

Latest updates in ElectroPhotoChemical reactions

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ABSTRACT

In the last twenty years, electrochemistry and photochemistry have attracted a renewed and still uprising interest in organic synthesis. Two of the most simple and abundant reagents, electrons and photons, became the key players in synthetic chemistry as cornerstones of developing greener and sustainable chemical processes. An interesting strategy that recently emerged is the possibility of merging the two worlds in what is called ElectroPhotoChemistry (EPC). In particular, this review will focus on the most recent contributions in the field. The basic principles of EPC will be presented along with a discussion of the published works of the last few years. Electrophotochemical oxidation/reduction reactions will be discussed, including in this section the transformations of a C–H bond to a C–X (X: heteroatom). In the C–H activation chapter the formation of C–C bond, starting from a C–H bond, will be considered. Finally, the miscellaneous chapter includes examples which do not clearly belong to the previous categories.

1. Introduction

Organic chemistry is always looking for new molecules, unprecedented synthetic pathways and innovative methodologies. Indeed, the last two decades have witnessed a tremendous progress in organic electrochemistry and photochemistry as powerful tools to design alternative strategies to the traditional synthesis [1,2]. The possibility of having electrons and photons as “controllable” reagents has opened the path to new routes. At the same time, the research of new catalysts, chromophores and electrode materials have also led the chemistry into a research golden age. However, as expected, the continuous growth of these two fields has brought to light some issues and limitations. Therefore, it is necessary to evaluate new approaches to overcome the problems. One of these strategies consists of merging electrochemistry and photochemistry in catalytic reactions: ElectroPhotoChemical Catalysis (EPCC).

Recently, two interesting perspectives by Ahmed and co-workers [3] and Lambert and co-workers [4] have been published, as well as a highlight by Ravelli and co-workers in 2019 [5]. As reviews, the work by Koning and co-workers [6] and, more recently, by Barham and co-workers [7] have to be mentioned as milestones contributions in the

field. Another recent publication by Lin and co-workers refers to the application of cyclovoltammetry in EPCC [8].

This review will summarise the works on EPCC of the last few years, starting with a brief introduction to the basic principles of EPCC, followed by a presentation focused on the discussion of the most significant results published in the last five years.

1.1. Electrophotochemical catalysed redox reactions

Moutet and Reverdy, in 1979, were the first authors to apply the concept of EPCC [9]. The paper shows that a radical generated in electrochemical conditions can become a high-potential photocatalyst. Indeed, by electrochemical oxidation, the authors gained access to the phenothiazine (PTZ) radical cation that can absorb light in the region between 375 and 550 nm (Fig. 1). The excited state has a calculated $E^*_{1/2} = 2.27$ V vs Ag/Ag⁺, much stronger than the $E_{1/2}$ of PTZ = 0.27 V vs Ag/Ag⁺.

The new photocatalytic species allows for the dimerisation of 1,1-diphenylethylene. To reconfirm the EPCC approach, tests conducted in the dark did not lead to any product. Some years later, using N, N, N', N'-tetraphenyl-*p*-phenylenediamine (TPPD) cation as a redox agent in

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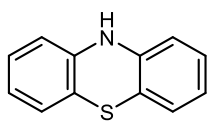
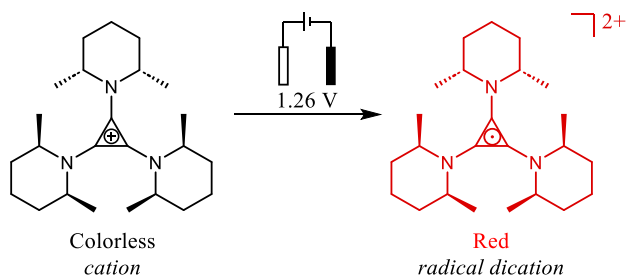
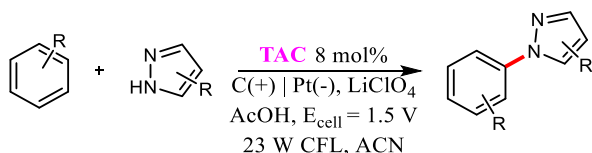


Fig. 1. Phenothiazine structure.



Scheme 1. Synthesis of the TAC radical dication.



Scheme 2. Optimised conditions for the benzene coupling.

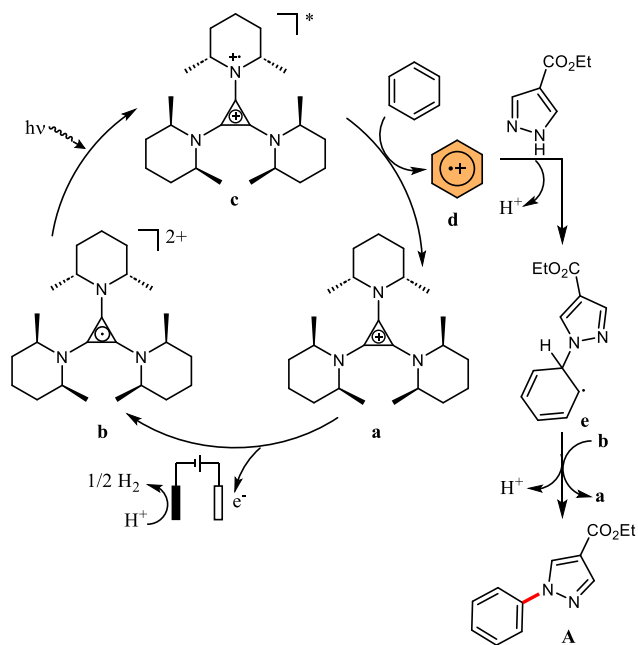
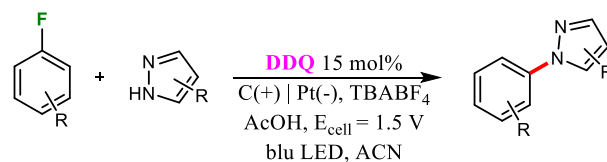


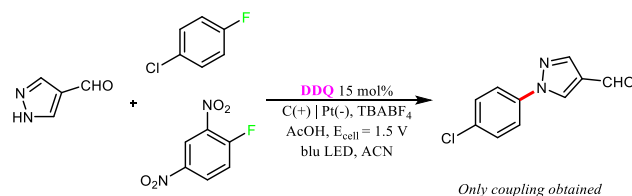
Fig. 2. Catalytic cycle proposed by Lambert and co-workers.

EPCC condition, the same authors could oxidise benzyl alcohol to benzaldehyde [10]. Other pioneering works were the ones of Carlsson and co-workers in the photochemistry of radical ions [11], Scheffold and co-workers with vitamin B12 [11], and Rusling and co-workers on the reduction of chloro-biphenyl [12].

After those seminal contribution, no other works in organic chemistry were published for almost forty years. Indeed, EPCC has always been known mainly as a methodology for wastewater treatment [13,14].



Scheme 3. Reaction condition for the SnAr.



Scheme 4. Example of chemoselectivity.

However, in 2013, Bandar and Lambert's attention was captured by the trisaminocyclopropenium (TAC) ion and by its ability to be reversibly oxidised in its stable form [15]. Back in the '70s, Yoshida had already demonstrated that this radical dication could be easily generated by electrochemical oxidation from the corresponding cation (Scheme 1) [16].

The calculated potential of the TAC photoexcited state is 3.33 V vs SCE, high enough to give access to challenges substrates such as benzene. Lambert and co-workers decided then to investigate its oxidative coupling. With a redox potential of 2.5 V vs SCE, benzene activation by photochemistry [17–20] and electrochemistry [21,22] is troublesome. However, with a fixed potential at 1.5 V and the appropriate light source (23 W CFL), benzene and derivatives have been coupled with N-heteroarenes, as depicted in Scheme 2 [23].

Derivatives endowed with EWG/EDG groups have been studied for the reaction scope, as well as triazole and a variety of substitute N-heteroarenes, the products being obtained in yields ranging between 30 % and 87 %.

The mechanism in Fig. 2 starts with the electrochemical oxidation of the monocationic species a, that evolves to the radical dicationic species b. Photoexcitation generates the active species c that will oxidise the aromatic ring by SET, forming the phenyl radical cation d that is then trapped by the N-heteroarene, followed by deprotonation. The radical e can now be easily oxidised by b or directly at the anode, generating the desired product A.

In addition to the mechanistic hypothesis, the authors also performed TD-DFT calculations on species e, suggesting an inversion between the HOMO and SOMO after photoexcitation, thus explaining the high oxidising potential of the catalyst. The group of Xu published an extension of these studies in 2021 using an acridinium salt [24,25], while Barham et al. by employing triphenylamine derivatives were able to expand the reaction scope toward more challenging substrates [26].

The year after, Lambert and co-workers published a new paper in which the nucleophilic aromatic substitution occurs on the carbon bearing the fluorine atom [27]. During the investigation, they noticed that an aromatic ring bearing an EWG and a fluorine atom did not afford the expected product of a C/N cross-coupling with heteroaromatics. Instead, an *ipso* substitution of the fluoride was observed. Optimisation of the reaction identified DDQ as the best catalyst, Schemes 3 and 4, with an excited state reduction potential, $E_{1/2}^* = 3.18$ vs SCE [28].

The protocol is relatively robust, allowing a broad scope of substrates with yields between 30 % and 90 %, and is also compatible with O-nucleophiles, even if lower yields are typically observed.

In this case, the DDQ radical anion obtained after oxidation of the fluoroarene cannot reduce the radical obtained after the coupling between the starting material as TAC in Fig. 2. Instead, the reduction

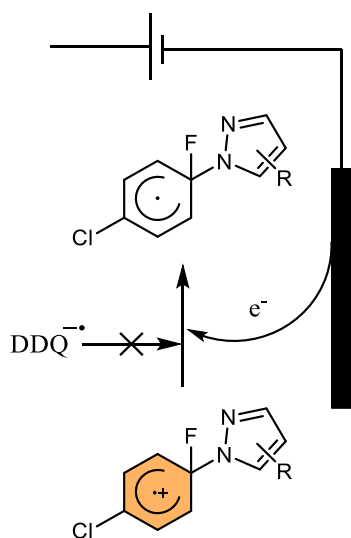


Fig. 3. Cathode-mediated reduction.

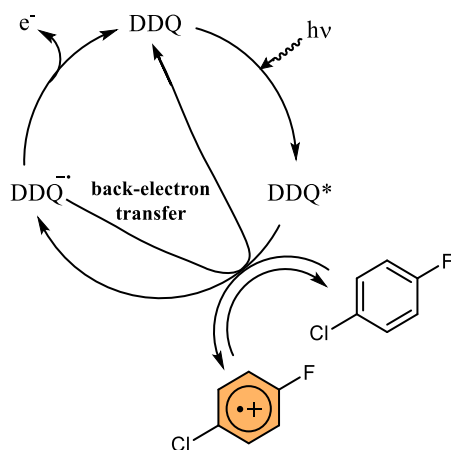
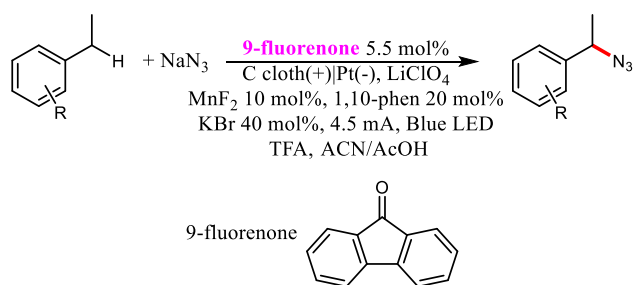


Fig. 4. Back-electron transfer mechanism.



Scheme 5. C-H azidation protocol.

happened at the cathode surface, as depicted in Fig. 3.

According to Lambert and co-workers, chemoselectivity is to be attributed to the mechanism. Indeed, by reacting a 1:1 mixture of 1-chloro-4-fluorobenzene and 1-fluoro-2,4-dinitrobenzene, only the chloro derivative reacts, while the nitro derivative remains unreacted.

The same result was observed with a mixture of 1-chloro-4-fluorobenzene and 4-fluoroanisole, where the latter did not react. To explain chemoselectivity, the oxidation potential difference and the Back-

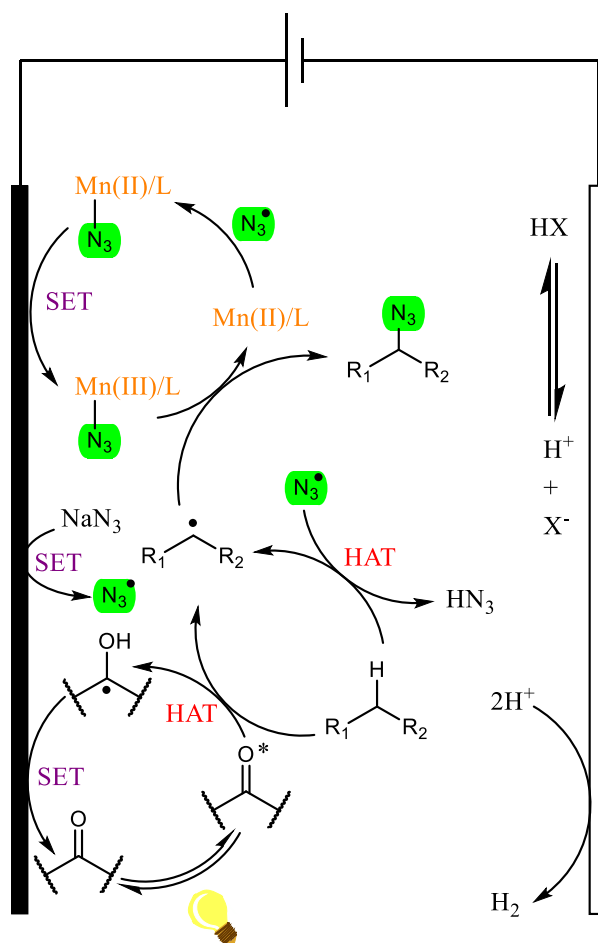


Fig. 5. Azidation proposed mechanism.

Electron Transfer (BET) process on the DDQ have been invoked (Fig. 4). If the oxidation of the fluoroarene is easily obtained in the reaction conditions, the BET results to be also extremely rapid, becoming competitive.

In 2021, Lambert and co-workers could directly C-H heterofunctionalise arenes with a slight change in the reaction conditions [29].

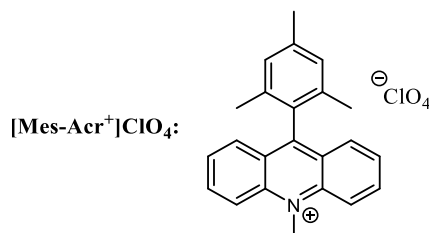
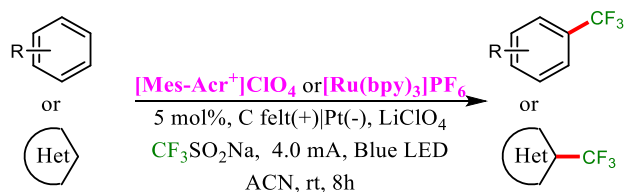
Lei and co-workers in 2020 proposed a new azidation protocol [30].

This methodology allows the azidation of a vast library of alkyl derivatives; primary, secondary and tertiary CH successfully react in the depicted condition (Scheme 5). Moreover, a good functional group tolerance has been observed.

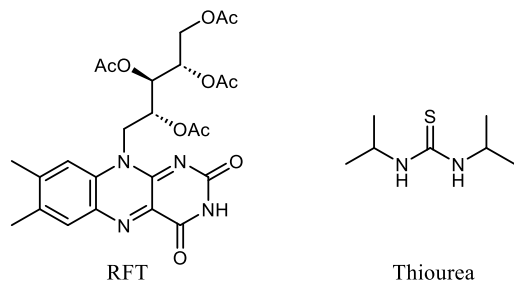
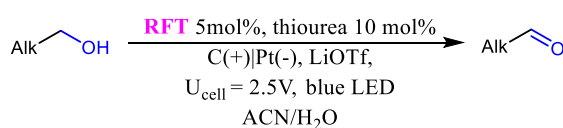
As regards the mechanism, investigations by CV, EPR and UV-Vis spectroscopy have been performed, and the results can be summarised as follows.

a) EPR studies confirm the presence of both the carbon radical and the N_3 radical; b) sodium azide has the lowest oxidation potential, therefore, it will be easily transformed in the radical species; c) in the dark the reaction still works but with a low rate, claiming for the role of HAT for the azido radical and the impact of the photocatalysis on this step; d) an increase of the Mn(II) catalytic loading decreases the reaction rate; this can be associated to the formation of an $Mn(II)N_3$ complex, fundamental for the delivering of the azido group on the alkyl moiety. However, the decreasing rate of the reaction supports the hypothesis of the role of HAT of N_3 . The data merging allowed the proposal of the following mechanism (Fig. 5).

Chemists are well aware of the importance of fluoro-containing compounds, especially for their peculiar biological properties compared to the corresponding hydrogen form [31–35]. In this context,



Scheme 6. EPCC trifluoromethylation.



Scheme 7. Optimised EPCC oxidation condition for inactivated alcohol.

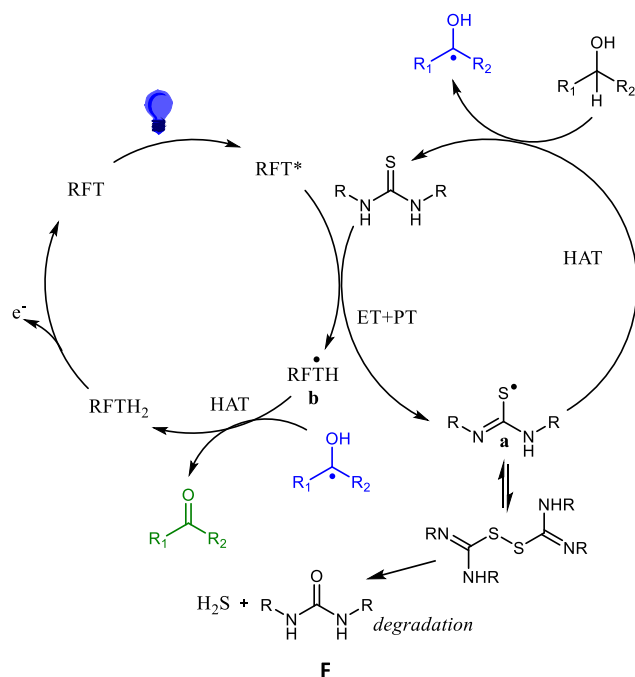
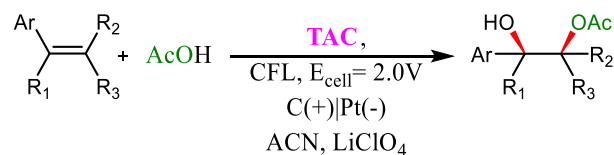


Fig. 6. Proposed mechanism for the alcohol oxidation.



Scheme 8. Electrophotocatalysed acetoxyhydroxylation of olefins.

Ackermann and co-workers published a paper on chemoselective trifluoromethylation by EPCC [36]. Best results have been obtained when acridinium salt, [Mes-Acr⁺]ClO₄ 5 mol% loadings (E*1/2 = 2.06 V vs SCE) [37], as a catalyst, in the presence of LiClO₄, acetonitrile as a solvent and galvanostatic conditions have been used. The CF₃ source of choice was the Langlois reagent, CF₃SO₂Na [37,38], while electrode platinum and graphite felt have been used as cathode and anode, respectively (Scheme 6). They also discovered that [Ru(bpy)₃]PF₆ worked well with only a 2 mol% loading during the optimisation.

Both EWG and EDG substituted arenes and heteroarenes have been used, obtaining a good yield of 50%–80%. To further increase the value of this work, the authors implemented the strategy with flow technologies. The setup consists of an electrochemical flow cell and a transparent coil reactor that will be irradiated by light, with a 76% yield and a 6-min residence time. The particular system setup demonstrates that the reaction works perfectly if the electrochemical and photochemical steps are separated in time and space.

EPCC can be used to update previous syntheses, especially the ones relying on “simple” photocatalysis or electrochemistry. In this regard, Lin and co-workers broadened the range of alcohol oxidation catalysed by flavin derivatives, including the inactivated ones [39]. Flavin is a well-known photocatalyst extensively used in different organic transformations [31]. In particular, riboflavin tetraacetate (RFT, Scheme 7) is an easily accessible oxidising agent with a potential, after photoirradiation, of +1.67 V vs SCE.

The catalytic activity of RFT was improved in the presence of thiourea as a co-catalyst [40]. Through various experiments, Lin's group was able to propose a plausible mechanism (Fig. 6) in which the synergistic interaction between RFT and thiourea has been demonstrated.

Photoexcitation of the riboflavin derivative allows the SET and the proton transfer from the thiourea, generating the radical species **a**. This species, by HAT process, generates the alcohol radical, thanks to another hydrogen atom transfer by the riboflavin **b**, and leads to the desired product. The fine-tuning of the cell potential makes possible to avoid degradation. The protocol works with a plethora of aliphatic alcohols in good to excellent yields, 53–90%.

Olefins are essential building blocks for valuable drug molecules [41]. As a consequence, their functionalisation remains a hot topic in organic chemistry. A few years ago, Lambert reported the acetoxyhydroxylation of aryl olefins by EPCC [42]. As previously mentioned, TAC is the chosen electrophotocatalyst in the presence of AcOH in potentiostatic conditions, as depicted in Scheme 8.

A wide scope has been obtained, including alkene-bearing electron-rich or electron-poor substituents, and mono/di/tri-substituted double bonds could be used without any problem. A decrease in regioselectivity has been observed only in the 1,2-disubstituted derivatives with a ratio of 1:1. Still, not only acetic acid but a variety of carboxylic acids have been employed, obtaining satisfying results. Finally, a multigram scale-up was successfully achieved thanks to the flow chemistry.

The implementation of new C–N bond formation methodologies is another important topic for an organic chemist. Various synthetic pathways on the subject are present in literature, for example, the Hoffmann-Löffler-Freytag reaction [43], the Buchwald-Hartwig [44,45] or the Ritter protocol [46,47].

Thanks to the Lambert group's work, EPCC has also shown potential for the C–H transformation into a C–N bond [48]. To investigate and certify the robustness of their methodology, they decided to work with

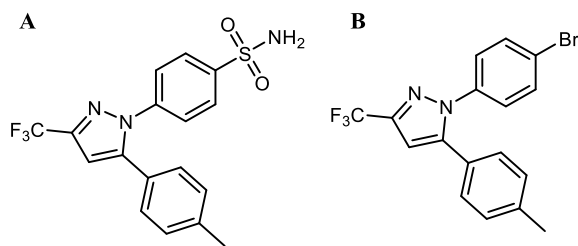
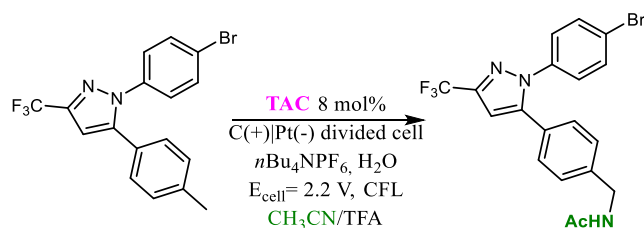
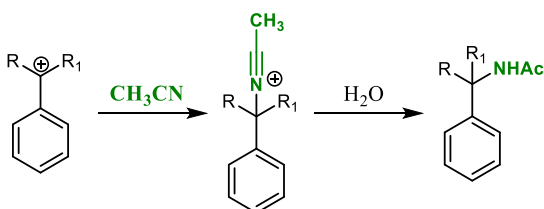


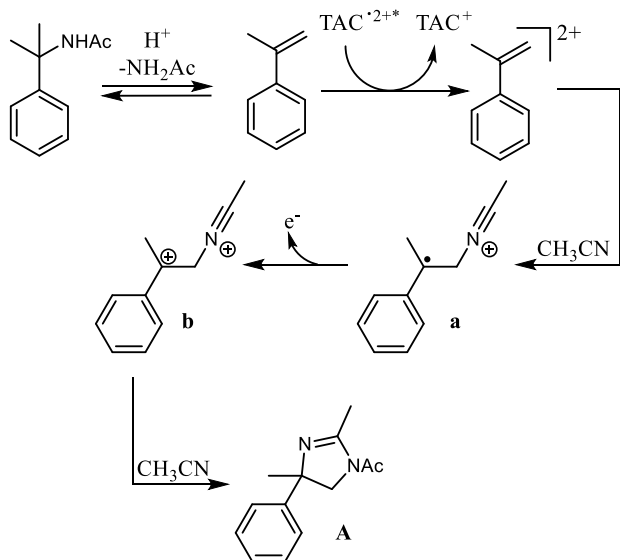
Fig. 7. A) Celecoxib structure B) Analogue used by Lambert's.



Scheme 9. C-H amination conditions.



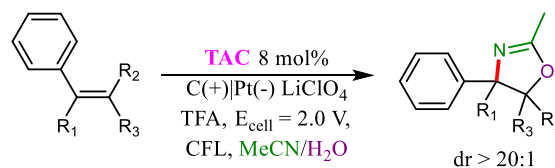
Scheme 10. Mechanism key points.



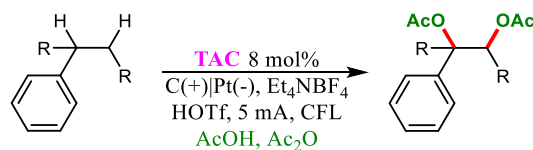
Scheme 11. Mechanism for the diamination of vicinal C-H bond.

an analogue of a complex molecule, celecoxib [49] (Fig. 7), a non-steroidal anti-inflammatory drug.

The C-H amination reaction on the benzylic position was performed in acetonitrile in a divided cell, in potentiostatic condition $E_{\text{cell}} = 2.2$ V vs SCE (Scheme 9). Platinum and graphite electrodes were used respectively as cathode and anode; as the light source, a CFL lamp was



Scheme 12. Aminooxygenation of olefins.



Scheme 13. Multioxygenation reaction of vicinal CH bonds.

used. As in previous papers, the EPCC catalyst is the trisaminocyclopropenium ion.

The possibility of using the solvent acetonitrile as the nitrogen source enhances the methodology value. As for the mechanism, the oxidation of the arene is promoted by the photoexcited TAC radical dication; a proton transfer, followed by formation of the benzyl radical allows its reduction by the oxidised TAC. At this point, the nucleophilic nitrogen can attack the benzylic cation, generating the ammonium moiety. The addition of water leads to the desired product (Scheme 10).

The tolerance of various functional groups was demonstrated, and the methodology could also be applied to complex molecules with yields typically higher than 50%.

The same year, Lambert and co-workers published also an article describing the diamination of vicinal C-H bonds (Scheme 11) [50].

It was suggested that, after obtaining the amide as previously reported, the presence of acid can produce, by elimination, the corresponding styrene. At this point, SET oxidation by TAC excited radical dication and solvent trapping lead to the radical cation **a** [51]. Oxidation generates the dication **b** that is attacked by the solvent again, leading to the desired product **A**.

Among the electrophotochemical oxidations, Lambert's group described the regioselective aminooxygenation of aromatic olefins (Scheme 12) [52].

Similar to the previous reaction, in this case, the water trapping by the oxidised olefin, followed by the solvent's attack, generates the desired product. High chemoselectivity is also obtained. Indeed, if an aryl ring and an aliphatic double bond are present in the substrate, only the aromatic ring one will react. Moreover, urethanes may be used as nucleophiles instead of water. The scope includes a variety of substrates, cyclic alkenes as well as trisubstituted olefins, leading to the products in moderate to high yields. In the same year, Xu and co-workers also published a paper on the C-H amination of arenes [53].

To conclude the section, it must be mentioned that the group of Lambert achieved the multiple oxygenations of adjacent C-H bonds [54]. Different examples of oxygenation reactions are known in literature, mostly limited to the monooxygenation product [55–57]. EPCC demonstrated its potentiality also for that transformation and, by fine conditions tuning, TAC as EPCC catalyst and acetic acid or acetic anhydride as a cheap oxygen source, in the presence of constant current the 1,2-diacetoxy derivative was obtained starting from the alkane (Scheme 13).

This methodology has been verified with many substrates, including unbranched and branched alkanes; heterocycles are also tolerated. A longer aliphatic chain allows the synthesis of tri- and tetra-oxygenated compounds. The scope also includes trifluoroacetamide, obtained with moderate to good yields. Finally, the application of the protocol for the synthesis of highly valuable products has been demonstrated. In

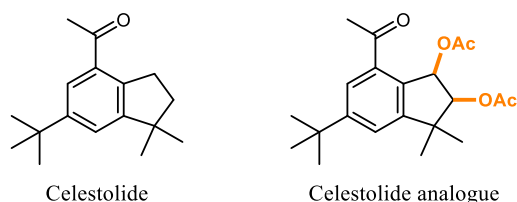


Fig. 8. Celestolide and Celestolide analogue structures.

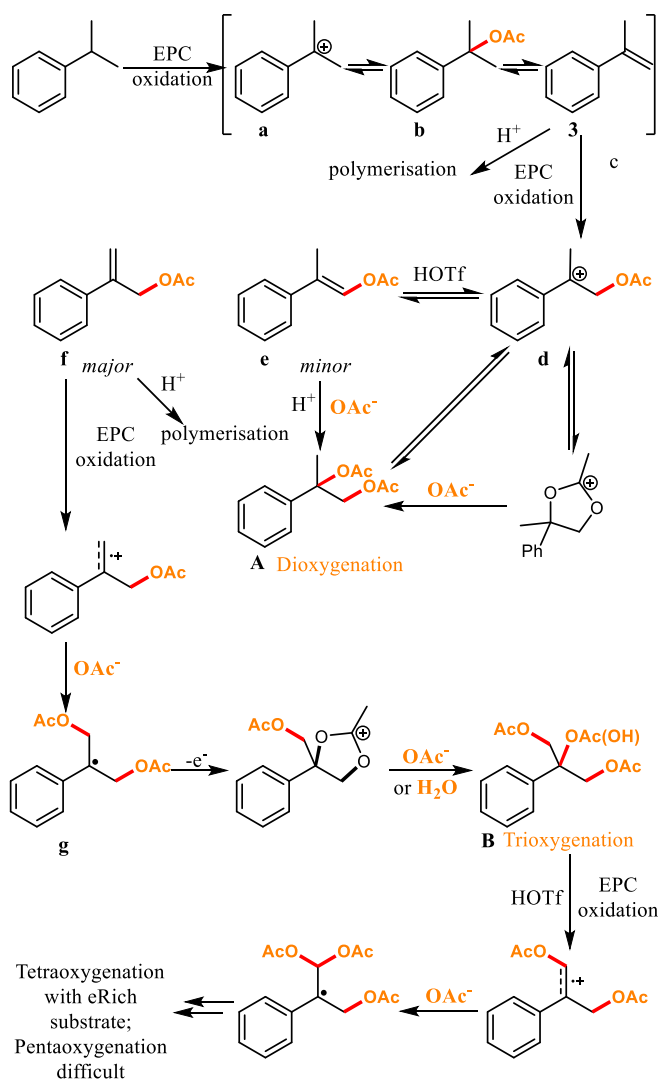


Fig. 9. Proposed mechanism.

particular, the focus has been pointed to the synthesis of an analogue of celestolide [58], a musk fragrance (Fig. 8) and its scaling up.

The mechanism starts with the EPCC oxidation of the substrate to cationic form **a**, in equilibrium, via acetoxy **b**, with the styrene derivative **c** (Fig. 9).

After EPCC oxidation and acetoxy addition, carbocation **d** is formed. In the presence of triflic acid, the two regioisomers **e/f** are generated. Isomer **e** in presence of an acetoxy source can afford the dioxxygenated product **A**. At the same time, **f** can undergo another EPCC oxidation process, followed by nucleophilic trapping from AcO^- generating the dioxxygenated radical **g**. At this point, the triacetoxy derivative **B** can be obtained by electron transfer and nucleophilic attack. Going further, the synthesis of tetraoxygenated and penta-oxygenated derivatives could

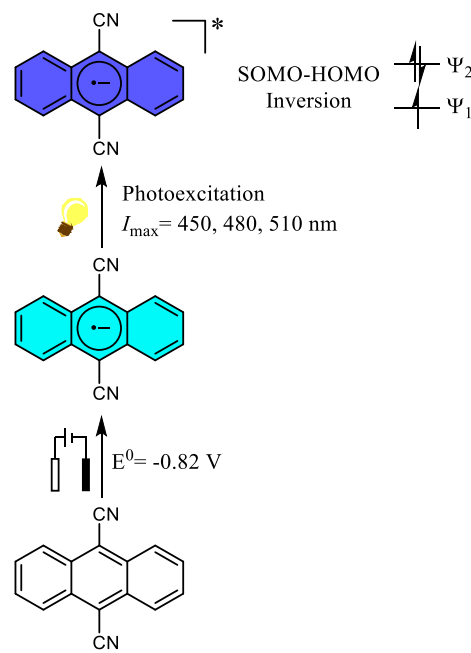
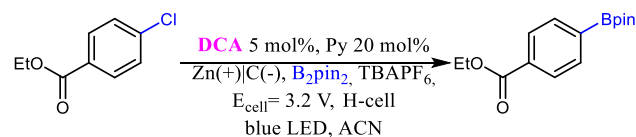


Fig. 10. DCA as EPC catalyst.



Scheme 14. Borylation reaction conditions.

occur but it results to be more difficult. Indeed, only electron-rich substrates can lead to the tetraoxygenated product, while the penta-functionalised derivative remains challenging to observe.

In another approach, the substrates are converted to a reduced form. The principal problem is achieving high reductive potential, usually limited to alkali metals [59], but these reactions are affected by water and moisture, and nitrogen-free manipulation is required in the case of lithium. Functional group compatibility is also an issue. On the other side, it is possible to apply strongly reducing potential in electrochemistry. However, long-time exposure will generate excess active intermediate, leading to overreduction and low selectivity.

König and co-workers used a consecutive photoinduced electron transfer to overcome the obstacles to achieve a strongly reductive radical anion [60]. In 2020, thanks to Lin's and Lambert's group collaboration, exploiting a radical anion instead of a radical cation, it was possible to generate a catalytic species with high reduction potential by photoexcitation. Their investigation started on dicyanoanthracene, which can easily form, by the meaning of electrochemistry, the radical anion ($E_{1/2} = -0.82$ V), which absorbs light in the range of the visible spectrum [61]. TD-DFT calculation suggests that the $\text{DCA}^{\cdot-}$ possesses an $E_{1/2} = -3.2$ V due to a SOMO-HOMO level inversion in the photoexcited state (Fig. 10).

The reaction under consideration for their studies was the reductive functionalisation of aryl halide, which has proved to be a reliable starting material in various synthetic strategies [62,63]. The authors focused on the functionalisation with borylated moieties of aryl chlorides, the less investigated substrates due to their high reduction potential. The standard reaction conditions are depicted in the following Scheme 14.

The robustness of the methodology has been demonstrated by the broad reaction scope, in which the tolerance of different functional

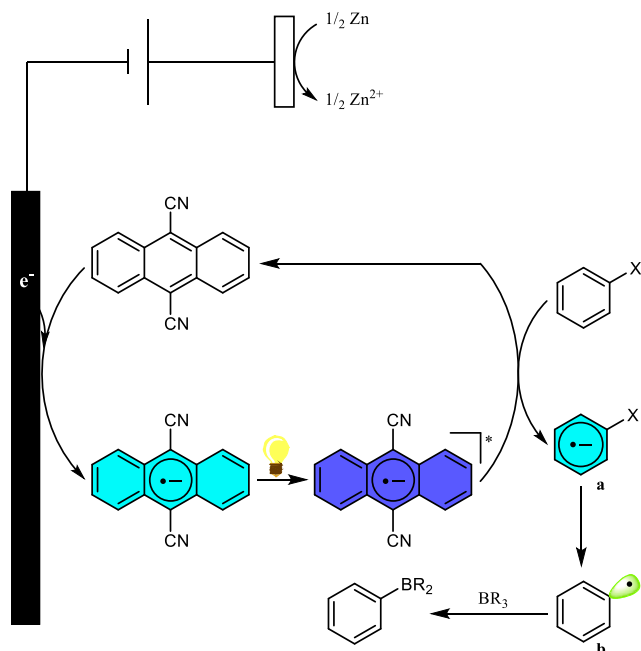


Fig. 11. Proposed mechanism.

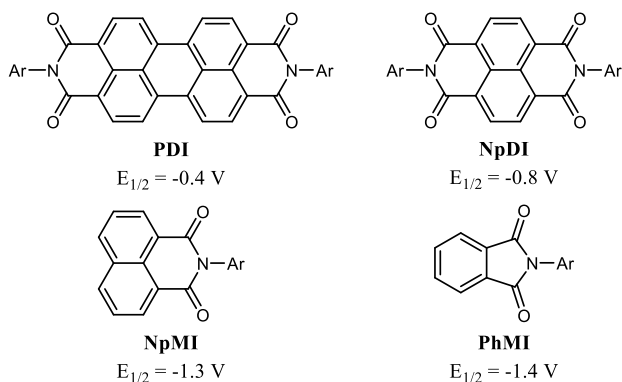


Fig. 12. Imide-based catalyst.

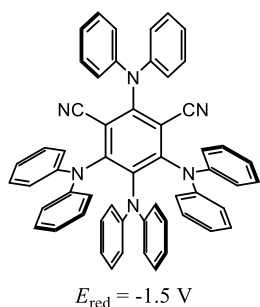
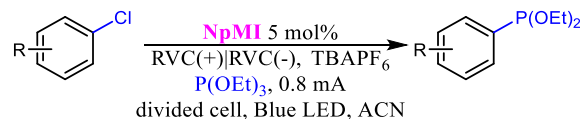
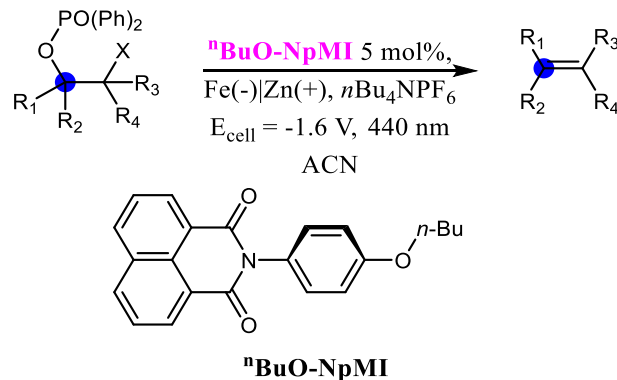


Fig. 13. 4-DPAIPN structure.

groups has been shown. However, in some cases, the yields dropped considerably. The authors explained this behaviour as the result of the competition between Back Electron Transfer and the cleavage of the C–Cl bond. Indeed, when bromine derivatives were used instead of chlorine, the reactivity was restored. The reaction also worked with stannanes and heteroaryls as trapping agents, with yields higher than 60 %.



Scheme 15. Reaction conditions of Wickens's protocol.



Scheme 16. Reductive cleavage protocol.

In the mechanism, the cathodic reduction and photoexcitation of the catalyst produces $\text{DCA}^{\cdot-}$ that, by SET on the aryl halide, generates the intermediate **a** as a radical anion. Cleavage of the C–Cl bond leads to the radical species **b**, which can be easily trapped by the corresponding reaction partner (Fig. 11). The Zn sacrificial anode affords the electron, closing the redox cell cycle.

In 2020, Wickens's group made use of an electron-primed catalyst to reduce challenging compounds [64]. Imide catalyst, as depicted in Fig. 12, by cathodic reduction, becomes an open-shell molecule that can absorb light, gaining access to a photoexcited open-shell state.

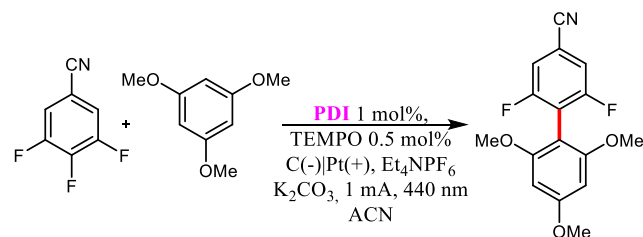
Especially using NpMI, the authors could phosphorylate various aryl chlorides (Scheme 15).

Further investigation on this class of catalysts disclosed new possibilities, as shown in a 2021 paper [65,66]. EPCC reduction allows the cleavage of C–N and C–O bonds. The catalyst used for this transformation belongs to the isophthalonitrile family, specifically the 4-DPAIPN depicted below (see Fig. 13).

After cleavage of the bonds mentioned above, it is possible to trap the radical with phosphorylating, borylating and heteroaryl moieties. The protocol also shows the possibility of exchanging an aniline group with an aliphatic amine, and if phenol is used, meta-substituted products are obtained.

The same year, König and Barham used an imide-based catalyst to further develop the C (sp³)-O reductive cleavage of phosphinated alcohol to the corresponding olefins (Scheme 16) [67].

DFT calculation, EPR studies and spectroscopic electrochemical investigations suggested the formation of an EDA complex followed by intramolecular charge transfer and SET as the reason behind the high selectivity of this reaction. Both cyclic and linear olefins have been



Scheme 17. Electrophotoreduction of aryl fluorides.

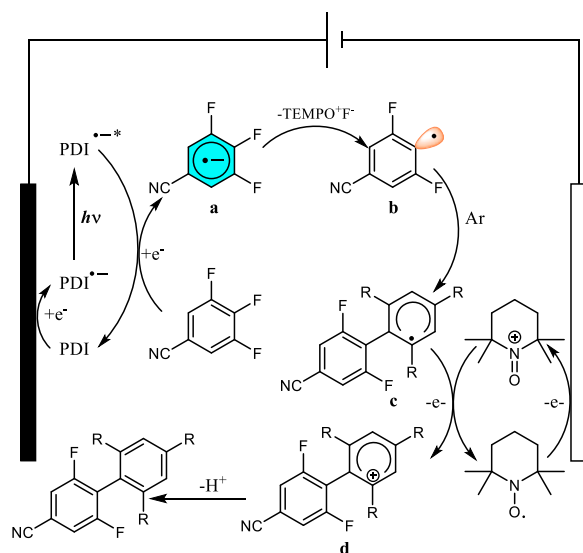
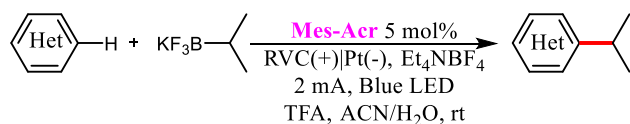


Fig. 14. Proposed mechanism by Wu's group.



Scheme 18. Reaction conditions for the C-H alkylation of heteroarene.

achieved; for the latter, the regioselectivity favoured the E-form. Z-selectivity could be achieved using DCA as the catalyst. The methodology is also specific for C (sp³)-OP bond if C-Halide and C (sp²) are present.

The previous section analysed the EPCC oxidation of aryl fluoride [27] developed by Lambert's group. In 2022, the group of Wu published the EPCC reductive arylation of fluoroarene with a metal-free approach (Scheme 17) [68].

The catalyst of choice was the imide-based PDI (see Fig. 12 for the structure). The reaction worked with a wide assortment of fluoroderivatives. The best results have been obtained with electron-poor substrates, and selectivity toward the cleavage of the C-F bond in para-position has been observed. When 2,3,4,5,6-pentafluoro-1,1'-biphenyl and 2,4-difluorobenzonitrile have been used, competition between ortho and para position has been achieved, with the ratio inversion in favour of the ortho substitution in the cyano derivative.

Radical trapping experiments supported by DFT calculation and KIE suggested the following mechanism.

Cathodic reduction and photoexcitation of PDI allow the SET to the aryl fluoride to generate the corresponding radical anion **a**. At the same time, the anodic oxidation of TEMPO to its cationic form makes easier the defluorination process and the formation of the corresponding aryl radical **b**. Then, the coupling partner can trap **b**, forming the diaryl radical **c**. Thus, SET with TEMPO⁺ generates the more stable diaryl cation **d** and regenerates TEMPO. Deprotonation of **d** leads to the desired product (Fig. 14).

1.2. Electrophotocatalytic C-H activation

In organic chemistry C-H activation remains one of the hottest topics, due to its versatility and the enormous variety of fields of application [58–62]. Not surprisingly, also the growing field of EPCC has studied this particular transformation. This section will focus on redox-neutral C-H functionalisation.

The first example has been published in 2019 by Xu and co-workers

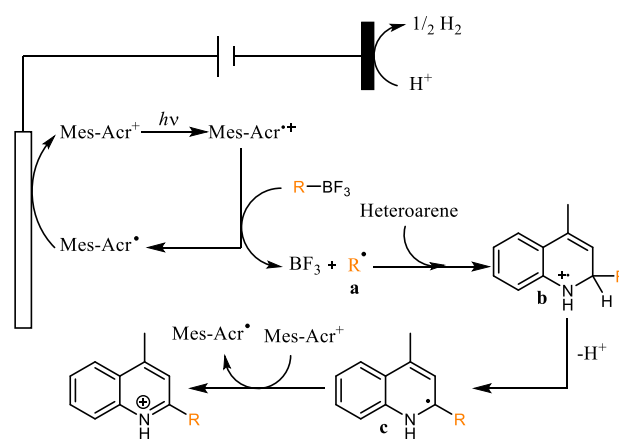


Fig. 15. Proposed mechanism for the EPCC C-H functionalisation.

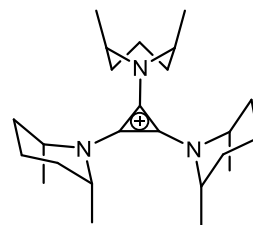
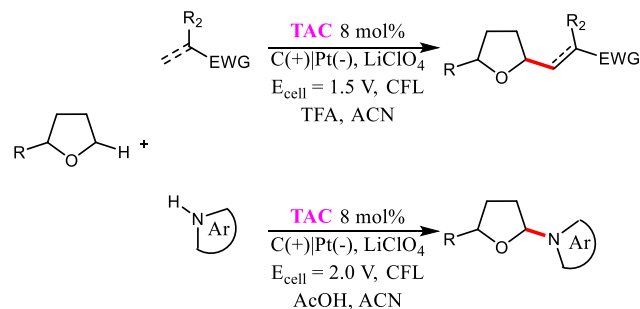


Fig. 16. 3D structure of TAC ion with the methyl groups in axial position.

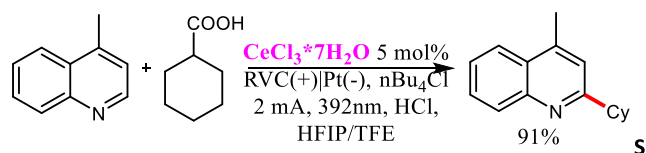


Scheme 19. Reaction conditions for the ether functionalisation.

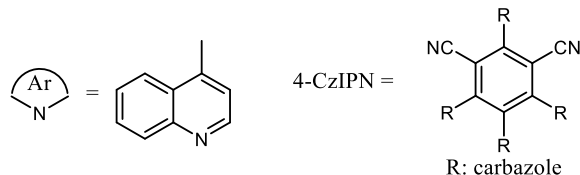
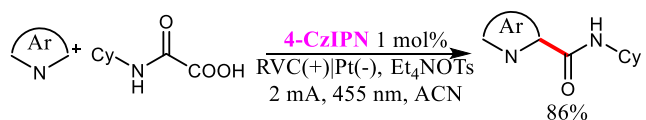
[69]. They performed the C-H alkylation of heteroarene using the stable and readily available organotrifluoroborate as the radical source (Scheme 18) [70], and Mes-Acr ion as catalyst (see Scheme 6 for the structure). The reaction has been tested with various substrates, from quinazoline to phthalazine and from isopropyltrifluoroborate to piperidine boron derivatives, with yields ranging from 50 % to 90 %. An interesting result has been obtained in the experiments in which acrylamide was used. Indeed, the EPCC conditions allowed a two-step reaction of addition-cyclisation leading to the 2-indolinone derivatives.

In the proposed mechanism (Fig. 15), photoexcitation of the catalyst generates the active Mes-Acr radical cation that, by SET, forms the desired alkyl radical, and the Mes-Acr radical is converted in the cationic forms by anodic oxidation. Due to the acidic environment, the protonated heteroarene readily reacts with **a**, forming the radical cation **b**. Deprotonation leads to **c** that, which is quickly reduced by the cationic catalyst form.

Lambert and co-workers were able to functionalise ethers by Minisci-type [71] reaction with high regioselectivity [72]. Previous works suggested the need of a HAT acceptor, such as Selectfluor, to increase the regioselectivity [73]. The authors chose the TAC ion as a catalyst due to



Scheme 20. Decarboxylative alkylation of heteroarene.



Scheme 21. Reaction conditions for carbamoylation.

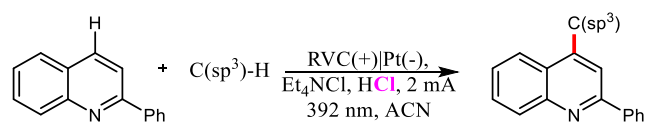
its high reduction potential (3.33 V vs SCE) and capacity to activate low reactive arenes. Calculations demonstrated that the aminyl character of the nitrogen can serve as a HAT acceptor when the catalyst is in its distonic form. In addition, the sensitivity of H transfer to steric hindrance is quite known [68], making TAC an even more suitable catalyst due to the hindrance generated by the methyl groups (Fig. 16).

Tetrahydrofuran is the principal ether used in this study as the partner of deactivated alkene, alkyne or heteroarene (Scheme 19).

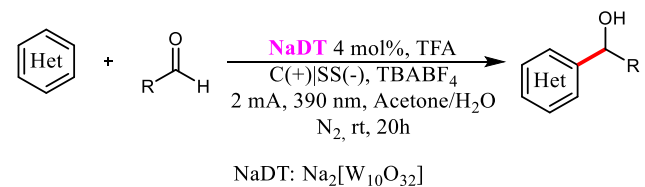
To summarise, the protocols envisioned by Lambert and co-workers offered an easy access to substituted ethers in moderate to excellent yields. The use of asymmetric ethers such as CpOMe or CyOMe surprisingly gave the product on the less hindered carbon instead of the C1 as in the other examples. Moreover, while the C–C coupling proceeds via a “common” EPCC cycle, with the electrophotoexcited TAC generating the alkyl radical by the HAT process, the picture is different when a C–N bond is to be formed. A second mechanism was hypothesised, but not proved, where the oxocarbenium is formed due to a SET after the HAT process. Moreover, the intrinsic steric hindrance of the TAC ion allows the achievement of high regioselectivity toward the radical formation position.

To upgrade further this new synthetic field, it has also been necessary to expand the carbon radicals' source, other than using different substrates. Decarboxylative C–H functionalisation has already been used for synthesising complex molecules [74–77]; however, metal catalysis or oxidants are necessary. Ackerman [78] and Li [79] reported two oxidant-free reactions using Ir and Co. Nevertheless, few carboxylic acids are compatible with the reaction conditions. Xu and co-workers decided to use aliphatic carboxylic acid as radical precursors [80,81]. The new radical source needed an adjustment of the reaction conditions compared to the boron derivatives. Indeed, a basic environment is necessary compared to the acidic one applied up to now. After optimisation, the best EPCC catalyst resulted to be $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ in the presence, unexpectedly, of HCl; RVC as anode and Pt as the cathode in galvanostatic conditions, with light irradiation centred at 392 nm have been used (Scheme 20).

The protocol here reported can tolerate a wide variety of aliphatic carboxylic acids bearing different functional groups such as unsaturated chains, ketone, etc. The methodology also works in the presence of complexes heteroarene skeleton. For example, a 62 % yield is achieved when voriconazole is used. Their successful alkylations have been applied in the decarboxylative carbamoylation using oxamic acid. Instead of a cerium (III) catalyst, 4-CzIPN was used (Scheme 21).



Scheme 22. Reaction condition for alkylation by alkane activation.



Scheme 23. EPCC hydroxyalkylation protocol.

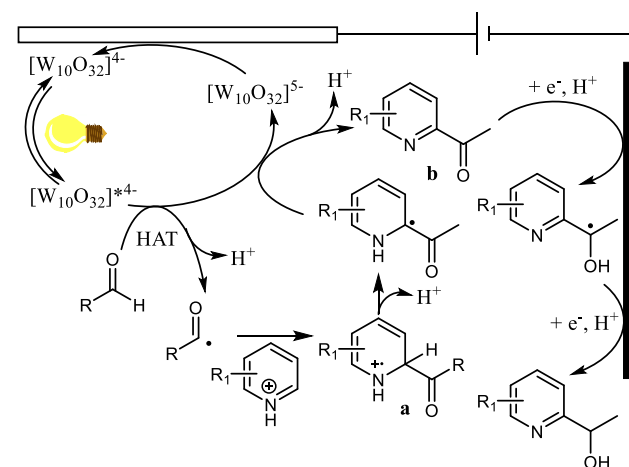
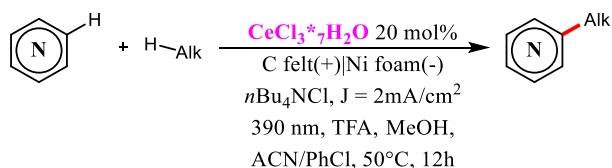


Fig. 17. Proposed mechanism for the hydroxyalkylation of heteroarene.

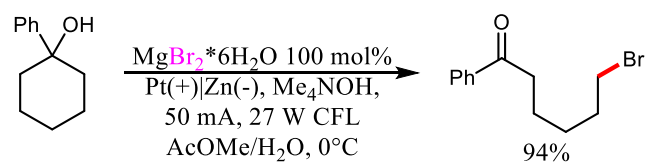
The scope has been repeated with the oxamic acid derivatives, and good results have been obtained. The difference between the two protocols is also reflected in the mechanism, particularly in the radical generation process. Ce(III), after anodic oxidation at Ce(IV), coordinates the carboxylic acid. At this point, photoexcitation generates the carboxyl radical that quickly undergoes decarboxylation with the consequent formation of the carbon-centred radical that the heteroarene partner traps. Deprotonation and reduction by the Ce(IV) leads to the desired product. 4-CzIPN, after photoexcitation, can reduce the carboxylate anion to the corresponding radical that once again undergoes decarboxylation. After radical trapping, two different pathways are possible: reduction by the 4-CzIPN in its distonic anion form, leading to the final product's protonated form, which will experience double SET transfer at the anode. In the other case, deprotonation generates the corresponding radical that oxidises the catalyst in its ground state. Further investigations suggested that the first path is favoured.

Alkanes are trivial compounds in organic chemistry due to their usual inertness toward most chemical reactions. A harsh environment, like alkali metals, metal complexes, etc., is required for their activations. However, Xu's group developed an EPCC protocol in which a C(sp³)-H donor is sufficient as the radical precursor (Scheme 22) [82].

Activation of the alkyl bond has been ascribed to the presence of chlororadical derived by the photoactivation of chlorine (0), obtained from the anodic oxidation of chloride. Controlled Cl₂ generation in small quantities results in a less dangerous reaction, as well as the decrease of side-products like alkyl chloride. The methodology can tolerate various functional groups on the alkyl chain and different heteroarene. An improvement of this methodology was reported by Ravelli and co-



Scheme 24. C–H functionalisation conditions with unactivated alkanes.



Scheme 25. Ring-opening bromination reaction conditions.

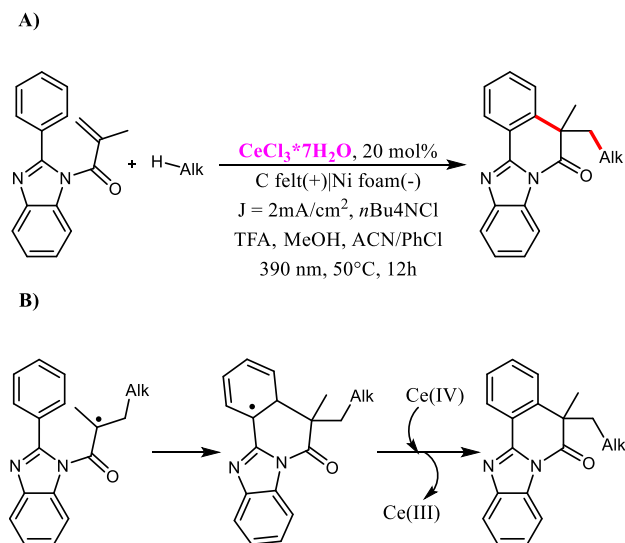


Fig. 18. a) reaction condition; b) highlight of the proposed mechanism.

workers in 2021 [83].

Until now, the C–H functionalisation has been “limited” to alkylation, amination and alkenylation. Liu’s group, however, was able to disclose an EPCC pathway in which C–H hydroxyalkylation of heteroarene is achieved (Scheme 23) [84].

The photoexcited form of the decatungstate with an $E_{red} = +2.44$ vs SCE can generate, by hydrogen atom transfer, the carbonyl radical that is then easily trapped by the cationic form of the heteroarene, acidic environment, forming the corresponding radical **a**. The intermediate, after deprotonation, is oxidised by the photoexcited catalyst, giving the corresponding ketone **b**. Sequential double reduction at the cathode leads to the final secondary alcohol (Fig. 17).

Besides N-heteroarenes, benzothiazoles and quinolines have been successfully reacted following the experimental protocol. Aldehydes, both aromatic and aliphatic, have been tested with good results.

Analogously to the work of Xu and co-workers [82], Zheng’s group published an article where N-heteroarene functionalisation with unactivated alkanes has been achieved (Scheme 24) [85].

Various N-containing arenes and alkanes have been used, pinpointing a good tolerance toward different functional groups. The postulated mechanism starts with the anodic oxidation of Ce(III) to Ce(IV), thus facilitating the coordination of methanol. Photoexcitation of the complex induces a ligand-to-metal charge transfer, with the consecutive generation of the methoxy radical and the Ce(III) catalyst. The HAT process leads to the alkyl radical that the N-heteroarene traps. The cationic radical formed can be oxidised at the anode, leading to the desired product. The redox cycle is closed by hydrogen formation at the cathode. Zeng’s and co-workers used the same protocol to synthesise alkylated benzimidazole-fused isoquinolines (Fig. 18) [86].

In an extension of this work, the synthesis of benzimidazole-fused isoquinolines by Si–H functionalisation has been described [87]. The authors considered the polarity-matching effect the driving force for the high chemoselectivity [88]. Indeed, the most hydric character of the

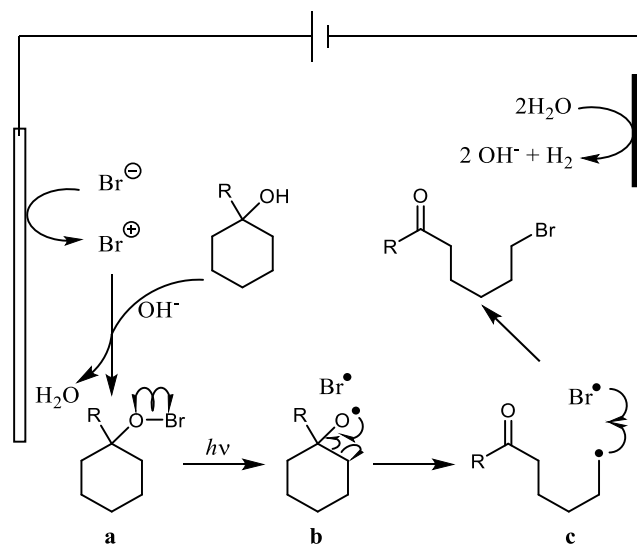
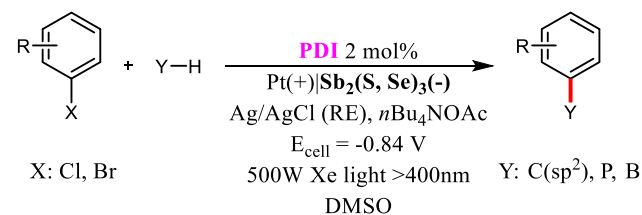


Fig. 19. Proposed mechanism for the ring-opening bromination.



Scheme 26. Aryl halides functionalisation protocol.

hydrogen atom in the Si–H bond promotes the selectivity of the hydrogen atom transfer step.

1.2.1. Miscellaneous

In the work of Onomura and co-workers, EPCC allows the ring-opening bromination of cycloalkanol (Scheme 25) [89].

The reaction works nicely with the 5-to-7-member rings and bridged bicyclic compounds.

In the proposed mechanism the formation of the bromonium ion from the anodic oxidation of the bromide anion has been postulated. The alkoxylation will easily attack the cation, generating intermediate **a**. Light irradiation of it will lead to the homolytic rupture of the O–Br bond. Intermediate **b** rearranged in the most stable form **c**, which will be trapped by the bromo-radical, producing the final desired product (Fig. 19).

Lei’s group achieved further developments on the topic in 2022 [90]. Ce(III) has been used as an EPCC catalyst, and the reaction scope has no longer been limited to the bromination reactions. Different functional groups, such as –CN, –SR, Cl, alkynyl, aryl, etc., have been used, achieving excellent results. This methodology allows the use of cyclopropanol and cyclobutanol as starting materials.

Wu and co-workers published a coupled photoelectrochemical/

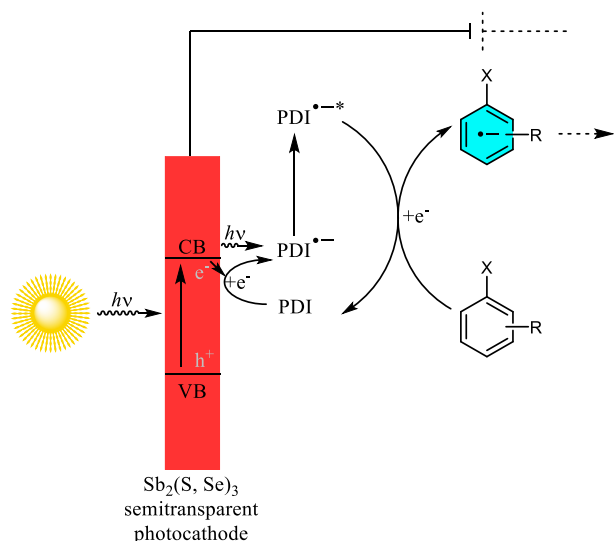
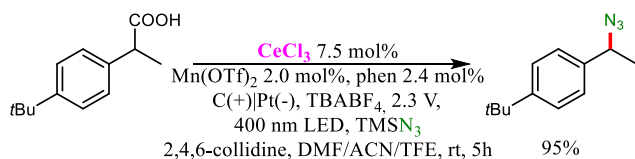


Fig. 20. Highlighting the photocathode role in the mechanism of aryl halide functionalisation.



Scheme 27. Reaction protocol for the decarboxylative azidation.

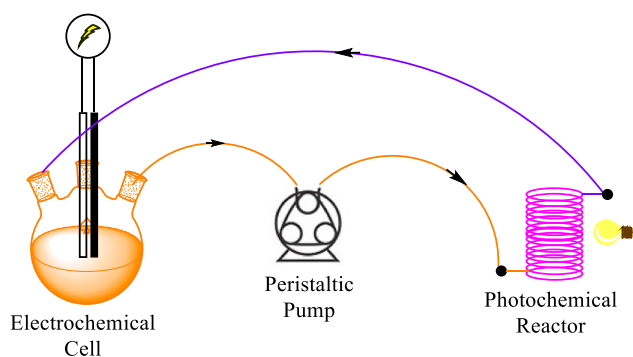


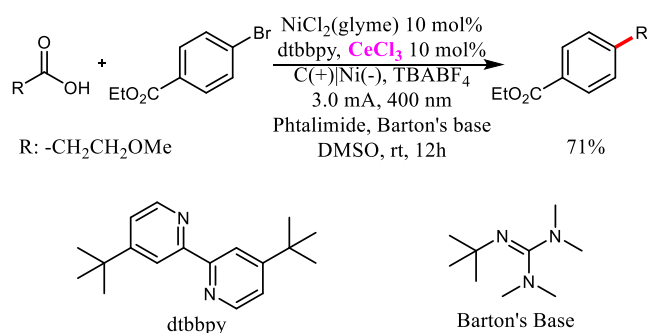
Fig. 21. Schematic hardware placement for the flow reaction.

photochemical reaction where aryl halides can be easily functionalised by different trapping agents using solar energy irradiation (Scheme 26) [91]. The sun is the most abundant source of energy present in our solar system. For this reason, they designed a p-type semiconductor photocathode ($\text{Sb}_2(\text{S}, \text{Se})_3$) that can promote an electron in its excited state once irradiated.

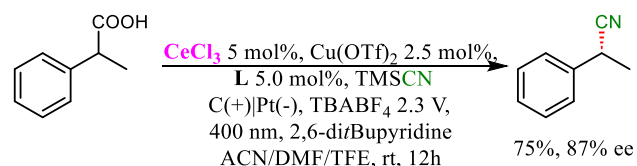
The excited electron can reduce the PDI photocatalyst (for structure, see Fig. 11), generating the corresponding radical anion. Thus, it can be easily photoexcited, achieving an $E_{\text{red}} = -1.86 \text{ V}$ vs SCE, sufficient for substrate reduction (Fig. 20).

The methodology is very effective. Indeed, different aryl/heteroaryl halides, both bromides and chlorides, have been successfully used with a yield range from 30 % to >95 %. In addition, the photocatalyst has been recovered up to 90 %.

Aliphatic carboxylic acids have an essential biological role [92] and are important building blocks for complex molecules [93]; hence, the



Scheme 28. Protocol for the decarboxylative coupling of carboxylic acid.



Scheme 29. Reaction conditions for the enantioselective decarboxylative cyanation.

attention to their synthesis and functionalisation. Fu and co-workers published the decarboxylative azidation of aliphatic carboxylic acid [94]. Their typical reduction potential is around +1.25 V vs SCE, and the authors opted for a Ce-based photocatalyst, assisted by an Mn co-catalyst as an azide donor (Scheme 27).

The mechanism starts with Ce(III) anodic oxidation to Ce(IV). After coordination with the carboxylate moiety and photoirradiation, the reductive decarboxylation is facilitated, with the carbon-centred radical's consequent formation. Meanwhile, the Mn(II) 1,10-phenanthroline complex coordinates the azido group. Anodic oxidation generates the Mn(III) active species that easily interact and trap the radical coming from the cerium cycle. Transmetalation of the N_3 group followed by oxidation by Mn(III), generates the corresponding product and regenerates the Mn(II) catalyst. The reaction has also been performed in flow conditions, as depicted in Fig. 21.

The flow experiment also highlights how it is not necessary that the two steps, electrochemical and photochemical, happen at the same time. Indeed, the radical is stable enough to be transported on the coil photoreactor.

Fu's group also published another article on the decarboxylative coupling of aliphatic carboxylic acids [95]. In this case, the synergy between two metal catalysts is necessary to afford the desired product, and Ce(III) was selected, in combination with Ni(II) catalyst, responsible of the coupling step (Scheme 28).

Other additives were necessary compared to the previous protocol (Scheme 26). Indeed, phthalimide suppresses the formation of by-products as the aryl bromide homocoupling and the protodehalogenation; Barton's base enhances the product yield. The reaction scope is wide and demonstrates the versatility of the method toward a considerable variety of substrates.

Finally, an enantioselective decarboxylation method has been recently published [96]. Once again, the combination of Ce(III) and another metallic catalyst, Cu(II), is the key to perform the

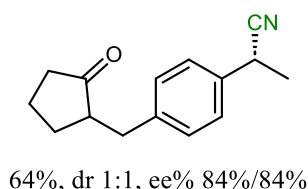


Fig. 22. Enantioselective decarboxylative cyanation from loxoprofen.

decarboxylative cyanation, while the addition of a chiral ligand allowed the control of the enantioselectivity of the reaction (Scheme 29).

Good to excellent enantiomeric excesses, up to 92 %, have been obtained. Although the scope has been “limited” to phenylacetic acid derivatives, various substituents are tolerated, and compounds like loxoprofen (Fig. 22) could be reacted without problems, achieving excellent yield and good enantiomeric excess.

The mechanism is comparable to the one aforementioned in the last articles. The key point is the stereocontrol generated from the chiral ligand coordinated to the Cu atom.

2. Conclusion

In the last decades, especially in the past ten years, EPCC has been increasingly applied to overcome issues in standard synthetic methodologies.

Its application spreads in the most diverse fields, leading to excellent and surprising results and opening new and unforeseen pathways for the synthesis of functionalised molecules. Noteworthy, different companies showed an increasing interest in the area. They contributed to creating appropriate devices to standardise and facilitate the reaction setup and help discover new EPCC synthetic protocols [97].

CRediT authorship contribution statement

F. Medici: Conceptualization, Writing - original draft, Writing - review & editing. **V. Chirolì:** Data curation, Writing - review & editing. **L. Raimondi:** Formal analysis, Writing - review & editing. **M. Benaglia:** Conceptualization, Supervision, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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