is high, which, added to their metal toxicity represent a drawback in large scale preparations deterring their applications for synthetic targets in industry.

Organic dyes[5] have also been used in replacement of the transition metal photocatalysts for more environmentally amiable synthetic approaches.[6–8] Although the environmentally friendlier organic dyes used as visible light photocatalysts have recognized fruitful applications in organic syntheses, other environmentally benign photocatalysts employed are those derived from vitamins, redox co-factors and natural pigments that are involved in or emulate *in-vivo* processes that can ensue organic transformations. This results in a more appealing approach for organic synthetic procedures, as catalytic processes bioinspired in Nature that use (photo)catalysts are energy balanced and more efficient.

More recently, naturally occurring pigments or natural organic molecules with potential antiviral activity have been utilized as visible light photocatalysts to effect organic synthetic transformations. All these refinements in catalytic processes, from the use of inexpensive visible light as a reagent, metal-free photocatalysts, and even more benign biomimetic photocatalysts, have transformed organic syntheses and are paralleling and surpassing the potential of biocatalytic[9] and photobiocatalytic[10] processes from the point of view of organic transformative scope, yields, regio- and stereoselectivity, as it is to be illustrated in this account.

In this regard, cobalt complex vitamin B_{12}, being an environmental benevolent biological (photo)catalyst bears advantages over transition metal (photo)catalysts.

Co-enzyme B_{12} (5`-deoxy-5`-adenosylcobalamine and methylcobalamine, Figure 1) is the only known cofactor in biological environments that contains a stable metal-C bond

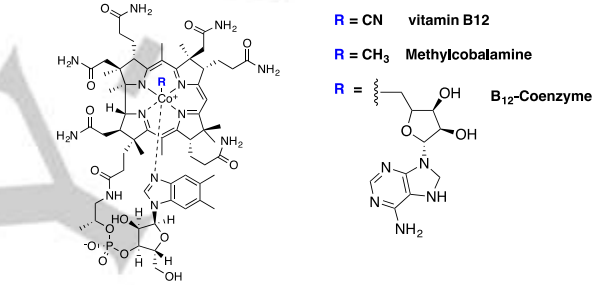


Figure 1. Structures of vitamin B_{12}, Methylcobalamine and Coenzyme B_{12}

Vitamin B_{12}-dependant enzymes participate in numerous biological reactions such as rearrangements, methyl transfer, and dehalogenations involving the scission and formation of the Co-C bond in the cofactor. These enzymes act under two basic modes of action: i.-homolytic formation or cleavage of the Co-C bond through a one electron process, generating the alkylcobal(III)amine when reacting with alkyl radicals, being the bond dissociation energy BDE of the Co-C bond only 26 kcal/mol;[11] in this way, coenzyme B_{12} serves as a source of 5`-deoxy-5`-adenosyl radical; and ii.-the heterolytic cleavage of the Co-C bond, which is observed in biological metal-catalyzed methyl transfer reactions. In the latter cases (i.e.: ii.-) the reduced Co(I) cobalamine, considered a potent nucleophile, partners with electrophilic alkylating agents by typical S_N2 reactions, furnishing an alkylcobal(III)amine (Figure 2).[12]

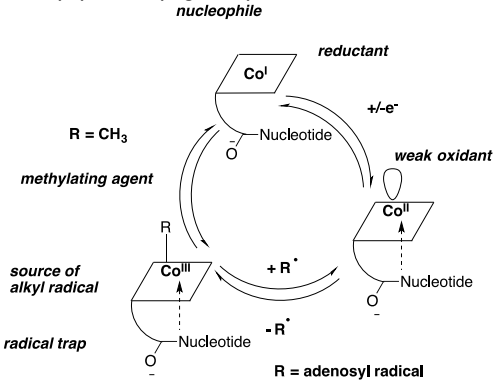


Figure 2. Dual mode of reactivity of the M-C bond at B_{12}-dependant enzymes

Analogously as the Co complexes, nickel square planar complexes have also been studied for methyl-coenzyme reductase which contains a Ni-porphinoid F430 cofactor. The corresponding organonickel(III) complex upon activation of alkyl halides by the supernucleophilic Ni(I) complex produces alkyl radicals.[13,14]

Profiting from the binary role of these Co (and Ni) complexes as reversible radical carriers or strong nucleophiles conditional to their oxidation states, an active area of research has emerged for the use of these complexes as efficient (photo)catalysts to attain numerous reductive, coupling and substitution reactions under light irradiation, thermolysis, chemical reductants and electrochemistry.

The photochemical reduction of cobalamine complexes has been accessed by using different photocatalysts as primary sources for harvesting the energy (primary photon), such as semiconductors like TiO_2 (absorbing UV light of 365 nm), organometallic photocatalysts such as the polypyridyl complexes of Ru and Ir, and organic dyes, such as Eosin Y, Rose Bengal, or Rhodamine B.[15] To this end, a recent review article[16] has uncovered the potential of combining Co-organic complexes (synthetic $Co(dmgH)_2LX$, where L is a ligand and X a counter anion) as 3-d metal co-catalysts and catalysts such as Eosin Y, mesityl acridinium perchlorate, and $Ru((bpy)_3(PF_6)_2$ for numerous organic transformations, such as carbon-carbon or carbon-sulfur bond formation reactions through the concomitant evolution of hydrogen gas (CCHE), dehydrogenation reactions, or dehydrogenative decarboxylation of carboxylic acids.[16] However, these synthetically useful Co-complexes such as cobaloxime(III) complex $Co(dmgH)_2LX$, Co(II)-acetylacetonate complex $Co(acac)_2$, and others will not be discussed in this account, as their structural features do not mimic or resemble vitamin B_{12}.

Numerous other chemical transformations have been achieved by using Co-complexes as photocatalysts, such as dehalogenations, additions to activated olefins, functional group migrations, dimerization, cyclopropanations, and cyclopropane ring opening or ring expansion reactions[16–18] and more recently dehydrohalogenation reactions.[19] Contributing reviews on vitamin B_{12}-catalyzed organic transformations either activated by light, heat or electrochemically have been advanced by authors such as Gryko[17], and Hisaeda.[20,21] In this account, vitamin B_{12} and some lipophilic derivatives will be considered in visible light photocatalysis. The photoinitiated transformations employing vitamin B_{12} and derivatives that have been previously reviewed by the literature are not going to be discussed in detail but acknowledged.[15–17,21]

Flavins,[22] such as riboflavin or vitamin B_2, have also been employed as photocatalysts in numerous organic chemical transformations and new photocatalytic examples where flavins intervene are going to be discussed.

Other naturally occurring molecules, such as pigments, are currently being employed as photocatalysts with great success and excellent organic reaction scope. Cercosporin, a deep red perylenequinonoid photosensitizing pigment isolated from the cultured mycelia of *Cercospora kikuchii* (i.e.: 1,12-*bis*(2-hydroxypropy1)-2,11-dimethoxy-6,7-methylenedioxy-4,9-dihydroxyperylene-3,10-quinone, Figure 3)[23] can be obtained through microbial fermentation like other naturally-occurring perylenequinonoid pigments, such as Hypocrellin A[24,25] and Hypocrellin B (an apoptosis inducer)[26], or Elsinochrome C[27] produced by endophytic fungi (Figure 3).

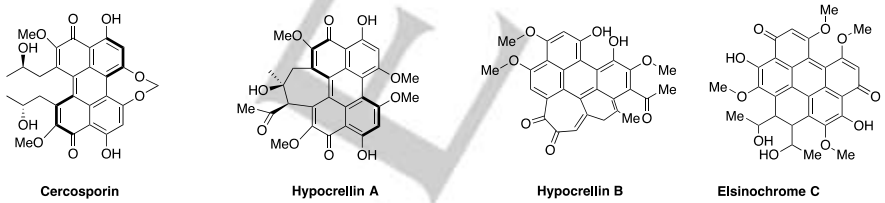


Figure 3. Structures of Cercosporin, Hypocrellin A, Hypocrellin B and Elsinochrome C.

Cercospora species have documented an important role as toxins in the pathogenesis of host plants. Cercosporin, Hypocrellin A and Hypocrellin B have been investigated from various aspects such as photophysics, photochemistry and photobiology, due to their properties as photosensitizers.[27–30] These pigments have recently found excellent applications as photocatalysts in organic synthesis, as is going to be discussed in this account. Surprisingly, none of these photocatalytic methods have been classified or discussed in the reviewing literature.

Cercosporin CP has found applications in photodynamic therapy as well,[31] due to its capacity for singlet oxygen generation. Also, its triplet state energy of 40.8 kcal/mol[32] turns it into an excellent photocatalyst for triplet energy transfer (EnT) sensitization.[33] EnT photocatalysis[34,35] is a mild and selective manner to access triplet states by means of indirect excitation. EnT processes have been employed in the recent past with proper photocatalysts such as $Ir(ppy)_3$, for the EnT-catalyzed coupling of carboxylic acids and aryl halides through nickel complexes.[36–38] CP-photocatalyzed EnT organic transformations will be discussed in this account. CP has also found recent applications in photocatalysis also through ET processes, towards the construction of C-C, C-O, and C-S bonds. Examples of the use of natural pigments as photosensitizers in organic synthetic procedures will be analyzed in this account from the synthetic and mechanistic aspects.

Other natural-occurring organic compounds with antiviral properties such as Emodin have currently been employed as photocatalysts for the synthesis of organic compounds, which will be discussed in this perspective.

Among all the visible light-photocatalyzed methods available in the literature to accomplish oxidation and reduction reactions, formation of C-O, C-C and C-S bonds, E / Z geometric isomerization reactions such as transition metal-, organic dye- and bio-catalyzed transformations, this account will concentrate on photocatalyzed methods employing organic natural compounds or some derivatives of such as photocatalysts that are involved in biological natural processes or have relevance in bioorganic transformations, such as vitamins, cofactors, or natural-occurring pigments in order to inspect another environmentally friendlier alternative to photocatalyzed organic

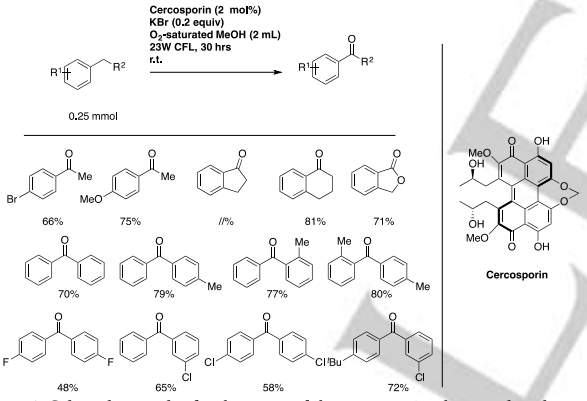
transformations. Enzyme-involved photocatalyzed organic transformations (i.e.: photobiocatalysis) will not be considered as they are under the realm of biotransformations. The next sections will deal with promoted bioinspired photocatalysts and their applications in organic syntheses to accomplish an array of relevant organic transformations useful to the organic chemists.

1.-OXIDATIONS

1.1.- Transforming methylene groups to carbonyls and sulfides to sulfoxides

Li, Rao and collaborators[39] have utilized Cercosporin (Scheme 1) as photocatalyst in the oxidation of benzylic C-H bonds to carbonyls, amines to aldehydes and sulfides to sulfoxides. Cercosporin can react either by ET or EnT pathways. In the EnT pathway, singlet excited cercosporin undergoes intersystem crossing to its longer-lived triplet state which directly reacts with molecular O_2 present in the solution to form highly reactive singlet oxygen $^1O_2$. In the ET pathway, the excited state of Cercosporin (triplet manifold), in the presence of a reductive substrate (sacrificial donor), is converted to Cercosporin radical anion, which by reaction with O_2 can generate superoxide anion $O_2^{\cdot-}$, (and $HO^{\cdot}$ and H_2O_2).[40–42]

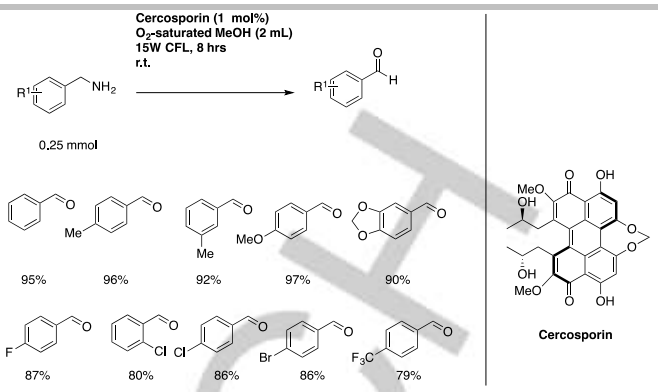
For the oxidation of benzylic positions, the optimized reaction conditions entail the use of benzylic derivatives (0.25 mmol), Cercosporin as photocatalyst (2 mol%), KBr (0.2 equiv.) as additive, in methanol as solvent (2 mL), in an oxygen-saturated solution, and irradiating with a 15 W compact fluorescent lamp (CFL) for 30 hrs. The scope of the transformation is illustrated in Scheme 1.



Scheme 1. Selected examples for the scope of the cercosporin-photocatalyzed oxidation of benzylic positions. Structures partially reproduced from ref. [39] with permission from The Royal Society of Chemistry

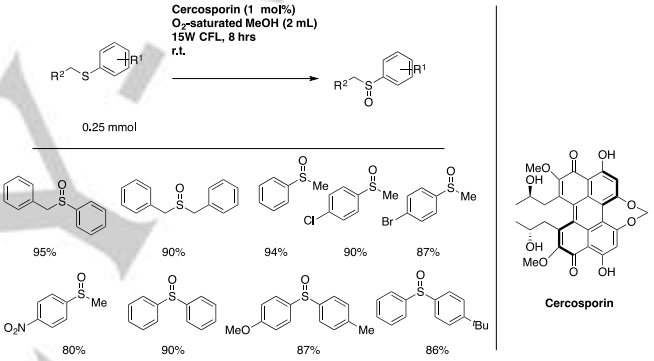
From Scheme 1, it is observed that benzyl derivatives bearing electron donating substituents afford better yields of oxidized products than substrates with electron-poor groups attached to the aryl rings.

The authors[39] also inspected the oxidation of amines into aldehydes. After a series of trial reactions, the optimized conditions to oxidize amines to aldehydes consisted in the employment of the amine (0.25 mmol), Cercosporin as photocatalyst (1 mol%), in oxygen-saturated methanol (2 mL), irradiating with a 15 W white CFL. The scope of the reaction is depicted in Scheme 2.



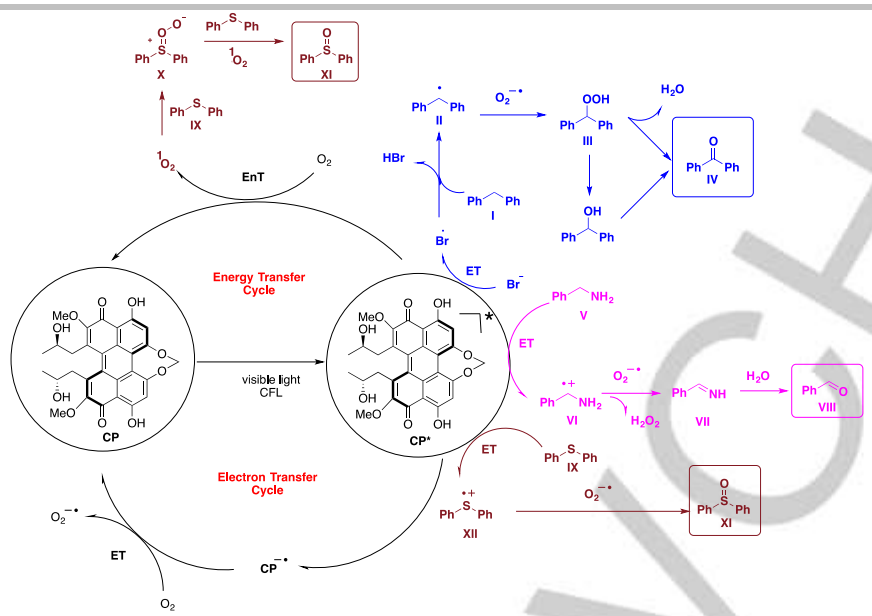
Scheme 2. Selected examples for the scope of the cercosporin-photocatalyzed oxidation of amines to aldehydes. Structures partially reproduced from ref. [39] with permission from The Royal Society of Chemistry

Benzylamines with electron rich- and electron-poor substituents render the respective benzaldehydes in excellent yields. The oxidation of sulfides to sulfoxides was also accomplished by this technique.[39] The scope of the transformation is illustrated in Scheme 3.



Scheme 3. Selected examples for the scope of the cercosporin-photocatalyzed oxidation of sulfides to sulfoxides. Structures partially reproduced from ref. [39] with permission from The Royal Society of Chemistry

The authors[39] investigated the reaction mechanisms. When Cercosporin, light or oxygen were absent, only trace amounts or no product was detected from reaction of benzylic C-H positions, amines and thioethers. The addition of radical scavengers such as TEMPO ((2,2,6,6-Tetramethylpiperidin-1-yl)oxyl) or 1,4-benzoquinone inhibited the three types of oxidations (benzylic C-H positions, amines and sulfides). Singlet oxygen scavengers such as 1,4-diazabicyclo-[2.2.2]-octane (DABCO) or NaN_3 did not influence the yields of the oxidation reactions of benzylic C-H bonds to carbonyls or benzylamines to aldehydes. However, the photooxidation of sulfides was significantly affected by the singlet oxygen scavengers DABCO or NaN_3, purporting that $^1O_2$ plays a relevant role in the oxidation of sulfides into sulfoxides by Cercosporin-EnT photocatalysis. Labelling experiments revealed that the carbonyl oxygen atom comes from molecular oxygen and not from methanol. Consequently, the authors[39] postulated that the photooxidations of benzylic positions and those of amines proceeded through single electron transfer pathways (ET), while the presence of $^1O_2$ and $O_2^{\cdot-}$ are responsible for the photooxidation of sulfides (both ET and EnT paths) to sulfoxides. A plausible reaction mechanism proposed by the authors is represented in Scheme 4.

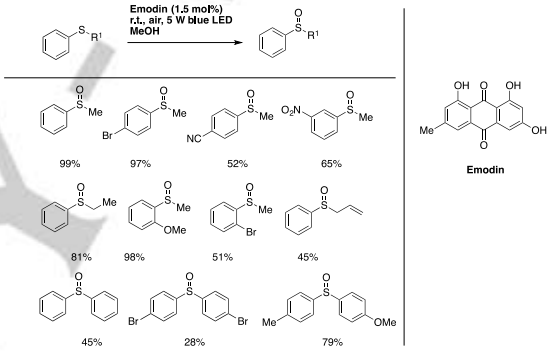


Scheme 4. Proposed reaction mechanism fort he oxidation of benzyl positions, phenylsulfides and benzylamines with Cercosporin. Structures partially reproduced from ref. [39] with permission from The Royal Society of Chemistry

In the proposed reaction mechanism (Scheme 4) when Cercosporin CP is excited by visible light, generates an excited state CP* which can oxidize bromide anion from KBr to bromine radical, this process being thermodynamically favorable ($E_{1/2}^{red}$ Br•/Br- = +1.79 V vs SCE and $E_{1/2}^{red}$ CP*/CP•- = +1.87 V vs SCE[43,44]). Bromine radical abstracts a hydrogen atom from diphenyl ethane **I** (blue pathway) to render the alkyl radical **II**, which through oxidation by O_2 or $O_2^{\cdot-}$ affords hydroperoxide **III**, which by ulterior loss of water renders diphenylketone **IV**. In turn, the radical anion of Cercosporin CP•- can be oxidized by O_2 to regenerate the photocatalyst into its active redox state CP, releasing superoxide anion $O_2^{\cdot-}$**.** In a similar fashion, the photooxidation of amines (pink pathway) proceeds through ET from CP* to amine **V**, rendering the radical cation of amine (**VI**) and CP•-. **VI** reacts with $O_2^{\cdot-}$ to afford imine **VII**, which is hydrolyzed to aldehyde **VIII**.

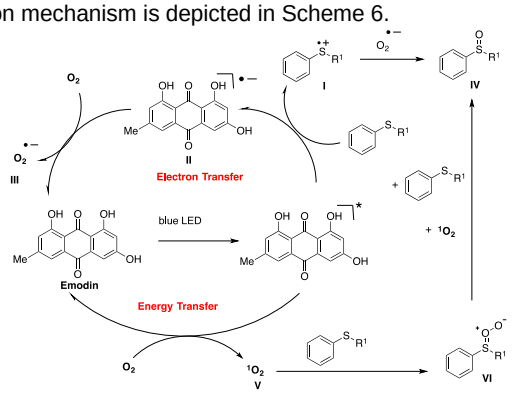
Regarding the oxidation of sulfides (brown pathway), the sulfoxide products are accounted for by two reactions pathways, i.e.: ET and EnT. In the EnT pathway (upper left corner, Scheme 4), sulfide **IX** reacts with $^1O_2$ to produce intermediate **X** which further reacts with $^1O_2$ and **IX** to yield sulfoxide **XI**. In the ET pathway (lower right corner, Scheme 4), photoexcited CP* reacts with sulfide **IX** to render radical cation intermediate **XII** which reacts with superoxide radical anion $O_2^{\cdot-}$ to afford sulfoxide **XI.**

Emodin (Scheme 5), a naturally occurring active component of several plants such as *Rheum palmatum* used in traditional Chinese medicine, has also been identified as having potential antiviral activity against coronaviruses such as SARS-CoV-2.[45,46] Zhang, Rao and colleagues[47] have very recently employed Emodin for the visible light-photocatalyzed oxidation of sulfides to sulfoxides in methanol as solvent in the presence of air, irradiating with a 5 W blue LED, The scope of the transformation is illustrated in Scheme 5.



Scheme 5. Scope of the Emodin-photocatalyzed oxidation of sulfides

The authors[47] investigated the reaction mechanism through probe experiments, employing radical scavengers such as TEMPO and singlet oxygen scavengers, such as DABCO. In both cases, they found a notorious decrease in sulfoxide product yield. The reaction necessitates either air or oxygen to proceed; light, and the photocatalyst are essential. A proposal of the reaction mechanism is depicted in Scheme 6.



Scheme 6. Proposed reaction mechanism fort he oxidation of sulfides with Emodin

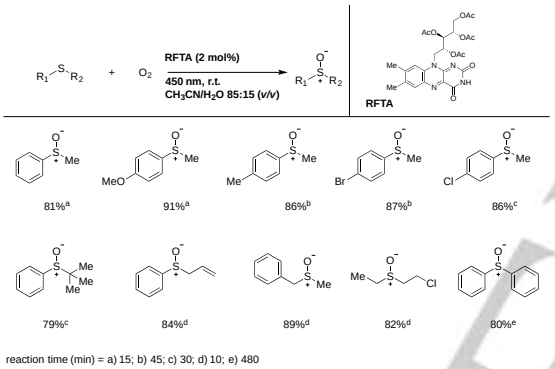
In the proposed mechanism (Scheme 6) photocatalyst Emodin is excited by visible light from a blue LED. Two possible pathways can be envisaged: an electron transfer (ET) pathway and an energy transfer (EnT) step. In the electron transfer path (upper right, Scheme 6), the sulfide substrate is oxidized by the

excited state of Emodin to a radical cation species **I**, yielding the radical anion of the photocatalyst Emodin, species **II**. The reductive power of **II** easily reduces dissolved oxygen to its radical anion species, anion superoxide **III**. Recombination of species **I** and **III** provides sulfoxide product **IV**. On the other hand, in the energy transfer step (lower right, Scheme 6), the excited Emodin photocatalyst in the presence of molecular oxygen generates singlet oxygen **V**. Reaction of **V** with sulfide renders intermediate **VI**, which through more singlet oxygen and thioether affords product **IV**. In both cycles, (EnT and ET), the photocatalyst is regenerated into its active photoredox state through reaction with oxygen.[47]

In 2016 Cibulka and colleagues[48] presented a metal-free protocol for aerobic photooxidation of sulfides to yield sulfoxides. This methodology employs a riboflavin tetraacetate derivate (RFTA) as photocatalyst (2 mol%), in acetonitrile-water solvent mixture under visible light irradiation at 450 nm.

The optimal reaction conditions and the substrate scope are shown in Scheme 7. Several examples are illustrated including substituted thioanisoles, benzylic and aliphatic sulfides with very good to excellent product yields in short reaction times.

This method also presents high selectivity without overoxidation of substrates to sulfones.



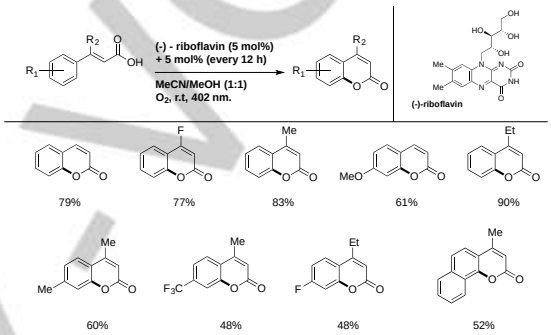
reaction time (min) = a) 15; b) 45; c) 30; d) 10; e) 480

Scheme 7. Photooxidation of sulfides mediated by RFTA: substrate scope

1.2.- Oxidative C-O Bond formation through intramolecular cyclization reactions. Syntheses of coumarin derivatives

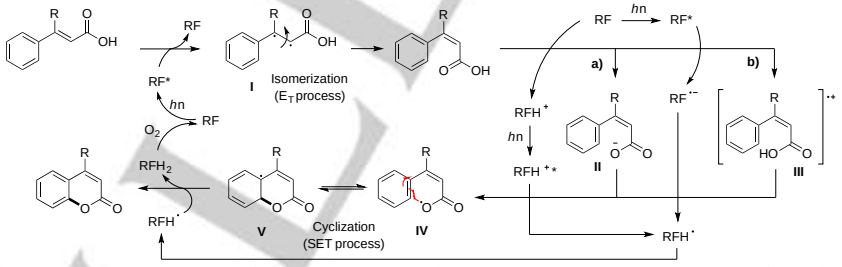
Matternich and Gilmour[49] have accomplished a very interesting strategy for coumarin synthesis with (-) – riboflavin (RF). They reported a one-pot methodology that employs (*E*) – cinnamic acids as starting material. The photocatalyst RF acts in two activation modes, first in a EnT -based doble bond isomerization followed by single electron transfer (SET) cyclization.

The authors found that the optimized reaction conditions consisted in the employment of (*E*) – cinnamic acid derivatives (0.1 mmol), 5 mol% of RF as photocatalyst in acetonitrile: methanol mixture under UV irradiation (402 nm) in presence of air. In order to explore the substrate scope, the authors investigated a series of structurally and electronically modulated substrates as illustrated in Scheme 8.



Scheme 8. Substrate scope of the photocatalyzed synthesis of coumarins by (-) – riboflavin (RF). Structures partially reproduced from ref. [49] with permission from The American Chemical Society

The study of the mechanism included control experiments, progress monitoring experiments and kinetic isotope effect studies. On the basis of these experiments and literature precedent, the authors postulated a mechanism such as that illustrated in Scheme 9.



Scheme 9. Proposed mechanism for the photocatalyzed synthesis of coumarins by (-) – riboflavin (RF). Structures partially reproduced from ref. [49] with permission from The American Chemical Society

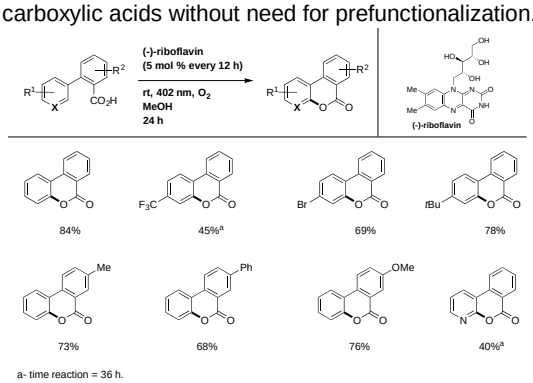
Initially, selective triplet state energy transfer (EnT) from excited photocatalyst to (*E*) – isomer substrate generates the biradical intermediate **I** (Scheme 9). Stereoselectivity of this step is due to the difference in photophysical properties of the geometrical isomers: the *Z* – isomer is not re-excited by EnT process as a consequence of the high triplet state energy (E_T RF = 49.8 kcal mol-1;[50] while E_T z-isomer > 50 kcal mol^{-1}) due the de-conjugation of the new geometry of the π-system. The authors postulated that the second step of the coumarin-ring formation can be explained by a single electron transfer process.

A SET catalyzed by RF can proceed by two different pathways: Scheme 9a deprotonation of substrate by RF yielding carboxylate anion **II** with subsequent photoexcitation at 402 nm to **IV**; or Scheme 9b excitation of RF which accepts one electron from *Z*-isomer substrate and yields the intermediate **III.** A) or b) pathways converge in forming the radical intermediate **IV** which can undergo cyclization to radical intermediate **V.** In the final step a H abstraction or SET/ proton transfer step yields the desired product. Reduced photocatalyst (RFH_2) is oxidized by O_2 to regenerate RF into its active redox state.

In another report, Gilmour and collaborators[51] have also achieved the photocatalytic synthesis of benzocoumarins from biarly-2-carboxylic acids. The protocol developed employs RF as photocatalyst (5 mol%), substrate (0.1 mmol) in MeOH under 402 nm irradiation at ambient temperature (Scheme 10). In order to solve partial photodecomposition, the initial catalyst loading was supplemented with an additional 5 mol% every 12 h.

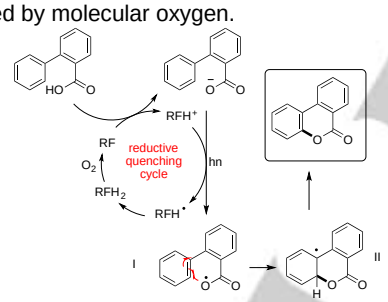
This method presents a broad functional group tolerance, including several substituents in the *para* position of the aromatic

A ring (-CF_3, -Br or alkyl). Also, substituents in B aromatic ring were explored (-Me, -OMe) with good yields of product formation. Scheme 10 also includes examples of substrate with extended π-conjugated system and a pyridine derivate. In all cases the benzo-3,4-coumarin derivatives were obtained in good yields from the biaryl carboxylic acids without need for prefunctionalization.



Scheme 10. Selected examples of photocatalytic synthesis of benzocoumarins. Structures partially reproduced from ref. [51] with permission from The American Chemical Society

Regarding the mechanistic aspect, the authors propose that single electron transfer from benzoic acid to excited state RF is possible ($E_{red}(^3RF^*/RF^{\bullet-})$ = +1.46 V vs SCE). In the hypothesized mechanism (Scheme 11) the initial protonation of RF generates the RFH^+ species with strong absorption band at 402 nm. The single electron transfer process between carboxylate anion and RFH^{+*} affords flavin radical ($RFH^{\bullet}$) and a carboxyl radical (**I**) which undergoes intramolecular cyclization to radical intermediate **II**. Oxidation and re-aromatization of **II** with $RFH^{\bullet}$ in a hydrogen atom transfer step or SET/ deprotonation reaction releases the product. Finally, the reduced riboflavin (RFH_2) can be re-oxidized by molecular oxygen.



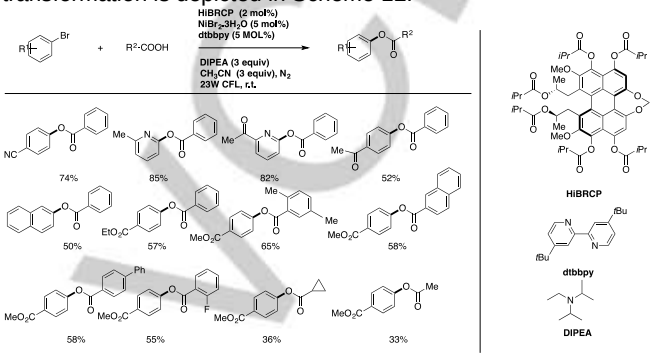
Scheme 11. Proposed mechanism for the formation of benzocoumarins with (-) – riboflavin. Structures partially reproduced from ref. [51] with permission from The American Chemical Society

A synthetically useful example of a photooxidation reaction has recently been exemplified by Rao and colleagues[33b] for the synthesis of kynurenine (Kyn) derivatives.

2.- FORMATION OF C-O BONDS THROUGH COUPLING REACTIONS

2.1.- Coupling reactions of aryl halides with benzoic acids

Zhang, Rao and colleagues[32] have synthesized an analogue of the naturally-occurring Cercosporin (*vide supra*), the hexa*iso*butyryl reduced cercosporin (HiBRCP), where the core perylenequinonoid moiety is converted to perylene by a reduction and acylation process (structure in Scheme 12), to catalyze through EnT a series of coupling reactions between benzoic acid derivatives and aryl halides, employing $NiBr_2$ and 4,4`-di*ter*tbutyl-2,2`-bipyridine (dtbbpy) as ligand in the presence of di-*iso*propylethylamine (DIPEA) as sacrificial donor in MeCN as solvent, irradiating with a 23 W CFL. The scope of the transformation is depicted in Scheme 12.



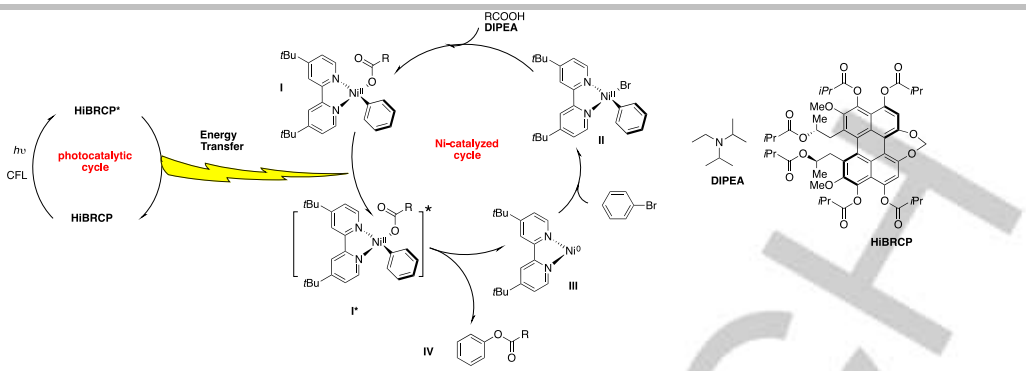
Scheme 12. Selected examples for the energy transfer-mediated organometallic catalyzed coupling of aryl bromides with arylcarboxylic acids photosensitized by HiBRCP. Structures partially reproduced from ref. [32] with permission from The American Chemical Society

Aryl bromides with electron withdrawing and neutral groups afford good yields of coupling products with benzoic acid. Also, different carboxylic acids, such as 4-phenyl-benzoic, 2-fluorobenzoic, cyclopropylcarboxylic, and acetic acid afford good yields of coupling products with methyl-4-bromobenzoate.

The large-scale cross coupling of 4-cyanobromobenzene (5.5 mmol) and benzoic acid afforded 64% yield of 4-cyanophenyl benzoate, according to the protocol in Scheme 12.

The authors[32] investigated the reaction mechanism (Scheme 13). Their findings show that a nitrogen atmosphere is needed, that photocatalyst HiBRCP, $NiBr_2$, ligand dtbbpy, DIPEA and light are necessary for the reaction to take place.

The critical step in the coupling reaction is the reductive elimination of the aryl-Ni(II)-carboxylate complex formed (**I**, Scheme 13). Two different modes of action can be envisaged: i.-the excitation of the complex by EnT (energy transfer from triplet excited HiBRCP*) and ii.-the oxidation via ET (electron transfer from triplet excited HiBRCP*) to form the Ni(III) complex. Being the oxidation potential of the Ni complex $E_{1/2}{}^{red}$cplxNi(III)/cplxNi(II) = +0.97 V vs SCE in DMSO, and the reduction potential of excited HiBRCP*, E_{red} HiBRCP*/HiBRCP$^{\bullet-}$ = +0.93 V vs SCE, ET from HiBRCP* to Ni complex **I** (Scheme 13) is precluded. However, the triplet energy transfer between HiBRCP and complex **I** (Scheme 13) is feasible (E_T HiBRCP = 54.2 kcal/mol). The fluorescence emission spectrum of HiBRCP* is quenched by addition of incremental amounts of Ni complex **I**, by a Dexter-type EnT process. Based on the results obtained, the authors[32] postulate a plausible mechanism such as that shown in Scheme 13.



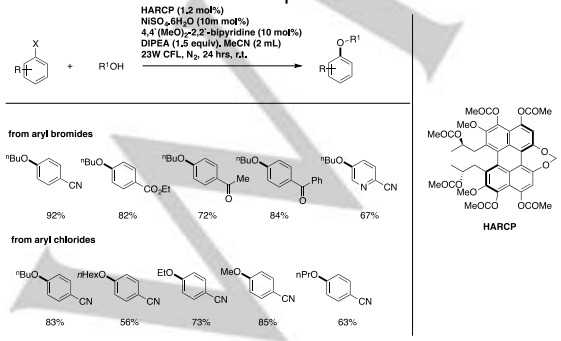
Scheme 13. Proposed reaction mechanism fort he coupling of aryl halides with benzoic acids. Structures partially reproduced from ref. [32] with permission from The American Chemical Society

In the proposed mechanism (Scheme 13) the Ary-Ni(II)-Br complex **II** is formed upon reaction of Ni(0)(dtbbpy) **III** with phenyl bromide. Complex **II**, in turn, reacts with carboxylate anion to furnish complex **I**, which by EnT from triplet excited HiBRCP* (photocatalytic cycle) renders excited I*, which undergoes reductive elimination to give product **IV**.

2.2.- Alkoxylation reactions of aryl halides towards the syntheses of aryl ethers

Li, Rao and colleagues[52] have also studied the alkoxylation of aryl halides employing HARCP as photocatalyst.

Aryl halides can be alcoxylated by a combination of Ni-based and transition metal-photocatalysis, with photocatalysts such as $Ir[dF(CF_3)ppy_2](dtbbpy)PF_6$, or semiconductors such as C_3N_4 or CdS.[53,54] For the dual catalytic combination of Ni and Ir catalysts for the alkoxylation of aryl halides, the redox potential for $E_{1/2}^{red}$ Ni(III)/Ni(II) = +0.71 V vs Ag/AgCl is within range of the measured E_{red} HARCP*/HARCP$^{\cdot-}$ = +0.87 V vs SCE, purporting that ET from HARCP* and Ni(II) is feasible. Analogously, the redox potential for the Ir catalyst $E_{1/2}^{red}$ Ir(III)/Ir(II) = -1.37 V is within range of that of HARCP, $E_{1/2}^{red}$ HARCP/HARCP$^{\cdot-}$ = -1.43 V vs SCE, indicating that ET from HARCP$^{\cdot-}$ to Ni(III) is also likely.[52] These correlated values could warrant that the alkoxylation of aryl halides with photocatalyst HARCP could take place efficiently under the dual HARCP / Ni catalysis. Indeed, the authors[52] found that a combination of aryl halide (0.2 mmol), photocatalyst HARCP (1.2 mol %), $NiSO_4.6H_2O$ (10 mol%), 4,4'-dimethoxy-2,2'-bipyridine ligand (10 mol%), DIPEA (1.5 equiv.) as sacrificial donor and alcohol (30 equiv.) in MeCN (2 mL) as solvent under N_2 atmosphere, irradiated with 23 W CFL for 24 hrs. at room temperature afforded the alcoxylated products in good yields. The scope of the transformation is depicted in Scheme 14.



Scheme 14. Selected examples for the HARCP-photocatalyzed alkoxylation of aryl chlorides with alcohols. Structures partially reproduced from ref. [52] with permission from Elsevier

If instead of alcohol, water (40 equiv.) is used in the reaction, the respective alcohols can be synthesized under analogous reaction conditions.[52]

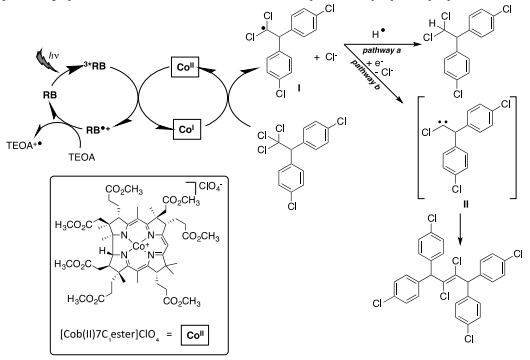
3.-REDUCTION REACTIONS

Vitamin B_{12}-derivatives have triggered much interest in radical remediation processes such as dechlorination reactions of pesticides. This is done in combination with photocatalysts able to mediate in the formation of the reduced Co(I) species which acts as the supernucleophilic reducing agent. For accomplishing this latter, prolonged visible light irradiation is needed. The use of the complex vitamin B_{12} derivative-Rose Bengal in the photoreduction of chlorinated organic compounds has been widely documented under continuous visible light irradiation.[55]

Reductive dehalogenation reactions promoted by vitamin B_{12} and derivatives have been inspired by the dehalorespiration of anaerobic bacteria such as *Sulfurospiririllum multivorans*.[21] Several substrates such as perchloroethylene (PCE),[56] 1,1-bis-(4-chlorophenyl)-2,2,2-trichloroethane (DDT)[57,58] and other toxic alkyl chlorides and bromides[57] have been efficiently reduced by means of photoredox reactions making use of B_{12} derivatives. For instance, some transformations reported employ TiO_2 semiconductors[59] or molecular photocatalysts such as cyclometalated iridium(III) complexes,[60] $Ru(bpy)_3^{2+}$ [61a] or organic red dyes[57,58] to absorb light and facilitate, through a photoredox mechanism, the formation of active Co(I) species which are crucial in the reduction process.[61b-h] As an example of these transformations, the proposed mechanism for the dechlorination of DDT mediated by heptamethyl cobyrinate perchlorate [Cob(II)7C$_1$ester]ClO_4 (a hydrophobic B_{12} model complex, see Scheme 15) and Rose Bengal (RB)[58] has been thoroughly studied by Hisaeda and colleagues and is presented in Scheme 15.[60] This halo-reductive Co-catalyzed mechanisms are pivotal to understanding vitamin B_{12} mode of catalytic action.

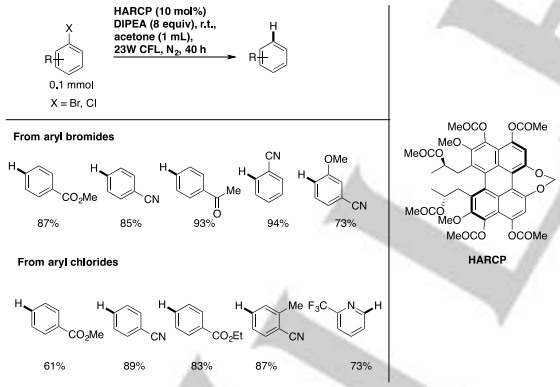
The authors[58] proposed that upon illumination of the primary photocatalyst Rose Bengal (RB), its triplet excited state is reached, which is oxidized by [Cob(II)7C$_1$ester]ClO_4 (Scheme 15). This oxidation affords RB$^{\bullet+}$ and the active Co(I) species of the B_{12} model complex which subsequently reduces DDT (via a single electron transfer event) yielding chloride and the carbon centered radical adduct **I** (Scheme 15). The RB$^{\bullet+}$ is reduced by triethanolamine (TEOA), a sacrificial donor, regenerating RB into

its active redox state. Radical adduct **I** (Scheme 15), can abstract a H atom from TEOA affording the reduced monodechlorinated product 1,1-bis-(4-chlorophenyl)-2,2-dichloroethane (DDD) (pathway a). In the presence of an excess of TEOA as electron donor, the authors[58] claim that radical adduct **I** (Scheme 15) can undergo an additional one electron reduction to form a carbanion that, upon chloride loss, forms the carbene species **II** (pathway b, Scheme 15) which dimerize yielding 1,1,4,4-*tetrakis*(4-chlorophenyl)-2,3-dichloro-2-butene (TTDB) (E/Z) (Scheme 15).



Scheme 15. Proposed mechanism for the dechlorination of DDT mediated by RB and [Cob(II)7C_1ester]ClO_4.

Li, Rao and colleagues[52] utilized a synthetic derivative of Cercosporin (CP), namely HARCP (Scheme 16), for the photoreduction of aryl halides. Synthetic derivative HARCP has improved redox properties with respect to CP (for instance, while $E_{1/2}^{red}$ CP / CP$^{\cdot-}$ = -0.46 V vs SCE, $E_{1/2}^{red}$ HARCP/HARCP$^{\cdot-}$ = -1.43 V vs SCE).[52] For the photoreduction of aryl halides employing HARCP as photocatalyst, the optimized reaction conditions consisted in the use of Ar-X (0.1mmol), HARCP (10 mol%) as photocatalyst, di-*iso*propyl-ethylamine (DIPEA , 8 equiv.) as sacrificial donor in acetone (1 mL), irradiating with 23 W CFL for 40 hrs. under N_2 atmosphere. The scope of the transformation is illustrated in Scheme 16 below.



Scheme 16. Selected examples for the photoreduction of aryl halides with HARCP. Structures partially reproduced from ref. [52] with permission from Elsevier

Shimakoshi and Hisaeda[62] have developed an oxygen-controlled dechlorination reaction of trichlorinated organic compounds employing a hydrophobic cobalamin derivative immobilized on TiO_2 as catalyst activated by UV light (365 nm) in alcohols as solvents. Under the presence of oxygen, trichlorinated substrates are converted to esters or amides (if amines are used as additives), whereas under inert atmosphere (N_2) partially dechlorinated compounds are obtained. This work has been reviewed before by Lloret-Fillol and collaborators[15] and by Hisaeda and collaborators.[21]

4.-CARBON-CARBON BOND FORMATION REACTIONS

4.1.-Arylation reactions

A great variety of coupling methods for the syntheses of arylated heteroarenes have been reported. These methods utilize transition metal-mediated transformations between pre-functionalized substrates and aromatics.[63] More recently, photoredox catalysis has contributed to the realm of synthetic methods for arylation reactions.[8,64-67] Seminal contributions by different researchers, such as Sanford,[68] König,[8] Xiao,[69] and Ackermann,[70] have revealed the relevance of the photocatalytic methodology. This approach has been very convenient for arylation of electron-rich heteroarenes. However, electron-deficient heteroarenes give poor yields of arylation products by photocatalysis.

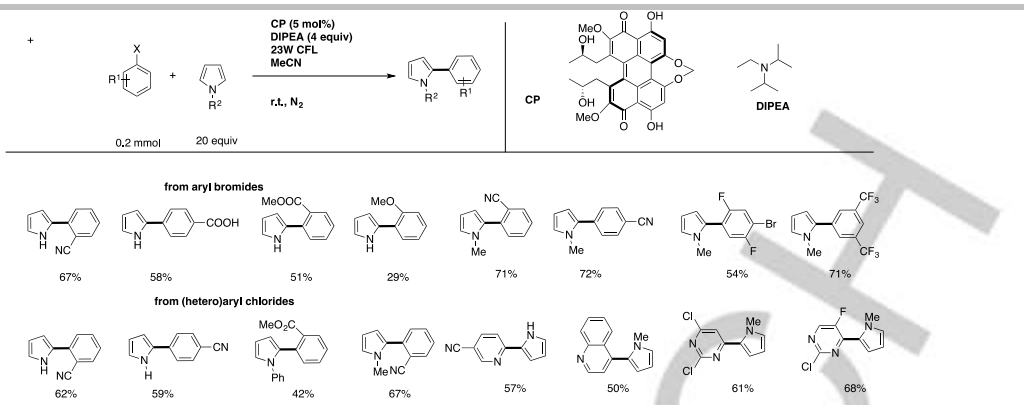
Tang, Rao and colleagues[71] have recently employed Cercosporin as photocatalyst in arylation reactions of (hetero)aromatics, starting from haloarenes (chlorides and bromides) and a family of pyrrole-derivatives.

Although chloroarenes and bromoarenes are difficult to activate towards their respective aryl radicals due to the high redox negative potentials unreached by the vast majority of standard photocatalysts (organometallics and dyes), the peculiar properties of Cercosporin enabled the photocatalyzed arylation reactions of aryl chlorides (and bromides) with heteroarenes to proceed effectively. In effect, the authors observed that the radical anion of Cercosporin, CP$^{\cdot-}$, attainable through vertical excitation of CP with a CFL in the presence of sacrificial donors such as di-*iso*propyl-ethylamine (DIPEA), has an extended half-lifetime of approximately one hour after illumination was interrupted.[31] The typical maxima absorption bands of CP$^{\cdot-}$ were located at 430 nm and 726 nm. Through femtosecond laser flash photolysis, a strong absorption difference ΔA at around 450-640 nm in both 430 nm and 726 nm excitation conditions was shown, which was assigned to the so-called CP$^{\cdot-}$* state (the excited state of the radical anion of CP), with a lifetime of 19 ps.

This extended lifetime of the radical anion intermediate of Cercosporin (i.e.: CP$^{\cdot-}$) enabled the authors to attempt irradiation of this intermediate and explore its reductive power and compare it to ground state radical anion CP$^{\cdot-}$ (which has redox potential of E_{red} CP*/CP$^{\cdot-}$ = +1.64 V[43,44]).

The authors[71] estimated through the Rehm Weller equation a value for the reduction potential of the excited radical anion of Cercosporin CP$^{\cdot-}$* to be -1.85 V vs SCE, demonstrating that it reaches or exceeds the reduction potentials of many substituted aryl chlorides. Consequently, the authors[71] embarked on the arylation of heteroaromatic compounds with Ar-Cl (and bromides) taking advantage of the high reductive power of CP$^{\cdot-}$* state.

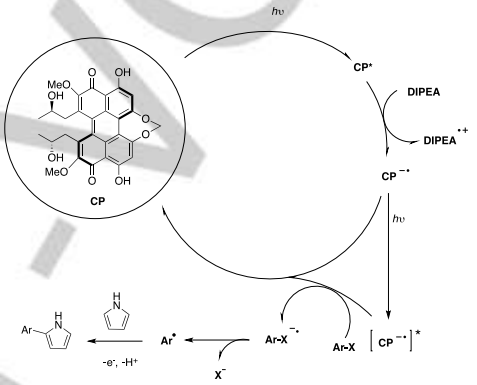
The optimized reaction conditions for the arylation consisted therefore in the use of halide (0.2 mmol), heteroarene (20 equiv.), Cercosporin (0.05 equiv.) as photocatalyst, DIPEA (4 equiv.) as sacrificial donor, MeCN as solvent (2 mL), under N_2 atmosphere, and irradiating with a 23 W CFL. The scope of the transformation is illustrated in Scheme 17.



Scheme 17. Selected examples for the arylation reactions of heteroaromatics with aryl halides photocatalyzed by CP. Structures partially reproduced from ref. [71] with permission from Elsevier

As observed from Scheme 17, both aryl halides with electron donating and withdrawing substituents afford good yields of coupling products. The authors[71] studied the reaction mechanism. Under O_2 atmosphere the yield of arylation decreased substantially, due to quenching of $CP^{\cdot-}$ by molecular oxygen. Light sources are necessary. However, irradiating with blue or green LEDs instead of CFL did not yield arylation products as these sources do not cover the maximum absorption spectra of $CP^{\cdot-}$*. Also, DIPEA was found to be essential in the reaction.
Control experiments found that CP is also necessary for the reaction to proceed. The fluorescence of CP* is suppressed upon incremental additions of DIPEA, forming the colored semi quinoid radical anion $CP^{\cdot-}$, which was confirmed by EPR spectra.[28] This quenching indicates an effective ET between CP* and DIPEA. By transient absorption spectroscopy, the excited radical anion of CP (i.e.: $CP^{\cdot-}$*) was characterized (*vide supra*).

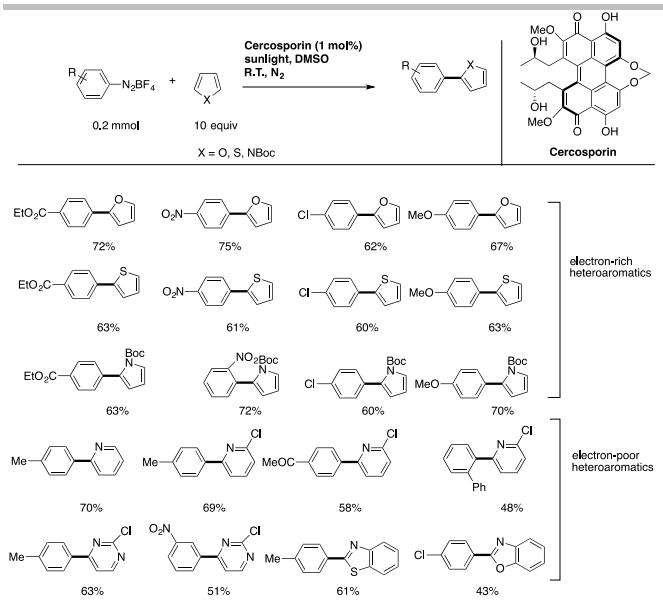
Radical trapping agents such as TEMPO and BHT inhibit the reaction significantly. When 4`-bromo-acetophenone and *N*-methyl pyrrole were added to a solution of generated $CP^{\cdot-}$ (which is formed by irradiating the mixture of CP and DIPEA with a CFL, and kept in the dark for no more than the lifetime of $CP^{\cdot-}$ radical anion, i.e. one hour), no arylation product of *N*-methyl pyrrole was found after 4 hrs in the dark. However, when this same mixture was irradiated with a 23 W-CFL lamp, the arylation product 1-(4-(1-methyl-1*H*-pyrrol-2-yl)phenyl)ethan-1-one was obtained in 62 % yield. This demonstrates that the excited radical anion of CP (i.e.: $CP^{\cdot-}$*) is formed in solution through two-step excitation process for the photoreductive activation of aryl chlorides and bromides. Although the authors do not point it out, the current methodology (two-photo excitation of a photocatalyst toward the construction of C-C bonds) is not the first example. In organic photocatalysis, this approach is being attempted in the last years affording good results due to the remarkable properties of excited radical ions, as attested by a recent review article in the field.[72]
Consequently, the authors proposed a reaction mechanism such as that depicted in Scheme 18.



Scheme 18. Proposed reaction mechanism fort he arylation of heteroaromatics from aryl chlorides. Structures partially reproduced from ref. [71] with permission from Elsevier

In the mechanism proposed (Scheme 18),[72] Cercosporin CP is excited by visible light and converted to the semi-quinoid radical anion of Cercosporin (i.e.: $CP^{\cdot-}$) by means of a reductive ET from DIPEA. $CP^{\cdot-}$, which is further excited by visible light into $CP^{\cdot-}$ * species, which can reduce aryl chlorides and bromides to their respective aryl radicals due to its rather negative redox potential (i.e.: -1.85 V vs SCE, *vide supra*). Aryl radicals in turn effect homolytic aromatic substitutions on the pyrrole rings, which after electron and proton transfers render the arylation products.

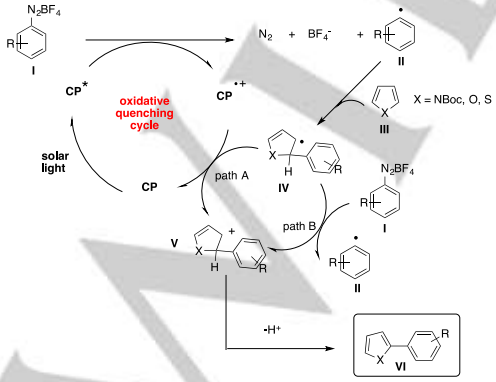
In another report, Zhang, Rao and collaborators[43] achieved the arylation of (hetero)aromatic compounds with aryldiazonium salts in the presence of Cercosporin as photocatalyst in DMSO as solvent under sunlight illumination. The remarkable finding in their study was the high reactivity obtained in the Cercosporin-photocatalyzed arylation of electron-deficient heteroaromatic compounds. The optimized reaction conditions found by the authors[43] resulted in the employment of 0.2 mmol of the diazonium salt, 10 equiv. of the arene compounds, Cercosporin (1 mol%) as photocatalyst, in N_2-saturated DMSO as solvent, under sunlight or blue LED illumination for 16 hrs. at r.t. The scope of the transformation regarding the heteroaromatic compounds is illustrated in Scheme 19.



Scheme 19. Selected examples for the Cercosporin-photocatalyzed arylation of electron rich and electron-poor heteroaromatics

As observed from Scheme 19, both electron-rich and electron-poor heteroarenes can be arylated in good yields with benzenediazonium salts having either electron-donor or electron-withdrawing groups attached to the phenyl ring when using Cercosporin as photocatalyst. Furans, thiophenes and pyrrole derivatives are arylated at the 2-position, unsubstituted pyridine is arylated at the 2-position as well, while 2-substituted pyridines are arylated at the 6-position. 2-Substituted pyrimidines are also arylated at the 6-position, while benzothiazole and benzoxazole are arylated at the 2-positions.

The authors[43] investigated the reaction mechanism. Control experiments confirmed that photocatalyst and light are necessary for the arylation reactions to proceed. Radical scavengers such as TEMPO (2,2,6,6-tetramethyl-piperidyne-1-oxyl) or 1,4-benzoquinone inhibited the reactions completely. Also, the presence of electron-transfer scavenger 1,4-dinitrobenzene halts the reaction. These observations imply that a radical mechanism is taking place during the reaction. The fluorescence of Cercosporin was suppressed upon incremental additions of benzenediazonium salt, purporting that an ET is taking place between excited Cercosporin and the diazonium salts. The proposed mechanism is illustrated in Scheme 20.



Scheme 20. Proposed reaction mechanism for the arylation of heteroaromatics from benzenediazonium salts

In the mechanism proposed (Scheme 20), Cercosporin CP is excited by solar light irradiation to CP*, which by reductive ET to benzenediazonium salt **I** produces aryl radical **II** (and Cercosporin radical cation $CP^{\cdot+}$, a strong oxidant with $E_{1/2}^{red}$ $CP^{\cdot+}/CP$ = +1.56 V vs SCE),[43] which in the presence of (excess) heteroaromatic compound **III** affords radical intermediate **IV**. This intermediate **IV** can either be oxidized by $CP^{\cdot+}$ (path A) to carbocation intermediate **V,** or by the benzenediazonium salt **I** (path B) affording more aryl radicals **II**. Carbocation **V** is deprotonated to afford arylated product **VI**.

4.2.-Acylation reactions

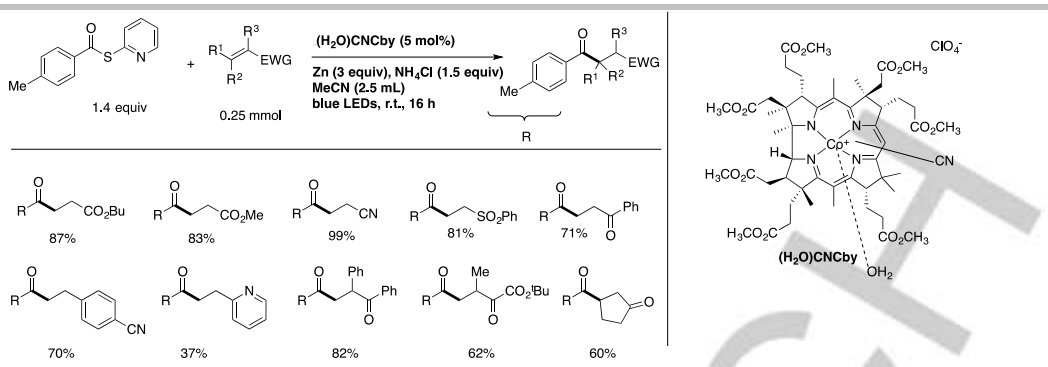
Acyl radicals are widely employed in Giese-type addition reactions to activated alkenes[73] or Minisci-type acylations of heterocycles.[74]

Acyl radicals are generally formed from homolytic scission of RCO-X bonds,[75-77] carbonylation of C-centered radicals,[78] or decarbonylation of α-ketocarbonyl compounds.[79-81]

Acyl radical generation by cobalt-catalysis is challenging, as the requirements for reducing conditions to produce the nucleophilic Co(I) species precludes the employment of standard acyl precursors such as acyl chlorides and carboxylic acid anhydrides. There are scanty reports on the employment of cobalt-catalysis to produce acyl radicals. Scheffold employed electrochemical methods for the acylation of olefins with anhydrides using acylcobalamine as an intermediate, although this is not a catalytic method.[82]

Ociepa, Gryko and colleagues[83] designed an experiment on the tenet that Co(I) would complex efficiently with an acyl derivative, and that by ulterior photocleavage of the Co-C bond would release the acyl radical. Among the acyl derivatives rehearsed, thioesters resulted the most promising. Due to the nucleophilic character of the acyl radical, electron-poor alkenes were chosen as coupling partners. The thioesters chosen as acyl radical precursors bear high electrophilic character on the carbonyl carbon. 2-Pyridylthioesters have been used as candidates for acyl radical surrogates in numerous reactions.[84-86] These thioesters are easily accessed from carboxylic acids and are friendlier alternatives to the previously reported Ru- or Ir-catalyzed methods for the acyl radical generation.[79-81]

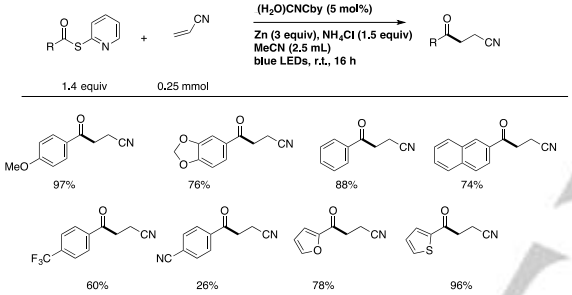
The authors[83-87] investigated the scope of the reaction in terms of the olefin and the carboxylic acid (the acyl part). Scheme 21 summarizes the scope of the reaction regarding the olefins with *S*-(pyridin-2-yl) 4-methylbenzothioate as the precursor of 4-methylbenzoyl radical.



Scheme 21. Selected examples for the acylation of olefins with S-(pyridin-2-yl) 4-methylbenzothioate by Co-photocatalysis

From Scheme 21, it is observed that olefins bearing electron-withdrawing groups such as CN, CO_2Bu, CO_2Me, SO_2Ph and electron-deficient aromatic rings afford acylation products efficiently.

The scope and limitations regarding the acyl radical precursor were also investigated. Scheme 22 summarizes selected examples of different thioesters employed in the acylation of acrylonitrile.

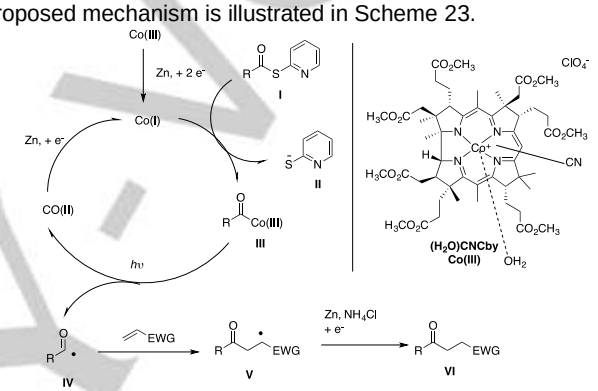


Scheme 22. Selected examples for the acylation of acrylonitrile with different thioesters

From Scheme 22 it can be observed that thioesters with both electron-rich and electron-poor aromatic rings can be used as thioesters capable of generating the acyl radical by Co-catalysis. Electron-neutral or small heterocycles can also be used as thioesters.

The use of Zn as a reducing agent precludes the presence of reducing functional groups in the substrates (i.e.: -CHO, SO_2F, $P(O)(OMe)_2$ and others), being a serious limitation to the reaction.

The authors[83] investigated the reaction mechanism assuming that the acylation takes place from a complex between the acyl moiety and Co(III) (structure **III**, Scheme 23), which in turn is formed from Co(I) and the thioester (Scheme 23). Absence of reducing agent Zn or light, did not furnish acylation product. The authors[83] managed to characterize by HRMS measurements the mass of complex **III**, having a value of 1155.7 (Co complex of 4-methylbenzothioate). The reaction with TEMPO, a radical scavenger, afforded the acylated -TEMPO adduct. An experiment with ND_4Cl, led to an acylated product with the deuterium label at the α-position of the electron-withdrawing group of the olefin moiety, and not α-to the carbonyl group of the acyl moiety. The proposed mechanism is illustrated in Scheme 23.

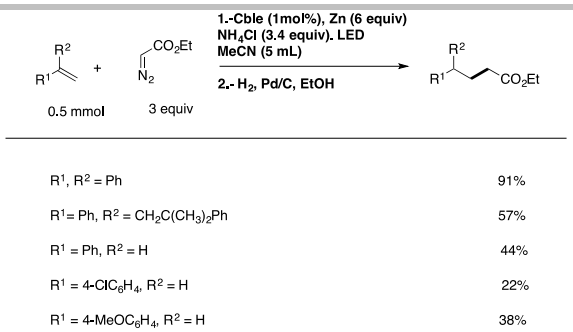


Scheme 23. Proposed reaction mechanism for he acylation of olefins

In the mechanism proposed (Scheme 23), the initial Co(III) photocatalyst is reduced by Zn to the supernucleophilic Co(I) species, which, in turn, reduces the thioester **I** to thiolate **II** and forms acyl-Co-complex **III** (Co(III)). This latter is cleaved by light to furnish the acyl radical **IV**, which adds to the terminal carbon of the electron-poor olefin to generate radical intermediate **V**. Intermediate **V** is reduced by Zn to a carbanion which is promptly protonated to afford product **VI**.

4.3.-Addition of alkyl radicals to olefins towards the construction of C-C bonds

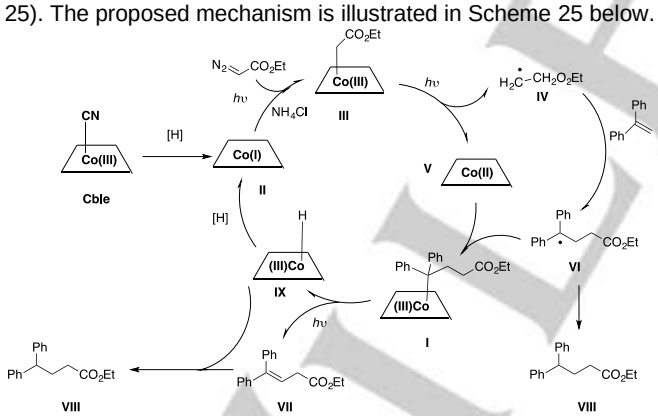
Chen and Zhang[88] have used hydroxycobalamine as photocatalyst in the reaction of styrenes with diazoacetate to form cyclopropane derivatives. However, Gyedik, Gryko and colleagues[89] have uncovered a novel way of reactivity when using electron-rich olefins (0.5 mmol) and diazoacetate (3 equiv) in the presence of a cobalester photocatalyst Cble (1mol%), Zn (6 equiv), NH_4Cl (3.4 equiv) in MeCN as solvent (5 mL) under irradiation (Scheme 24). The scope of the reaction is illustrated in Scheme 24.



Scheme 24. Selected examples for the scope of the C-H functionalization of olefins. Structures partially reproduced from ref. [88] with permission from The American Chemical Society

It should be mentioned that both olefinic and saturated products are obtained. For reasons of simplicity, the authors[89] decided to reduce the olefinic product by hydrogenation on Pd/C, as shown in Scheme 24.

The methodology proposed by the authors[89] also allowed the functionalization of enamines and enol ethers. The authors studied the mechanism of the reaction. Spin traps such as phenyl-*N*-*tert*-butylnitrone and 2,2,6,6-tetramethyl(piperidin-1-yl)oxyl (TEMPO) afforded the corresponding alkyl adducts derived from diazoacetate. Due to the contrasting results obtained by Chen and Zhang[88] with the cyclopropanes as final products, the authors[89] decided to investigate whether a cyclopropane is a reaction intermediate in the current studied methodology. For that purpose, the authors subjected 2,2-diphenylcyclopropane carboxylate to the above reaction conditions (conditions from Scheme 24). The cyclopropane was found to be recovered intact after 24 hrs., demonstrating that a cyclopropane is not an intermediate in this Co-catalyzed transformation with Cble as photocatalyst. A mass spectrum of the crude reaction mixture revealed peaks at mass 1718.9, corresponding to a Co-intermediate such as **I** (Scheme 25). The proposed mechanism is illustrated in Scheme 25 below.



Scheme 25. Proposed reaction mechanism. Structures partially reproduced from ref. [88] with permission from The American Chemical Society

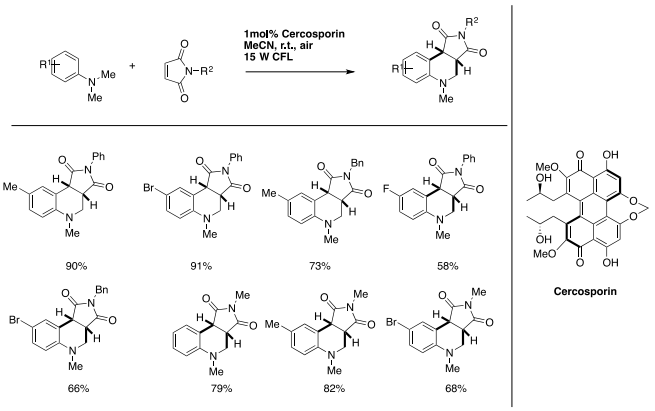
In the proposed reaction mechanism (Scheme 25), the Cble Co-complex is reduced by Zn to the catalytically active Co(I) complex **II**, which combines with diazoacetate to afford alkyl-Co-complex **III,** where the extra proton comes from NH_4Cl (demonstrated using ND_4Cl). Complex **III**, is, in turn, cleaved by light to release alkyl radical IV and Co(II) species **V**. Alkyl radical **IV** combines with 1,1-diphenylethylene to form tertiary alkyl radical **VI**, which is captured by Co(II) (species **V**) to form Co(III) complex **I.** This latter complex **I** is cleaved by light to release olefin **VII**, and the hydrido Co(III) complex **IX**. Alternatively, olefin **VII** abstract H from **IX** to generate **VIII**.

4.4.- C-C bond formation through intramolecular cyclization reactions.

Synthesis of pyrrolo[3,4-c]quinolones and pyrrolidine derivatives [3,4-c]quinolones are structural cores of several bioactive molecules such as caspase-3 inhibitors,[90] 5-HT4R antagonists,[91] and ADAMTS inhibitors.[92]

Besides annulation reactions that employed strong oxidants such as ^{t}BuOOH, $K_2S_2O_8$ and high temperature,[93-97] polypyridyl complexes of Ir and Ru have been employed as photocatalysts for the syntheses of [3,4-c]quinolones.[98-101] Metal-free photocatalysis has also been used, albeit sparingly, for the synthesis of [3,4-c]quinolones.[102] All these methods rely on the sp^3 C-H annulation of electron rich *N,N`*-dimethylanilines and maleimides, where through an oxidative ET, a radical cation of the amine is formed, which by deprotonation renders an α-amino-carbon radical which attacks the maleimide double bond generating a radical adduct that further realizes an aromatic homolytic substitution on the ancillary ring forming a new C-C bond.

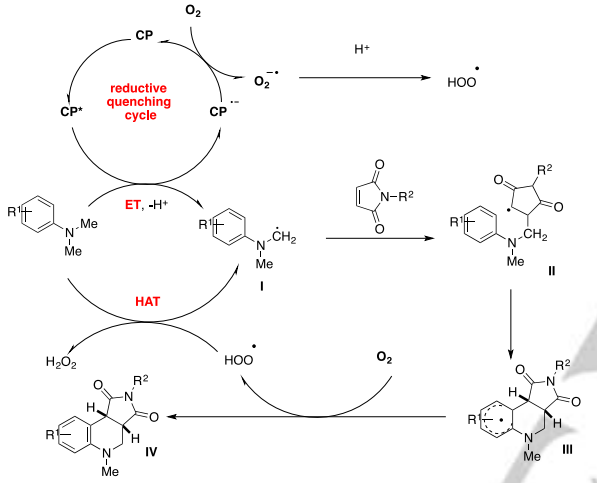
Rao and colleagues[103] have accomplished the photocatalytic synthesis of [3,4-c]quinolones employing Cercosporin as photocatalyst starting from *N,N´*-dimethylaniline derivatives (0.25 mmol), *N*-phenylmaleimide (0.25 mmol), Cercosporin (1 mol%), MeCN (2 mL), at room temperature, under air, irradiating with a 15 W CFL for 20 hrs. The scope of the reaction is illustrated in Scheme 26.



Scheme 26. Selected examples for the Cercosporin photocatalyzed synthesis of [3,4-c]quinolones. Structures partially reproduced from ref. [103] with permission from Royal Society of Chemistry

In order to investigate the reaction mechanism, the authors[103] employed radical scavenger TEMPO, and

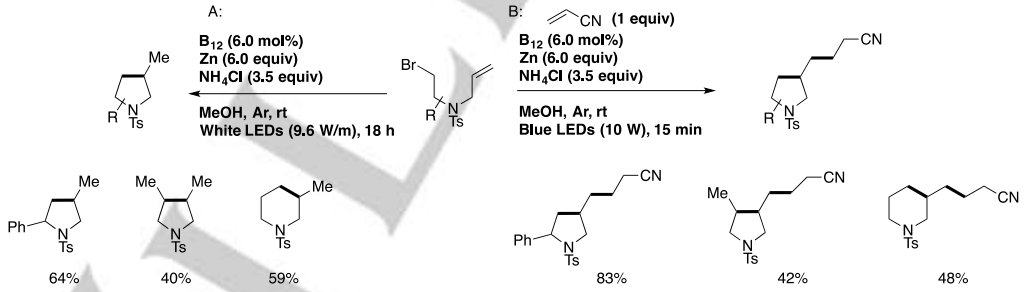
encountered complete lack of reaction. Knowing the ability of Cercosporin to produce singlet oxygen, an experiment was designed in the presence of histidine under the optimized reaction conditions. Under these conditions (presence of histidine), the [3,4-c]quinolone products were found in similar reaction yields as without histidine, purporting that singlet oxygen is not an intermediate in the reaction. Fluorescence quenching experiments of Cercosporin with 4-methyl-*N,N`*-dimethylaniline revealed an electron transfer sequence between excited Cercosporin and the aniline ($E_{red}$ CP*/CP$^{\bullet-}$ = +1.87 V vs SCE; $E_{1/2}^{red}$ $Me_2NPh^{\bullet+}/Me_2NPh$ = +0.79 V vs SCE). The Stern Volmer plots indicate that *N,N`*-dimethylaniline can suppress the emission of Cercosporin in de-oxygenated MeCN solution. Deuterium isotope effect experiments revealed that both electron/proton (ET/H+) and hydrogen atom transfer (HAT) steps are involved in the formation of α-aminoalkyl radical **I** (Scheme 27). The authors[103] suggested a probable mechanism such as that shown in Scheme 27.



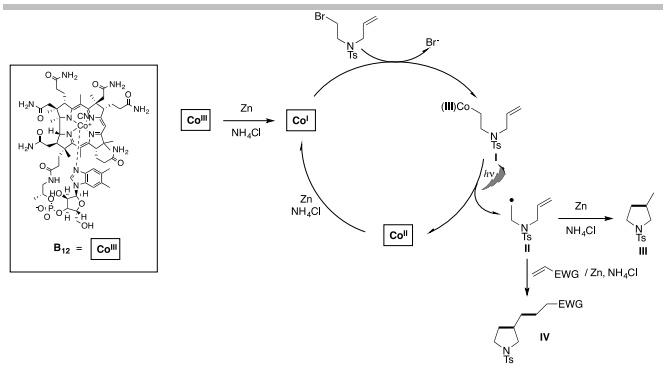
Scheme 27. Proposed reaction mechanism fort he syntheses of [3,4-c]quinolones. Structures partially reproduced from ref. [103] with permission from Royal Society of Chemistry

In the proposed reaction mechanism (Scheme 27) excited Cercosporin (CP*) generates radical intermediate **I** upon reaction with *N,N`*-dimethylaniline through electron transfer ET and deprotonation. Intermediate **I** reacts with maleimide to form radical intermediate **II**, which by homolytic aromatic substitution forms cyclohexadienyl radical intermediate **III**, which in turn is rearomatize to product **IV** through molecular oxygen, forming hydrogen peroxyl radical in the process. This latter (i.e.: peroxyl radical) could abstract H radical from *N,N`*-dimethylaniline to form more radical intermediate **I** (and hydrogen peroxide) through a hydrogen atom transfer (HAT) sequence. The active form of the photocatalyst is regenerated through reaction with molecular oxygen, closing the reductive catalytic cycle.

Gryko and collaborators[104] reported a native vitamin B_{12} (cyanocobalamin)-catalyzed intramolecular cyclization of bromoalkenes for the synthesis of pyrrolidines and piperidines (Scheme 28, equation A), whereas upon addition of an electron deficient olefin to the reaction media dicarbofunctionalization takes place (Scheme 28, equation B). Both reactions employ native vitamin B_{12} as catalyst, Zn/NH_4Cl as reducing agent, in methanol as solvent under visible light irradiation; the reaction without the addition of the electrophilic olefin proceeds under visible light irradiation as opposed to the dicarbonfunctionalization where blue LEDs are necessary for maximizing the reaction yield. Regarding some mechanistic aspects,[104] the reaction is initiated by reduction of Co(III) in B_{12} to Co(I) promoted by Zn/NH_4Cl. The supernucleophilic Co(I) form of B_{12} reacts with the bromoalkene affording an alkylcobalamin **I** (Scheme 29) and bromide anion. Alkylcobalamin **I** (Scheme 29), upon light irradiation, generates the Co(II) form of B_{12} and radical adduct **II** (Scheme 29) that can participate in two distinct pathways: i) be reduced by Zn/NH_4Cl generating 3-methylpyrrolidine **III** (Scheme 29); or ii) react with an electron deficient alkene (if present in the reaction media) affording, through a tandem reaction, the substituted pyrrolidine **IV** (Scheme 29). The catalytically active Co(I) form of B_{12} could be generated upon reaction of the Co(II) form with Zn/NH_4Cl, closing the catalytic cycle.



Scheme 28. Selected examples for the vitamin B_{12} catalyzed radical cyclization of bromoalkenes (equation A) and the tandem dicarbofuntionalization of bromoalkenes with an electrophilic olefin (equation B). Structures partially reproduced from ref. [104] with permission from Thieme



Scheme 29. Plausible reaction mechanism for the vitamin B_{12}-catalyzed radical cyclization of bromoalkenes, and the tandem dicarbonfuntionalization of bromoalkenes with an electrophilic olefin. Structures partially reproduced from ref. [104] with permission from Thieme

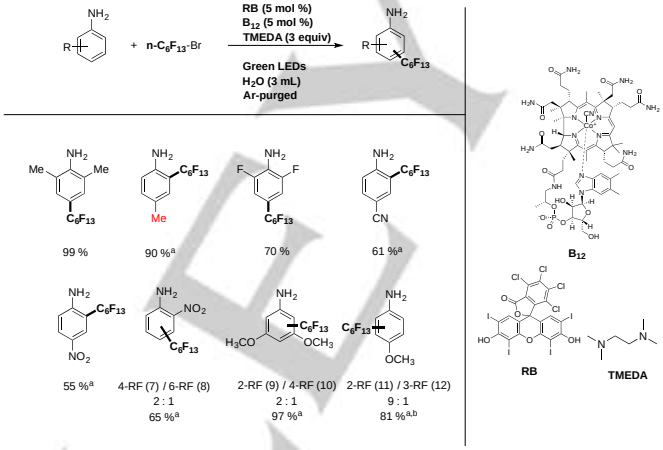
4.5.-Perfluoroalkylation reactions. Formation of C_{Ar}-C_nF_{2n+1} bonds

Fluoro(alkyl)-substituted organic compounds are widely applied in many fields such as agrochemistry, medicinal chemistry, materials science, etc., making the development of more environmentally concerned protocols highly sought-after synthetic strategies. On this subject, radical fluoroalkylation reactions have been extensively studied.[105]

Hisaeda and collaborators,[106] developed a bioinspired electrochemical protocol for the trifluoromethylation and perfluoroalkylation of aromatic compounds employing heptamethyl cobyrinate perchlorate [Cob(II)7C_1ester]ClO_4, a hydrophobic vitamin B_{12} derivative as catalyst. In this reaction,[106] which has been previously reviewed,[21] the vitamin B_{12} derivative catalyst is electrochemically reduced to its active Co(I) form, and light (hν > 420 nm) is only needed for promoting the homolytic cleavage of the Co(III)-R_F adduct (formed upon reaction of the Co(I) form of the catalyst with perfluoroalkyl iodides (R_F-I) affording the reactive perfluoroalkyl radicals and regenerating the [Cob(II)7C_1ester]ClO_4 catalyst.

In a recent report[107] our group has developed a methodology for the fluoroalkylation in water or aqueous media of electron rich arenes by the dyad Rose Bengal (RB) and Cyanocobalamin (natural vitamin B_{12}) as the catalyst and co-catalyst, respectively.

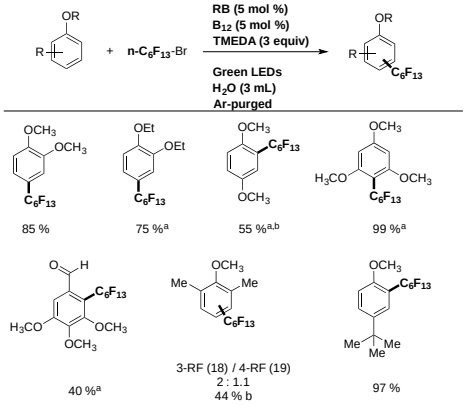
The optimal reaction conditions for perfluorohexylation of aniline derivates, shown in Scheme 30, consist in the use of substrate (0.2 mmol), catalyst (RB, 5 mol%) and co-catalyst (vitamin B_{12}, 5 mol%), perfluorohexylbromide (3 equivalents) as perfluoroalkyl radical source, organic base *N,N,N`,N`*-tetramethylethylendiamine (TMEDA, 3 equiv.) in water (or water mixtures) under green light irradiation (525 nm). The protocol was compatible with a wide range of aniline derivates with both electron withdrawing and donating groups. The scope of the reaction is illustrated in Scheme 30.



a Water : Acetonitrile (1:1) used as solvent. b 1 equiv of n-C_6F_{13}-Br

Scheme 30. Scope of photocatalyzed perfluorohexylation of anilines by RB/B_{12}. Structures partially reproduced from ref. [107] with permission from The Royal Society of Chemistry

The possibility of all-alcoxy-substituted arenes as candidate substrates was considered for this methodology. The results of the photocatalyzed perfluorohexylation of alcoxy-substituted arenes under the optimized reaction conditions are illustrated in Scheme 31.

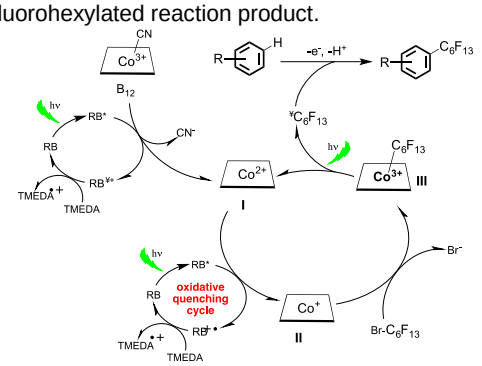


a Water : acetonitrile (1:1) used as solvent. b 0.6 mmol of substrate and 1 equiv of n-C_6F_{13}-Br

Scheme 31. Selected scope of photocatalyzed perfluorohexylation of alcoxy-substituted benzenes by RB/B_{12}. Structures partially reproduced from ref. [107] with permission from The Royal Society of Chemistry

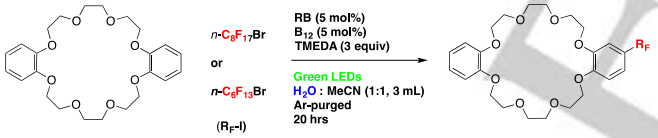
Several experiments were made to cast light into the mechanism of the reaction including Stern-Volmer quenching and trapping experiments with TEMPO and UV-vis. measurements. All these experiments led the authors[107] to propose the mechanism illustrated in Scheme 32.

Initially vitamin B_{12} undergoes one electron reduction promoted by the excited state of RB, affording, upon cyanide loss, Cob(II)alamin (**I**). The reaction continues with reduction of Cob(II)alamin by an additional RB oxidative photocatalytic cycle to afford Cob(I)alamin (**II**) that reacts with Br-C_6F_{13} generating the Co(III)-C_6F_{13} complex **III** and bromide anion. Upon light absorption, complex **III** releases a •C_6F_{13} radical and regenerates the cob(II)alamin. Finally, the •C_6F_{13} radical formed reacts with the arene via a homolytic aromatic substitution mechanism affording the perfluorohexylated reaction product.



Scheme 32. Photocatalyzed perfluoroalkylation of arenes by RB/B_{12}: proposed mechanism. Structures partially reproduced from ref. [107] with permission from The Royal Society of Chemistry

Finally, the utility of the protocol in the late-stage fluoroalkylation of dibenzo-24-crown-8 was evaluated as shown in Scheme 33.

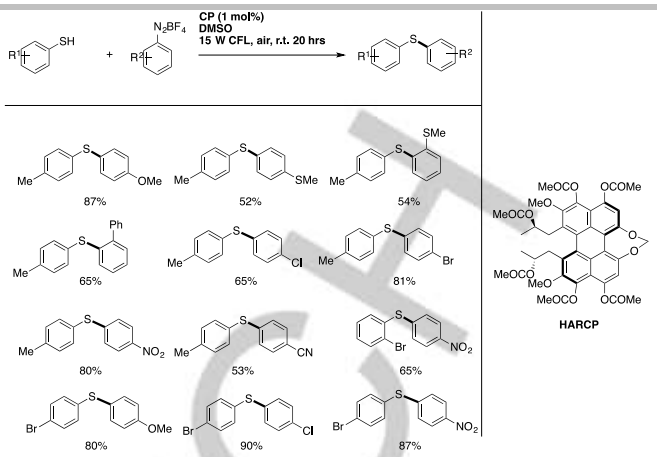


Scheme 33. Late-stage perfluoroalkylation of dibenzo-24-crown-8. Structures partially reproduced from ref. [107] with permission from The Royal Society of Chemistry

5.-FORMATION OF C-S BONDS. SYNTHESIS OF SULFIDES

Aryl sulfides are conveniently synthesized through coupling reactions of aryl halides, aryl boronic acids or triflates with thiols mediated by Pd,[108] Cu,[109] Ni,[110] Co,[111] Fe,[112] or In.[113] However, these methods suffer from the use of toxic or expensive metal catalysts or high temperatures. Photocatalytic methods employed for aryl sulfide formation rely on the use of metalorganic photocatalysts.[114,115]

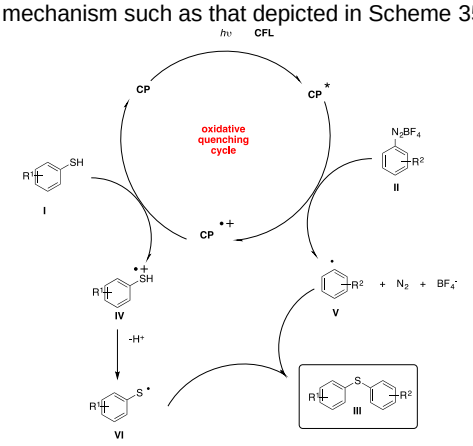
Li, Rao and collaborators[116] have utilized Cercosporin (CP) as photocatalyst for the photocoupling reaction of aryldiazonium salts with sulfides to yield diary sulfides in good yields. The optimized reaction conditions consisted in the use of benzenediazonium salts (0.3 mmol), aryl thiols (0.25 mmol), photocatalyst CP (1 mol%), in DMSO as solvent (2 mL) in air atmosphere irradiating with a 15 W CFL for 20 hrs. The scope of the transformation is illustrated in Scheme 34.



Scheme 34. Selected examples for the scope of the CP-photocatalyzed arylation of sulfides

Aryl diazonium salts bearing electron donating and withdrawing groups can couple with aryl sulfides in good yields. The authors[116] studied the reaction mechanism. Control experiments confirmed that the photocatalyst CP, and the light source are necessary to obtain the diaryl sulfides. Being CP a well-known singlet oxygen generator through EnT mechanism, the authors used singlet oxygen inhibitors such as DABCO and NaN_3 in the reaction mixture. The reactions proceeded effectively, and the diaryl sulfide products isolated in substantially the same yields as without the singlet oxygen inhibitors, purporting that an EnT pathway is not operating in the reaction mechanism for formation of diaryl sulfides with CP.

Radical scavengers such as 1,4-benzoquinone, BHT or TEMPO inhibited the reaction notoriously, suggesting a radical pathway in the mechanism of the reaction. Based on these results and other literature precedent, the authors[116] suggested a reaction mechanism such as that depicted in Scheme 35.



Scheme 35. Proposed reaction mechanism for the coupling of arylbenzene diazonium salts with aryl sulfides

In the proposed mechanism (Scheme 35), visible light-excited CP* reduces aryldiazonium salt **II** to aryl radicals **V** ($E_{1/2}^{red}$ CP^{+}/CP* = -0.77 V vs SCE, $E_{1/2}^{red}$ ArN_2BF_4/Ar · = 0 V), while forming the radical cation of $CP^{\cdot+}$. The radical cation of CP (i.e.: $CP^{\cdot+}$ being a strong oxidant with $E_{1/2}^{red}$ $CP^{\cdot+}$/CP = +1.56 V vs SCE[43]), in turn oxidizes sulfide **I** by ET to sulfide radical cation **IV** ($E_{1/2}^{red}$ $PhSH^{\cdot+}$/PhSH = + 0.83 V),[117] which is promptly deprotonated to radical **VI**, effecting a radical-radical coupling reaction with **V** to render product **III**.

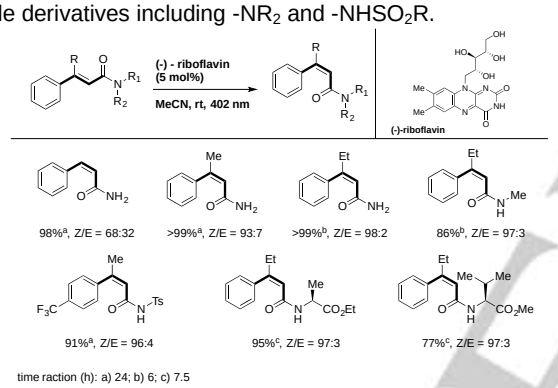
6.-E / Z ISOMERIZATION

The *E* / *Z* isomerization process is central in many biological mechanisms such as in product biosynthesis and in the mammalian visual cycle. This thermodynamically unfavorable E / Z isomerization process is easily performed in nature, but difficult to replicate in the laboratory.

Organometallic Ir(III)-based photocatalysts have been employed in geometrical *E* / *Z* isomerization of styrenyl derivatives.[118-120] The sensitized isomerization mechanisms of stilbenes, styrenes and fumarates have been investigated by various authors.[121-123] In these experiments, stoichiometric quantities of sensitizers were used. However, no polarized unsymmetrical alkenes were studied despite their synthetic potentials.

In the 1960s, it was reported that the presence of vitamin B_2 (Riboflavin) present in the eyes of mammals and fish could induce the *E* / *Z* contra thermodynamic isomerization of retinal.[124]

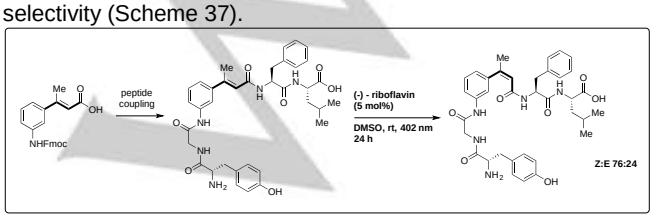
In section 4.3.-, an *E to Z* sensitized isomerization process was introduced to account for a carbon-oxygen bond formation reaction. Burley, Gilmour and colleagues[125] have reported a photocatalytic *E* to *Z* isomerization of cinnamides using RF as photocatalyst. The protocol developed employs 5 mol% of RF in acetonitrile under 402 nm irradiation as shown in Scheme 36. This geometrical isomerization reaction tolerates a wide range of amide derivatives including -NR_2 and -$NHSO_2R$.



Scheme 36. Selected examples of photocatalytic isomerization of cinnamides. Structures partially reproduced from ref. [125] with permission from Elsevier

The authors propose a selective energy transfer process from the excited photocatalyst to the starting *E* material, while the EnT from the *Z* isomer would be inefficient due the allylic strain causing chromophore deconjugation. This assumption is supported by a Stern-Volmer photo-quenching study and X-ray crystallographic analysis of (*Z*)-3-phenylpent-2-enamide.

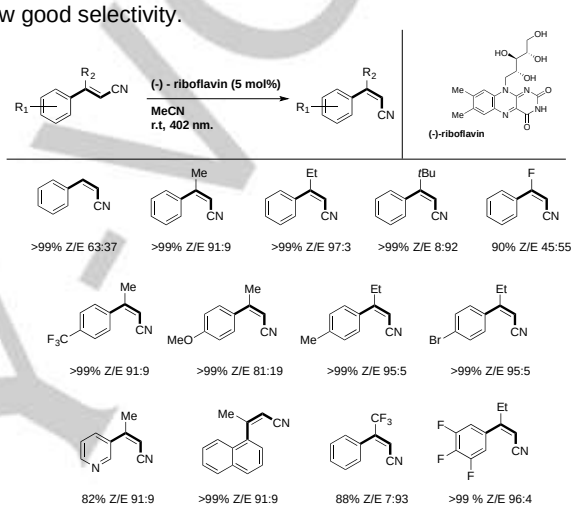
To explore the application of this method in modulation of peptide conformation, a penta-peptide (N-Tyr-Gly-Gly-Phe-Leu-C) was prepared by solid phase peptide synthesis. Replacement of the Gly residue in position three with a cinnamide-based amino acid was accomplished by Fmoc-based coupling methods. The pentapeptide and the photocatalyst were dissolved in deuterated dimethylsulfoxide and irradiated at 402 nm for 24 h. The geometric alkene isomerization was observed with good selectivity (Scheme 37).



Scheme 37. Photocatalytic isomerization of a model penta-peptide with (-) – riboflavin. Structures partially reproduced from ref. [125] with permission from Elsevier

In a 2017 report, Gilmour, Neugebauer, Metternich and co-workers[126] developed a photocatalytic *E* to *Z* isomerization of α, β – unsaturated nitriles analogous to the intermediate opsin-derived protonated Schiff base in the visual cycle.

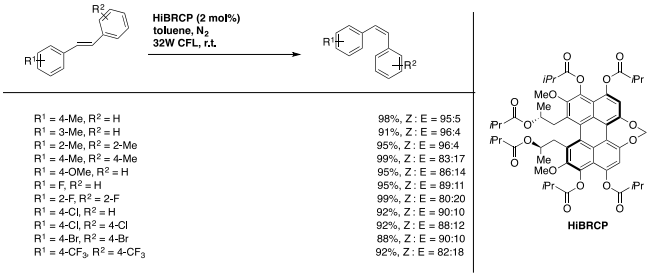
The optimal reaction conditions (Scheme 38) include 5 mol% of RF as photocatalyst in acetonitrile as solvent under 12 h of UV-light irradiation (402 nm). The authors proposed that β-substitution would increase the reactivity by raising strain in the product. Several examples are illustrated in Scheme 38; isomerization with *t*Bu group affords only traces of the *Z* isomer. Also, aromatic compounds with *p*-substituents (-R, -OCF_3) can be present. Heteroaromatic compounds and large π-systems also show good selectivity.



Scheme 38 – Photocatalytic isomerization of cinnamonitriles: optimal conditions and substrate scope.

Based on the favorable triplet energy of HiBRCP (E_T HiBRCP = 54.2 kcal mol^{-1}, structure in Scheme 12, *vide supra* and Scheme 39, *vide infra*), Zhang, Rao and colleagues[32] have very recently inspected the possibility of geometrical *trans-cis* isomerization of *E*-olefins by EnT utilizing HiBRCP as photosensitizer. The kinetics of geometrical isomerization are ruled by the thermodynamic feasibility, that is $\Delta E_T = E_T$ (alkene) – E_T photosensitizer < 0. If a *trans*-to-*cis* geometrical isomerization is to be conducted, then the thermodynamic energetic requirement is E_T (*trans* alkene) < ET photosensitizer < E_T (*cis* alkene). For *E*-stilbene (and *E*-stilbene derivatives), E_T = 49.4 kcal/mol, while for *Z*-stilbene, E_T = 54.3 kcal/mol, which fulfils the above requirement.

The authors inspected a series of *E*-stilbene derivatives for their geometrical isomerization to their respective *Z*-geometrical forms. The scope of the reaction is illustrated in Scheme 39.



Scheme 39. Geometrical Isomerization of Stilbene Derivatives Photocatalyzed by HiBRCP

In the cases depicted in Scheme 39, HiBRCP photosensitizes conveniently the *E/Z* isomerization of a series of stilbene derivatives, providing high yields of the respective *Z* isomers.

7.-REDOX POTENTIALS AND PHOTOPHYSICAL PROPERTIES OF BIOINSPIRING CATALYSTS

Table 1. Properties of Bioinspiring Photocatalysts

Photocatalyst PC	λ_{abs}, nm	λ_{em}, nm	E^{S1}, eV[a]	E^{T1}, kcal/mol[b]	$E_{1/2}^{red}$ PC/PC$^{\cdot-}$ V, *vs* SCE[c]	$E_{1/2}^{red}$ PC$^{\cdot+}$/PC, V, vs SCE[d]	E_{red} PC*/PC$^{\cdot-}$ V, vs SCE[e]	E_{red} PC$^{\cdot+}$/PC* V, vs SCE[f]	E_{red} PC*/PC*$^{\cdot-}$ V, vs SCE[g]	Ref.
CP[h]	476	503	2.10	40.8	-0.46	+1.56	+1.64	-0.54	-1.85	43,44, 52, 56, 66, 71
HARCP[i]	455	503	2.30	55.6	-1.43	+1.20	+0.87	-1.10		56 52
HiBRCP[j]	(425)[k] 460	515 (675)[k]	2.35	54.2	-1.42	+1.20	+0.93	-1.15		32
Emodin	427				-0.246					47, 127
Vitamin B_{12}[l]	363[n] (550)[k]	337 (250)[o]			Co(III)/Co(II) = +0.21 Co(II)/Co(I) = -0.83					128
[Cob(II)7C_1ester]CO_4[l]	375 (547,580)[k]				Co(III)/Co(II) = +0.45 *vs* SCE Co(II)/Co(I) = -0.64 *vs* SCE					20, 127
RF[m]	(343)[k] 440			49.8	-1.18		+1.46			129

a.-Singlet state energy. b.- Triplet state energy. c.- Reduction potential (half wave) of ground state of the photocatalyst. d.- Oxidation potential of ground state of photcatalyst. e.- Reduction potential from the excited state of the photocatalyst. f.- oxidation potential from the excited state of the photocatalyst. g.- redox potential of the ground state radical anion to excited radical anion. h.- Cercosporin. i.- hexacetyl reduced Cercosporin derivative . j.- reduced derivative of Cercosporin, with CO^{i}Pr groups. K.- shoulder. l.- vitamin B_{12} and [Co(II)7C_1ester]ClO_4 do not absorb light directly, but function as co-catalyst. Their complex with substrates will absorb light to cleave Co-substrate bond. m.- Riboflavin . n.- measured in water. o.- excitation wavelength, *Anal. Methods*, 2017, 9, 4052.

8.-CONCLUSIONS AND OUTLOOK

Visible light-bioinspired photocatalysis, which employs organic compounds or complexes found in Nature or some derivatives of such which behave as photocatalysts that have relevance in bioorganic transformations such as vitamins, cofactors, or naturally-occurring pigments, has been used for a large group of organic transformations, such as oxidation and reduction reactions, carbon-carbon and carbon-sulfur bond formations and geometrical isomerizations. The photocatalysts employed are vitamin B_{12} (and lipophilic derivatives), vitamin B_2, natural pigments from the *Cercospora* family, and compounds with known antiviral activity.

Cercosporin and related compounds employed have been shown to photocatalyze many organic transformations either by electron transfer, ET, or energy transfer, EnT, processes, which bespeak of the versatility of these catalysts. Vitamin cofactors as photocatalysts have shown fruitful applications in numerous transformations, such as reduction, carbon-carbon, and carbon-oxygen bond formation reactions and *E to Z* isomerization processes.

Among the synthetic organic transformations that need to be further explored by the use of these “bioinspired” catalysts are those involving the generation of nitrogen-centered radicals, silyl radicals, and selenium-centered radicals. Regarding the Cercosporin and Cercosporin-derived photocatalysts, albeit their employment has enjoyed a burst of applications, other useful reactions remain understudied, such as halogenation, perfluoroalkylation reactions, and carbon-nitrogen bond formation reactions. From a methodological perspective, flow systems have sparingly been applied when using bioinspired photocatalysts, which could be a subject of future study.

From the environmental perspective, a change of the above-studied reactions with the bioinspired photocatalysts in friendlier reaction media, such as water or aqueous mixtures of organic solvents, would emphasize their amiable utility.

Undoubtedly, the employment of “bioinspired” photocatalysts is a step further towards an environmentally friendlier approach in organic syntheses, imitating Nature energy-balanced processes and choice of (photo)catalysts.

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Keywords: bioinspired photocatalysis •organophotocatalysis • cercosporin photocatalysis • vitamin-photocatalyzed • C-C bond formation through photocatalysis • C-S bond formation through photocatalysis • C-O bond formation through photocatalysis • Energy transfer organo-photocatalysis

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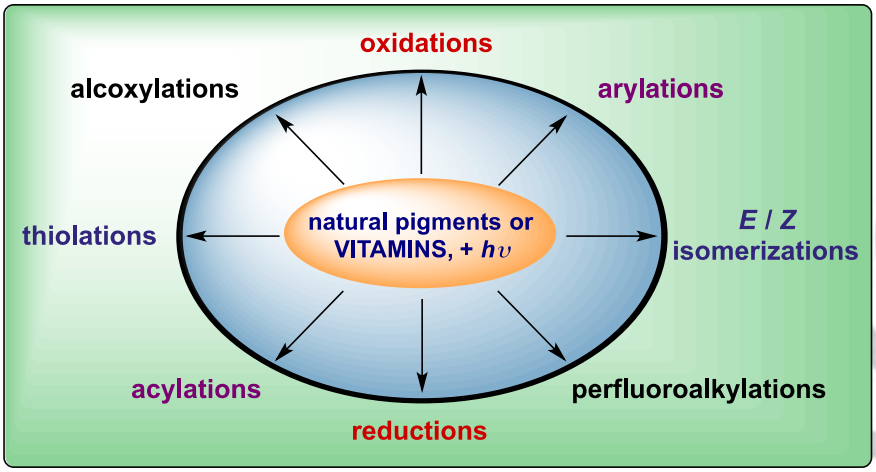

The use of natural organic pigments, vitamins and small organic molecules with antiviral activity can function as visible light photocatalysts for oxidation, reduction, C-O, C-C, and C-S bond formation reactions, and E/Z isomerizations. The use of these photocatalysts brings about advantages ranging from a lower environmental impact as compared to the use of classical photocatalysts such as organic dyes or transition metal photocatalysts and convenience in large scale syntheses in the pharmaceutical industry. Redox potentials and photophysical properties of bioinspiring catalysts are presented.