HIGHLIGHT

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Merging photochemistry with electrochemistry in organic synthesis†

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Photochemistry and electrochemistry are two powerful tools in organic synthesis as reflected by the recent resurgence of both research areas. Despite the impressive advances achieved so far, both synthetic technologies suffer from innate disadvantages. The constructive merging of photochemistry and electrochemistry, therefore, offers the potential to overcome the distinct flaws of one method through the advantages of the other, so that novel reaction pathways that are unachievable with individual methods can be envisioned. This Highlight article describes recent breakthroughs using this promising concept of merging photochemistry with electrochemistry in organic synthesis.

The recent resurgence of photoredox catalysis[1] and synthetic electrochemistry[2] has changed the landscape of modern organic synthesis tremendously, by bringing forth a multitude of innovative chemical transformations previously thought to be impossible. Both research areas share the common feature of using electrons as reagents to generate open-shell radical intermediates, and thus many transformations have translated from photoredox catalysis to electrochemistry and *vice versa*. Photoredox catalysis can take advantage of its redox-neutral nature to facilitate net-redox-neutral transformations. However, such a characteristic inevitably requires a stoichiometric amount of oxidant/reductant with each turnover of the photocatalyst in the net-oxidative/reductive transformation. This flaw is not seen in green electrochemical synthesis because oxidation and reduction occur simultaneously on the anode and cathode, respectively. On the other hand, radicals that are electrochemically generated in direct electrolysis may easily undergo undesirable over-reduction/oxidation, radical homocoupling and electrode passivation due to inefficient mass transfer at the interface of the electrode surface and bulk solution. Redox mediators, that shift the electron transfer step from a heterogeneous process at an electrode to a homogeneous process, circumvent these drawbacks of direct electrochemical synthesis.[3]

Though photoredox catalysis and electrochemistry share the common feature of radical intermediate generation and thus are often mentioned together and compared alongside one another, little attention has been paid to the concept of merging photochemistry with electrochemistry in organic synthesis.[4] The adoption of photochemistry and electrochemistry in organic synthesis has been known since the 1980s (*vide infra*) but the development in this field has been slow. The recent renaissance in photocatalysis and electrocatalysis has led synthetic chemists to reconsider this approach in organic synthesis. The constructive merging of photochemistry with electrochemistry can create a scenario in which each techniques' flaws can be perfectly compensated for by their respective advantages, thus making possible novel reaction pathways which are unachievable with individual methods (Scheme 1).

The adoption of this emerging but highly promising strategy using photoelectrochemical cells (PECs) and photoelectrochemical catalyst-mediated electrolysis in organic synthesis is
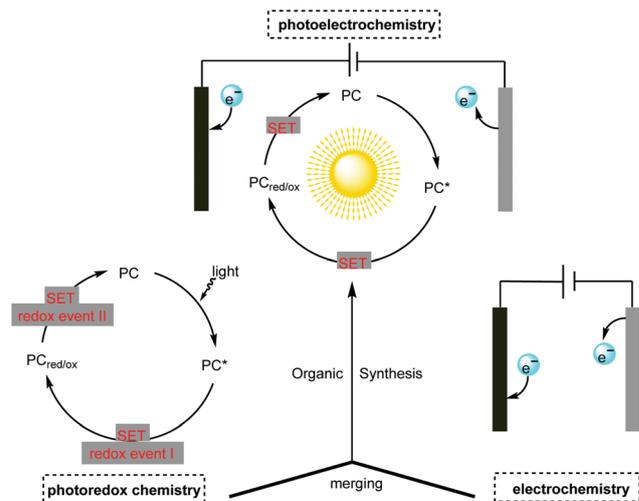
Scheme 1 Concept of merging photochemistry with electrochemistry in organic synthesis, PC = photocatalyst, SET = single-electron transfer.

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still in its infancy. However, recent breakthroughs suggest that it is a very promising technique well suited to the continuous pursuit of greener and more sustainable organic synthesis. Herein, we highlight recent advances in organic synthesis featuring the creative adoption of this emerging concept. We also cover the fundamental aspects, reaction scopes and mechanisms of the integration of photochemistry with electrochemistry in organic synthesis.

One salient feature of electrochemistry, as discussed previously, is the replacement of the chemical oxidant/reductant in the net-oxidative/reductive photochemistry process with a traceless electron "reagent". Minisci alkylation[5] of heteroarenes with photoredox catalysis generally requires a stoichiometric amount of oxidizing reagent such as a peroxydisulfate salt ($S_2O_8^{2-}$) or hypervalent iodine. Replacing those oxidants with reagent-free electrochemistry as demonstrated by Xu and co-workers[6] provided a multitude of functionalized heteroarenes using primary, secondary and tertiary alkyltrifluoroborates (or 1,4-dihydropyridine) with excellent regio- and chemoselectivity (Scheme 2). Various heteroarenes (substituted quinolines, isoquinoline, acridine, benzothioazole, imidazo[1,2-b]pyridazine and purine) as well as some bioactive compounds such as voriconazole, camptothecin, fasudil and quinine were all well tolerated.

With respect to the mechanism, the photoelectrochemical redox catalyst [Mes-Acr$^+$]ClO$_4^-$ **1** is initially irradiated (with blue LEDs) to its highly oxidizing excited state **2** (E^{red} = 2.06 V $vs.$ SCE in MeCN). This undergoes a single-electron transfer (SET) with the organotrifluoroborate leading to the acridinyl radical **3** and an alkyl radical. Regeneration of the organic dye [Mes-Acr$^+$]ClO$_4^-$ **1** takes place at the anode via another SET with the stable radical **3**. The alkyl radical, on the other hand, proceeds via a typical Minisci-type radical addition to the protonated heteroarene. The short lifetime of radical cation **4**
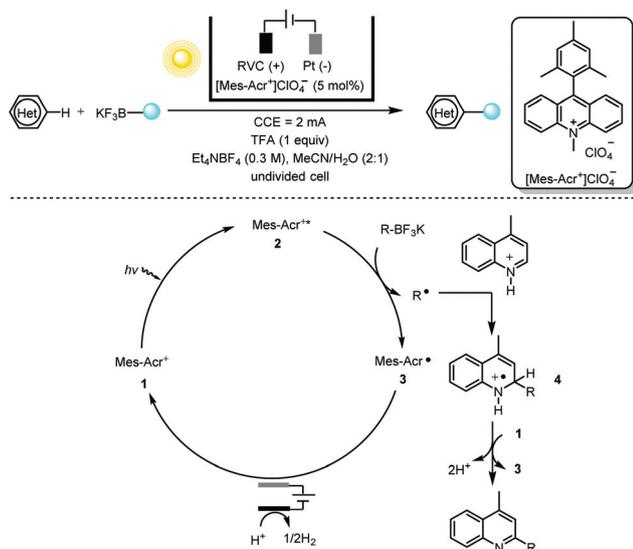
suggests that it is oxidized by the ground state of [Mes-Acr$^+$] ClO$_4^-$ ($E_{p/2}^{red}$ = −0.57 V $vs.$ SCE in MeCN) rather than at the anode. This creative merger of photochemistry and electrochemistry using the photoelectrochemical redox catalyst [Mes-Acr$^+$]ClO$_4^-$ not only obviates the need for a chemical oxidant but also overcomes the drawback of over-oxidation of electrochemically generated electron-rich alkyl radicals.

Alcohol oxidation using riboflavin photocatalysts has been extensively investigated in past decades.[7] However, this catalytic method is limited to benzylic alcohols, as aliphatic alcohols are generally not applicable. To address this challenge, Lin and co-workers carried out an extensive mechanistic study of flavin-catalyzed alcohol oxidation using a thiourea co-catalyst (Scheme 3).[8] They found that the major decomposition pathway of thiourea during the canonical flavin/thiourea co-catalysis under an O_2 atmosphere involved the formation of thiourea dioxide. With this key mechanistic understanding in mind, they creatively used electricity to replace O_2 in the photocatalytic oxidation of alcohols to circumvent the problem of thiourea degradation. The photochemical oxidation of alcohols by flavin alone relies heavily on the oxidation potential of the flavin excited state, and thus only activated alcohols could be used. In contrast, the thiourea-mediated photoelectrochemical flavin catalysis takes advantage of the HAT (hydrogen atom transfer) of thiourea-based radicals generated by means of flavin oxidation, and so previously untouched aliphatic alcohols could be oxidized using this novel photoelectrochemical protocol.

The energy-transfer relay of electrochemistry and photochemistry is capable of generating much more potent catalysts than can be obtained using either photochemistry or electrochemistry alone. The direct C–H amination reaction constitutes a straightforward route to important organic compounds bearing an aryl C–N moiety; these are prevalent in pharmaceuticals, agrochemicals and natural products. Typical synthetic methods for these targets require the substrate to bear a
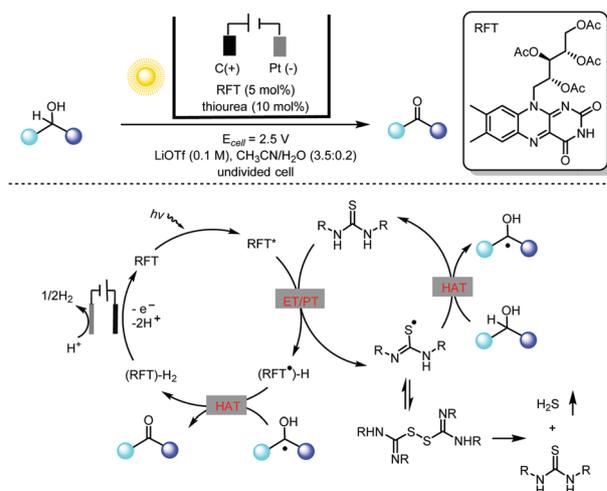

Scheme 2 Photoelectrochemical C–H alkylation of heteroarenes with organotrifluoroborates, 34−99% yields. RVC = reticulated vitreous carbon; CCE = constant-current electrolysis; TFA = trifluoroacetic acid.

Scheme 3 Photoelectrocatalytic oxidation of unactivated alcohols via flavin/thiourea co-catalysis, 53−96% yields. RFT = riboflavin tetraacetate; HAT = hydrogen atom transfer; ET = electron transfer; PT = proton transfer.

directing group[9] and/or the reactions to be conducted at elevated temperatures.[10] Lambert and co-workers[11] showed that the combination of photochemistry with electrochemistry could be applied to direct C–N coupling reactions between arenes and various azoles with moderate to good *para*-selectivity (Scheme 4). The bench-stable, colorless trisaminocyclopropenium (TAC) ion catalyst **5** was electrochemically oxidized to the corresponding stable radical di-cations **6**, which could undergo photoexcitation using visible light to produce the deep red, highly oxidizing excited species **7** (3.33 V *vs.* SCE) capable of oxidizing the inert benzene (2.48 V *vs.* SCE) and halogenated benzenes under very mild reaction conditions. The authors also showed that this electrophotocatalytic system could efficiently facilitate S_NAr reactions of unactivated aryl fluorides at ambient temperatures in the absence of base.[12] The generation of a potent photoelectrochemical catalyst *via* the integration of photochemistry and electrochemistry is reminiscent of the *N,N,N′,N′*-tetraphenyl-*p*-phenylenediamine (TPPD) cation-radical-catalyzed alcohol oxidation described by Reverdy[13] in 1982 and the methylene blue (MB)-mediated sulfide oxidation described by Chiba[14] in 1998.

In addition to the homogeneous redox-mediated photoelectrochemical synthesis, heterogeneous photoelectrodes can be employed. The transformation of solar energy to chemical fuels using PECs is a widely studied topic due to the high oxidizing/reducing capacity of the photoanode/photocathode generated upon illumination.[15] Typically, a photoanode is used to oxidize water to oxygen while a photocathode is used for the reduction of water to hydrogen. The advanced concept of using PECs in organic synthesis has recently been adopted by organic chemists in the oxidation of benzyl alcohols, tetralin,[16] furans,[17] cyclohexane[18] and biomass-derived 5-hydroxylmethyl-

furfural[19] due to its high oxidizing power in the presence of a photoanode (such as $BiVO_4$ and WO_3).

Hu and co-workers found that the abundant and robust haematite photoanode was applicable in the highly *ortho*-selective, non-directed arene C–H amination reaction with a wide range of azoles in hexafluoroisopropanol (Scheme 5).[20] Key to the observed high *ortho*-selectivity seemed to be the formation of intermediate **8** which possessed a hydrogen bond between hexafluoroisopropanol and pyrazole. This method was also successfully applied in the late-stage functionalization of several pharmaceutical compounds. In a manner that was mechanistically distinct from that of canonical photoredox catalysis, the light absorption was achieved by a heterogeneous haematite semiconductor and thus the photogenerated oxidizing hole was localized in the valence band (VB) of the haematite photoanode. Regeneration of the catalyst was then realized *via* the migration of photoexcited electrons to a counter electrode (Pt in this case) to form hydrogen. In addition, the charge transfer in this photoelectrocatalysis from the edge of the VB to the substrate for oxidation differed from that in electrochemistry in which the electrons are transferred from the substrate to the Fermi level of the electrode.

To probe the potential for energy saving in electrochemical synthesis using PECs, Wu and co-workers conducted a direct comparison of a PEC (using $BiVO_4$ as the photoanode) and an electrochemical approach in the P–H/C–H cross-coupling reaction. They found that nearly 90% external bias input is saved when the PEC drives the desired C–P bond formation in comparison to similar yields achieved with an electrochemical cell. Specifically, to produce a current of 5.0 mA required an external applied voltage of 0.1 V (*vs.* Ag/AgCl) for the $BiVO_4$ PEC system while 1.5 V (*vs.* Ag/AgCl) was needed for a glassy carbon electrochemical system.[21]

Photochemistry and electrochemistry can also be effectively coupled in a custom-made manner. For instance, Stahl and co-workers[22] adopted a combined electrochemical/photochemical method for dehydrogenative $C(sp^3)$–H/N–H coupling with sp^2
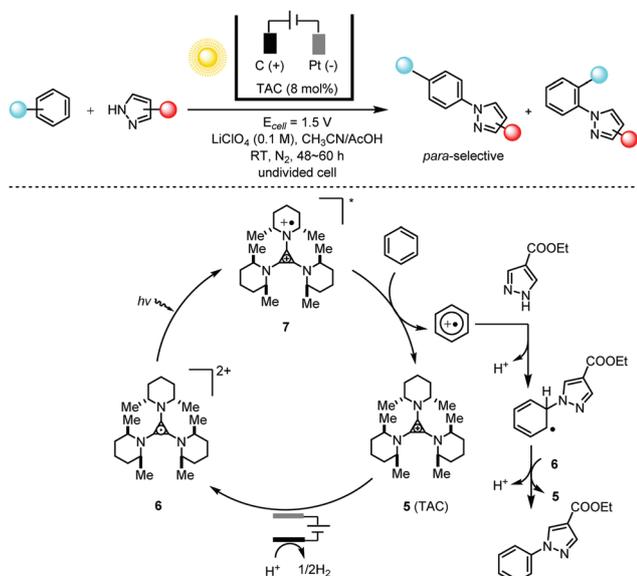
Scheme 4 Direct C–H amination *via* electrophotocatalysis using a TAC radical di-cation catalyst, 30–83% yields, *para/ortho* selectivity of up to 11 : 1. TAC = trisaminocyclopropenium.
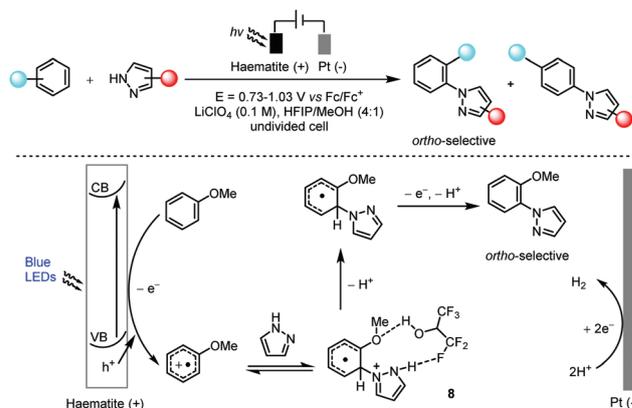
Scheme 5 Photoelectrocatalytic arene C–H amination using a haematite photoanode, 10–89% yields, *ortho/para* selectivity of up to 14 : 1. Fc = ferrocene; HFIP = hexafluoroisopropanol; CB = conduction band; VB = valence band.

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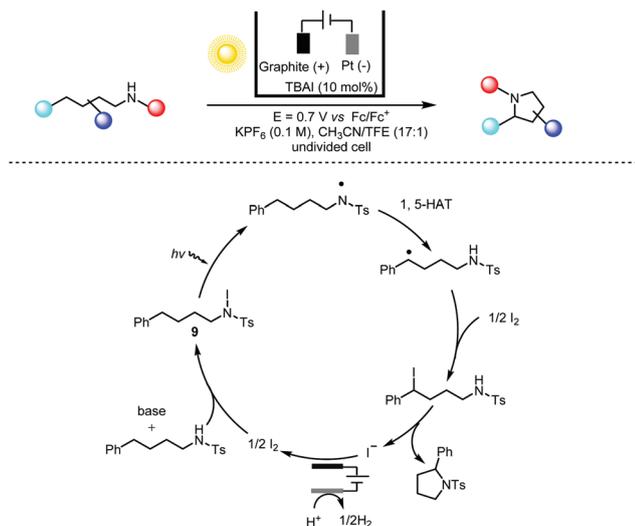
Scheme 6 Photoelectrochemical amination of C(sp^3)−H bonds, 44–86% yields. TBAI = tetrabutylammonium iodide; HAT = hydrogen atom transfer; TFE = trifluoroethanol.

and sp^3 N–H bonds in a Hofmann–Löffler–Freytag-type reaction[23] (Scheme 6). The rationale for choosing iodine as the electrochemical mediator stems from the fact that the I$^−$/I$_3^−$/I$_2$ redox couple is about 0.4 V lower than that for bromide and 1–1.5 V lower than those for the electrochemical PCET (proton-coupled electron transfer) and ET-PT-ET (electron transfer-proton transfer-electron transfer) reactions. On the other hand, the light-induced homolysis of the N–I bond of intermediate **9** mitigates the tendency of the N-iodo intermediates to undergo β-elimination to form HI and imine under thermal conditions. Therefore, this photoelectrochemical Hofmann–Löffler–Freytag reaction offers significantly improved functionality compatibility (especially for electron-rich aromatics) in the direct C–H amination reaction. This constructive merging of electrochemistry (for a desired redox chemical transformation) and photochemistry (for the effective cleavage of certain chemical bonds) is again reminiscent of the early contributions from Scheffold and co-workers in the nucleophilic alkylation and acylation of electron-deficient olefins using vitamin B$_{12}$ as the reductive photoelectrocatalyst in the 1980s.[24]

In summary, recent advances in organic synthesis that merge photochemistry with electrochemistry using PECs and redox-mediated electrolysis have been accomplished. This emerging yet promising concept integrates the merits of both photochemistry and electrochemistry while overcoming their flaws: (1) no stoichiometric amount of oxidant/reductant is needed. (2) The photoelectrochemistry is capable of generating much more potent catalysts than can be obtained using either photochemistry or electrochemistry alone. (3) It is possible to incorporate modified photoelectrodes in organic synthesis (with PECs). (4) The approach offers great opportunities to creatively integrate photochemistry with electrochemistry to meet the specific requirements of certain reactions. Following these exciting breakthroughs, future studies should focus on the adoption

of this new concept in forming chemical bonds that are otherwise difficult or impossible to produce using conventional synthetic methods. The mild reaction conditions, rich sources of photoelectrochemical redox mediators and photoelectrodes, and convenient energy-input tuning *via* the light source and applied potential make the merging of photochemistry and electrochemistry a highly promising strategy for meeting the green and sustainable requirements of modern organic synthesis. We envisage that more applications and developments of this emerging concept in organic synthesis will arise in the near future.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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