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Perspective

The Photoredox Paradox: Electron and Hole Upconversion as the Hidden Secrets of Photoredox Catalysis

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ABSTRACT: Although photoredox catalysis is complex from a mechanistic point of view, it is also often surprisingly efficient. In fact, the quantum efficiency of a puzzlingly large portion of photoredox reactions exceeds 100% (i.e., the measured quantum yields (QYs) are >1). Hence, these photoredox reactions can be *more* than perfect with respect to photon utilization. In several documented cases, a single absorbed photon can lead to the formation of >100 molecules of the product, behavior known to originate from chain processes. In this Perspective, we explore the underlying reasons for this efficiency, identify the nature of common catalytic chains, and highlight the differences between HAT and SET chains. Our goal is to show why chains are *especially* important in photoredox catalysis and where the thermodynamic driving force that sustains the SET catalytic cycles comes from. We demonstrate how the interplay of polar and radical processes can activate hidden catalytic pathways mediated by electron and hole transfer (i.e., electron and hole catalysis). Furthermore, we illustrate how the phenomenon of redox upconversion serves as a thermodynamic precondition for electron and hole catalysis. After discussing representative mechanistic puzzles, we analyze the most common bond forming steps, where redox upconversion frequently occurs (and issometimes unavoidable). In particular, we highlight the importance of 2-center-3-electron bonds as a recurring motif that allows a rational chemical approach to the design of redox upconversion processes.

■ INTRODUCTION

Photoredox catalysis is a powerful strategy for generating reactive intermediates under relatively mild conditions. It has enabled a myriad of previously inaccessible and challenging synthetic transformations.[1−7]

Photoredox catalysis uses light energy to separate charges via photoinduced electron transfer. If electrons move one at a time (i.e., via *Single* Electron Transfer (SET)), radicals and ions are formed simultaneously. These features account for several characteristics of photoredox catalysis such as the commonly observed transitions between radical-ions, radicals and ions, the need for the borrowed electron to be recovered again at the end of the cycle, and peculiar energy landscapes where transition between electronic states are often negotiated via electron transfer. Furthermore, photoredox catalytic cycles are multistep reaction sequences. As they involve more than one reacting partner, often of different charges and spin states, it is hard to expect them to proceed with perfect efficiency, especially considering that many reactive species are "hot" and can follow multiple reaction paths (Scheme 1A). A priori, one would expect that this complexity could lead to a large number of possible side-reactions. Yet, photoredox catalysis often defies these low expectations. Why is that and why are the efficiencies so high?

Our purpose of this Perspective is to answer these questions. We will start by outlining the reasons for mechanistic complexity of photoredox reactions and continue by giving examples of their surprising efficiency, connect this efficiency to the presence of catalytic chains, define different types of chains, and show how such catalytic chain reactions depend on the presence of electron and hole upconversion. After introducing redox upconversion as the thermodynamic precondition for the presence of catalytic SET chains, we illustrate how redox upconversion can resolve mechanistic puzzles. We continue by discussing upconversion through the prism of thermodynamics and molecular orbital (MO) theory. After outlining typical reaction patterns leading to redox upconversion, we discuss why the deprotonation of radicals can be an alternative to radical atom transfer reactions.

■ KEY FEATURES OF PHOTOREDOX CATALYSIS

Nature of the Catalyst. Obviously, the term "photoredox catalysis" includes "photo", "redox", and "catalysis". The "photo" part is clear—the overall process is promoted by light. However, having both "photo" and "redox" in the same name creates an ambiguity relative to the "catalysis" part because several types of catalysis are possible. Examining the nature of the catalytic species reveals that it is not obvious.

A general requirement for "catalysis" is that the catalyst is regenerated in its initial form after each cycle. Thus, photons *cannot* be a true catalyst in a **photo**redox process. According to the IUPAC, species that promote the reaction but are consumed should be classified as "activators". The real catalyst

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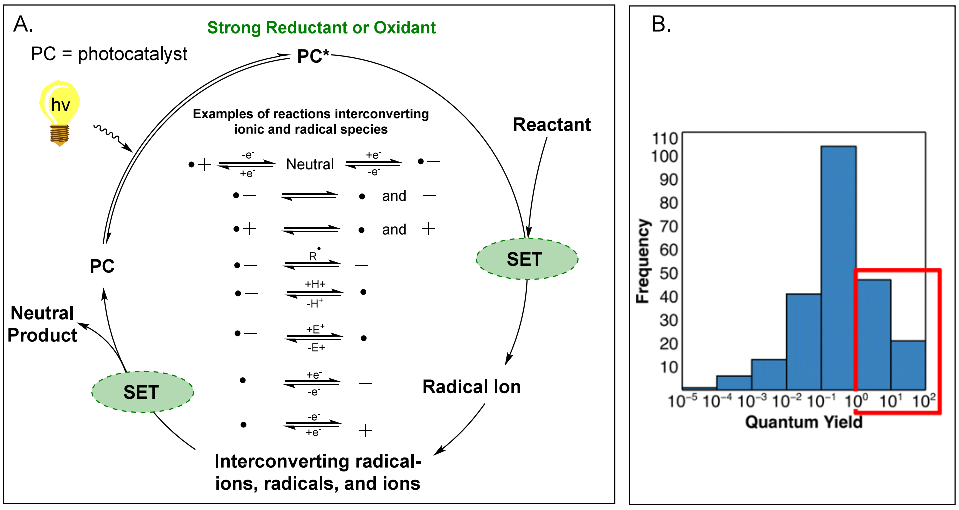
Scheme 1. (A) A Simplified Representation of a Photoredox Cycle; (B) A Histogram of Literature QYs for Photoredox Reactions from Swierk et al. (Reprinted from [Talbott, E. D.; Burnett, N. L.; Swierk, J. R. Mechanistic and Kinetic Studies of Visible Light Photoredox Reactions. *Chem. Phys. Rev.* 2023, *4* (3), 031312] with the Permission of AIP Publishing[8])[a]



[a] QYs > 1 highlighted in red.

in a typical scenario shown in Scheme 1A is the "photocatalyst", i.e., the molecule absorbing the photon. The excited photocatalyst uses its energy to initiate a sequence of processes (a photoredox catalytic cycle), which often starts with electron transfer from the excited catalyst to a substrate (oxidative or reductive quenching). Finally, the photocatalyst returns to its ground state, in its original redox state. In this scenario, the photons are simply the source of energy that fuels the first step of the catalytic cycle. At the end of the cycle, the photon's energy is used up and ***one*** molecule of the product is formed. Another photon is needed to form the next molecule of the product. Due to common imperfections like back electron transfer (BET) or decay of the catalyst's excitation before the first electron transfer step (*vide infra*), the quantum yield (QY), i.e., the number of product molecules per absorbed photon, should be somewhat or even very much lower than unity.

Furthermore, catalytic cycles must be *overall redox-neutral.* Electrons (or holes) are "borrowed" at the beginning of the cycle and "returned" at the end. The initial source of borrowed electrons or holes is the excited photocatalyst, but much like a loaned sum of money, the borrowed electrons can participate in multiple transactions before being "returned to the bank". From that point of view, electrons and holes have the potential to play the role of true catalysts in photoredox reactions. In this Perspective, we will concentrate on this potential, showing that, although it is often hidden, it is likely to be of key importance in reaction design.

The Photoredox Paradox: Mechanistic Complexity vs Surprising Efficiency. Another interesting feature is that photoredox cycles often contain "radical-polar" crossover steps. Here, both reactants and products are closed-shell species, while many of the intermediates have unpaired electrons. This crossover can occur via two scenarios: (a) simple electron transfer and (b) reaction of open-shell and closed-shell molecules that form and break chemical bonds. The latter type of processes often involves the formation of either two-center, three-electron (2c,3e) bonds in the reductive mode or two-center, one-electron (2c,1e) bonds in the oxidative mode.

In the context of this mechanistic complexity, the high efficiency of many photoredox reactions appears remarkable—both in terms of the chemical yields and, even more so, in terms of quantum efficiency (i.e., the yield per each absorbed photon). The presence of anomalously high QYs (>1) in photoredox reaction was revealed by the early work of Jacobi von Wangelin and co-workers,[9] in aromatic substitutions, and by Yoon and co-workers[10] in photoredox-initiated cycloadditions. The ubiquity of this trend was further highlighted in a recent work by Swierk et al.,[8] who systematically analyzed published QYs for photoredox transformations. Inspection of their data, reproduced in Scheme 1B, immediately reveals a surprisingly large proportion (~30%) of QYs to be greater than unity! Unlike typical photochemical reactions,[11] many photoredox cascades exceed the standard of perfect quantum efficiency by making *more* than one product molecule per absorbed photon.

How can the QY exceed unity (>100%) and why do QYs exceed 1 *so often*? Clearly, this is a common occurrence that indicates the presence of a light-independent catalytic process, which is important to analyze from a fundamental perspective.

At first glance, a QY of >1 suggests that a photon serves as a catalyst in this process. A QY of 2, for example, would suggest that a single photon can promote two catalytic turnovers and hence can be considered a catalyst with a turnover number (TON) of 2. However, examples of photons serving as formal catalysts where energy is transferred from the excited product to the starting material, i.e., quantum chain reactions, are quite rare.[12−17]

■ WHY DO SO MANY PHOTOREDOX QUANTUM YIELDS EXCEED 100%?

The QYs of photoredox processes depend on a number of factors. For the primary photochemical step, those are (a) efficiency of formation of the productive excited state and (b) the presence of its deactivation pathways (radiative and nonradiative decays, state crossings, etc.) and their competition with the one desired path on the route to the target product. The efficiency of BET and the rate of escape from the solvent cage for the initially formed ion pair also contribute to lowering of QY.[18] Furthermore, QY is also impacted by the chemical yields of each of the intermediate states in the ground state part of the catalytic cycle.

The observed QY is the multiplication product of each of the imperfect individual yields of a potentially multistep cascade. Loss in any of the cascade steps would lower the quantum efficiency.

A corollary of that is that, unless all of the photo- and nonphotochemical steps proceed with 100% efficiency, it is inevitable that the measured QYs are lower than the real photochemical QY. Hence, one would expect the measured photoredox QYs to be quite small and certainly lower than unity. However, as stated above, these QYs are often >1. What is missing?

In this Perspective, we show that the short answer to this question often is "redox upconversion".

REDOX UPCONVERSION: THE THERMODYNAMIC PRECONDITION TO SET CHAINS

But what is "redox upconversion"? What does "upconversion" mean in this context? And how is it connected to photoredox catalysis?

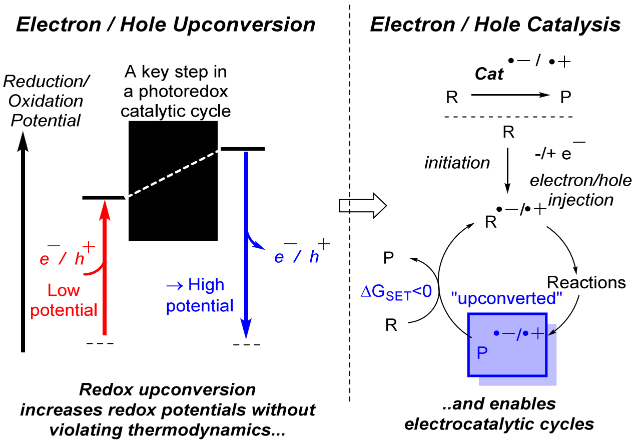
Upconversion is the transformation of something of "low quality" to something of "high quality". For example, upconversion of photons is a process where photons of low energy are converted to photons of higher energy. Photon upconversion is well-known to photochemists who found it useful in numerous ways.[19,20] However, electron and hole upconversion were only conceptualized relatively recently.[21]

Electron upconversion converts a weaker reductant into a stronger reductant while hole upconversion is the analogous transformation of weaker oxidants into stronger oxidants.[22] Collectively, both of these phenomena can be described as redox upconversion.

Such processes look unlikely, because they increase the energy of electrons (or holes). Indeed, redox upconversion is unfavorable in simple exergonic electron transfer (e.g., SET processes) where the thermodynamically preferred electron transfer always *decreases* redox potential. However, even though one would expect that raising the redox potential is intrinsically thermodynamically unfavorable (endergonic), there is a subset of chemical reactions defying these expectations. Indeed, the redox potential can *increase* spontaneously in an *exergonic* transformation as long as electron transfer is coupled with another thermodynamically favorable process, e.g., forming chemical bonds.

Importantly, when redox upconversion is exergonic, it serves as a thermodynamic foundation for electron catalysis and hole catalysis (Scheme 2).[23] Such catalysis was conceptualized for organic reactions by Studer and Curran.[24] It is important for radical reactions, especially since very strong reductants can evolve from heteroatom-containing precursors under basic conditions as shown by Murphy and co-workers.[25] In this Perspective, we show that redox upconversion, i.e., electron upconversion (reductive pathways) or hole upconversion (oxidative pathways), serves as the thermodynamic condition for the existence of SET chains in catalysis.

Scheme 2. (Left) The Paradox of Redox Upconversion: A Reactant with a Lower Redox Potential Is Converted into a Product with a Higher Redox Potential; (Right) Redox Upconversion Creates an Efficient Hole/Electron Catalyzed Electrocatalytic Cycle Where the Radical-Ion of the Product Transfers the Catalytic Hole (or a Catalytic Electron) to a Fresh Molecule of Reactant, Starting the Catalytic Cycle Anew



DIVERSITY OF CHAIN PROCESSES

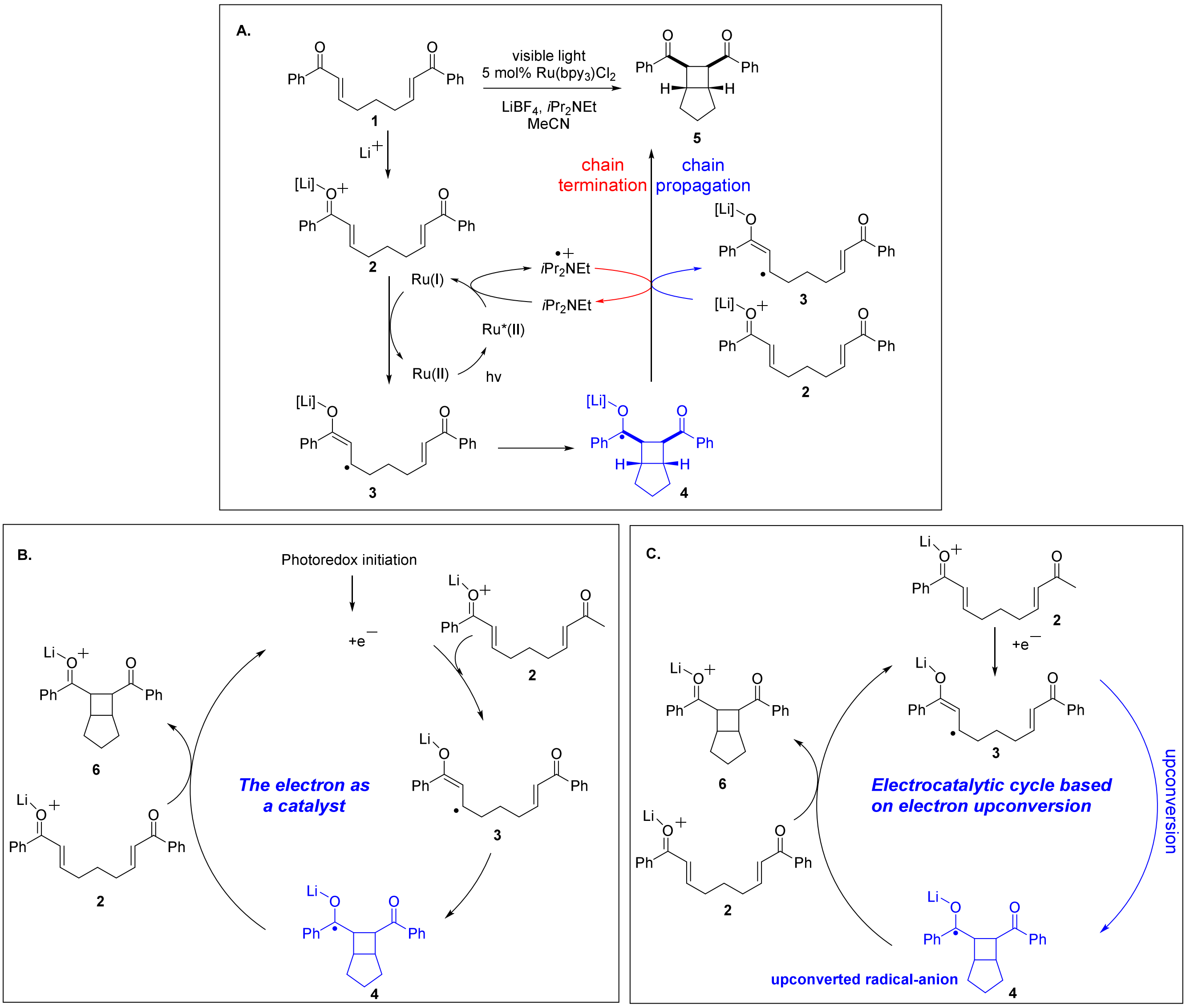
As discussed above, even though a QY > 1 seems to require a single photon to promote many catalytic cycles, photons themselves cannot be catalysts. Instead, this situation is only possible if the real catalyst is different, i.e., if a nonphotochemical chain process is initiated by the photochemical excitation.

The involvement of chain processes in photoredox catalysis has been documented in a number of cases, most notably in the early studies by Jacobi von Wangelin[9] and Yoon[10] (vide infra). An important example provided the key evidence for the presence of nonphotochemical catalytic cycles in photoredox catalysis (Scheme 3). At first glance, one could describe the photocatalytic [2 + 2] cycloaddition of enones by a typical photoredox cycle.[26,27] This cycle can be initiated by the reductive quenching of photoexcited $Ru(bpy)_3^{2+}$ by an amine donor. The reduced Ru(I) species formed in this step transfers a single electron to the Lewis acid-activated enone to transform the latter into a radical-anion. Intramolecular cycloaddition of the enone radical-anion leads to a cyclobutyl ketyl radical-anion. The cycle can be closed by returning one electron from the product radical-anion to the photogenerated amine radical-cation (Scheme 3A).

However, there is a problem with this simple picture. This fully reasonable catalytic cycle can only account for <1% of the reaction product as follows from the experimentally determined QY for this reaction (measured directly as 77, and estimated as 135 after corrections for the nonproductive energy-wasting processes that partially deactivate the photocatalyst's excited state). From this perspective, the real catalytic cycle accounting for >99% of the observed product formation has to be different. A more instructive way to represent the true catalytic cycle is to use the electron as a catalyst (Scheme 3B).[24] Indeed, when the same reaction was promoted electrochemically, 76% of the product was formed with only 30% of the theoretically required electrical charge.[28−30]

The third way to describe the true catalytic cycle for electron catalysis is based on electron upconversion, i.e., transformation of weaker reductants into stronger reductants, introduced in Scheme 2. We will provide more detail on how to achieve and use electron upconversion later. Here, it is sufficient to say that

Scheme 3. Three Representations of the Photochemically Induced Intramolecular [2 + 2] Cycloadditions:[10] (A) The Original Representation with the Photoredox Cycle; (B) The Representation in Which the Electron Is a Catalyst as Conceptualized by Studer and Curran; (C) Electron Upconversion Connects Electron Catalysis with Molecular Structure and Reaction Thermodynamics



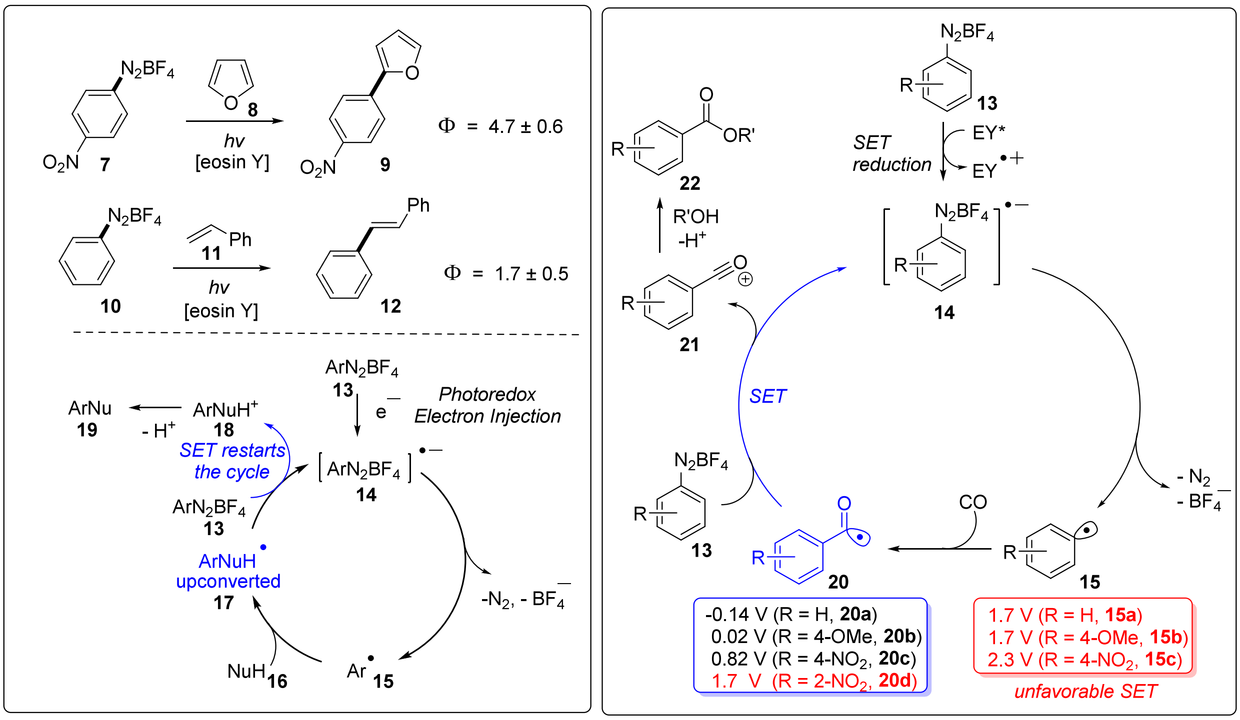
it connects electron catalysis to reaction thermodynamics. Most importantly, since the electron here is not free but associated with a molecular carrier, electron upconversion has the added benefit of being based on molecular structure and, hence, is useful for the practical design of electron-catalytic processes. From the energy point of view, *electron upconversion is the reason why electron catalysis works*! The electron can be a catalyst *only* if it is "upconverted" within each catalytic cycle, so it can be reinjected into a new molecule of the neutral reactant.

The cascade in Scheme 3 provides an example of electron upconversion because the product radical-anion is a reductant that is better than the reactant radical-anion. Hence, the product radical-anion can reduce another molecule of the neutral substrate. Such exergonic electron transfer establishes a true electrocatalytic cycle that does not need the influx of photons for sustained operation. In this perspective, we will show how electron upconversion can be used to systematically identify the possibility of productive SET-based catalytic chains in photoredox processes.

Jacobi von Wangelin[9] also found QYs > 1 in a very different family of reactions, i.e. the photoredox heterobiaryl coupling and the Heck-type olefination of arenediazonium salts. Interestingly, similar photoredox-catalytic processes using the same catalyst were found to have QYs much smaller than unity. A reasonable mechanistic hypothesis involves photoredox-mediated electron injection into the diazonium salt followed by dediazotation and aryl radical formation. Although the aryl radical is a rather poor reductant,[31] it can react with an electron rich π-system of either furan or styrene to form a more reducing delocalized π-type radical that can transfer an electron to another diazonium salt reactant, restarting the cycle.

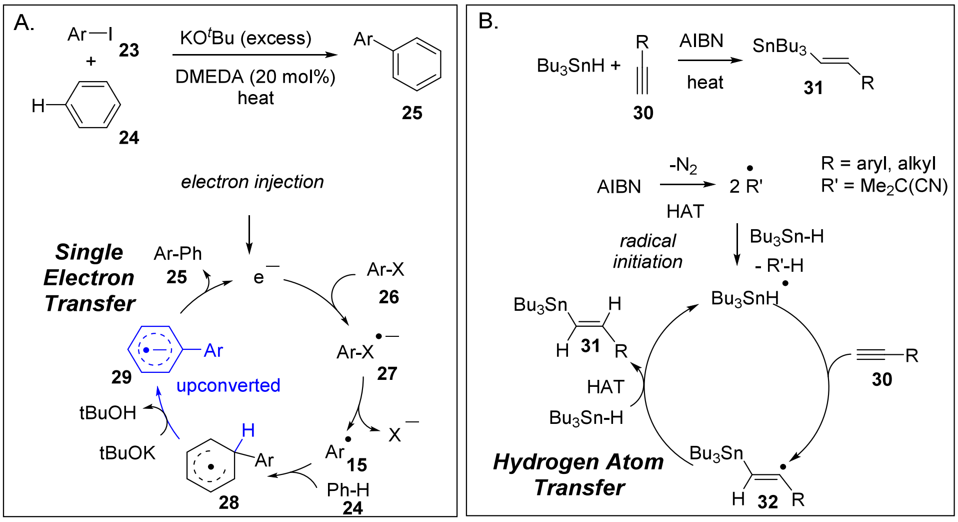
The authors attributed the surprising quantum efficiency of the two reactions in Scheme 4 (left) to "a radical chain". However, there is more than one way to establish a self-propagating chain: (1) a classic radical chain based on X- or H-atom transfer (XAT or HAT), and (2) an electron-catalytic chain based on electron transfer (Scheme 5). Radical chains based on atom transfer have been used as a reliable design

Scheme 4. (Left) Electron Catalytic Chains in Photoredox Heterobiaryl Coupling and Heck-Type Olefination; (Right) Electron Catalytic Chains in Photoredox Carbonylation of Arene Diazonium Salts[a]



[a] Transformation of aryl radicals into acyl radicals facilitates electron transfer.

Scheme 5. Comparison of a SET Chain (A) in Base-Catalyzed Cross-Coupling[24] **with a HAT Chain (B) in Radical Addition to an Alkyne**



element in the development of efficient radical cascades for decades.[32,33] The presence of such chains is the reason why substoichiometric amounts of radical initiators can achieve high conversions and yields.

However, many chains observed in photoredox chemistry are different, yet this difference is not generally acknowledged. Such chains are based on electron transfer (not atom transfer) and are observed when the product radical-ion can transfer either an electron or a hole to the neutral substrate. No bond scission is needed for the initiation of electron-catalytic chains. Instead, the catalytic cycle is started via electron or hole injection, which can be done, with some degree of control, via electrochemical or photochemical initiation, but as outlined below, it needs redox upconversion to be sustained.

As one can see from Scheme 5, classical radical chains and SET chains are conceptually different as they include initiation and propagation steps of a completely different nature. However, distinction between these processes is not always made clear as illustrated by a conclusion made after discovering reactions propagated via SET chains: "In reality, QYs can exceed unity in cases where the products of the photocatalytic reaction induce (radical) chain reactions".[9]

The distinction between electron transfer and atom transfer is important not only because those processes are initiated,

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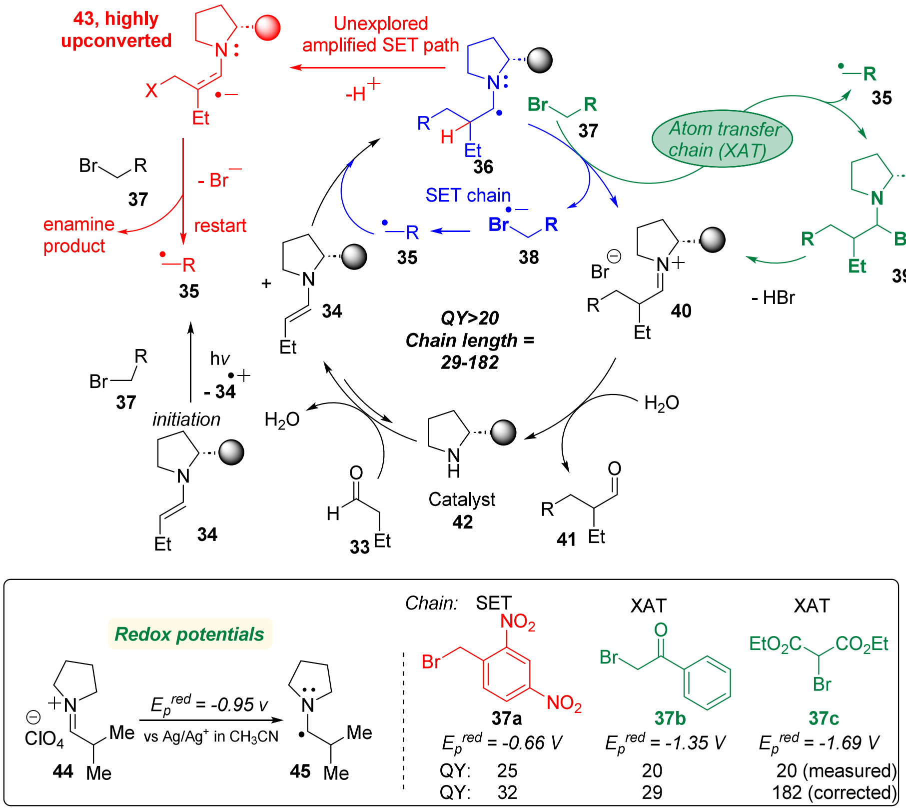
Scheme 6. Comparison of XAT Chain (Green) with Two SET Chains (Blue and Red) In Photochemical Alkylation of Enamines[36] (the Organocatalytic Part of the Overall Cascade Is Omitted)



sustained, and controlled using different tools but also because the electronic nature and reactivity of radicals and radical-ions are quite different. Even though IUPAC simply defines a radical-ion as "a radical that carries an electric charge", distinctions between these species are significant. For example, typical neutral radicals have the unpaired electron in a nonbonding MO while typical radical-anions have the unpaired electron in an antibonding MO etc.[34] As a consequence of that and the inherent charge effects, radical-anions are much better reductants. Importantly, the oxidation of radical-anions can produce stable neutral products satisfying the octet rule.

Interestingly, photoinitiated SET chains, similar to the one in Scheme 5A, were known well before the recent renaissance of photoredox catalysis. In an early example, Kornblum reported the photoreaction of *p*-nitrocumyl chloride with sodium azide to have a QY of 6000 and concluded "with such QYs there can be no doubt that these are chain reactions".[35]

In spite of the above, the distinction between the atom-transfer and the electron transfer processes has been explicitly considered only in a few cases. A rare example where this duality is discussed is the work of Bahamonde and Melchiorre on photoredox activation of enamines (Scheme 6).[36] In this sequence, excitation of enamine **34** leads to SET to alkyl bromide followed by reductive C−Br bond scission with the formation of alkyl radical **35**. This radical adds to another molecule of the enamine to generate an α-amino radical **36**. The new radical has an interesting duality—it can react with the alkyl bromide either by SET or via radical atom-transfer abstraction (XAT). In both cases, a new alkyl radical **35** is generated. Comparison of the redox potentials shows that SET is only exergonic for the dinitro-substituted bromide, whereas the less electron-deficient bromides have to react via the XAT chain. The chain presence is revealed by the measured QYs = 20−25. After correction for the inefficiency of the initiation steps, the true lengths of these chains are even higher (TONs of up to 182). This analysis suggests that the XAT and SET types of chains may coexist, but distinguishing between the two is not trivial.

Furthermore, one can also suggest a third alternative. As radicals are known to be much more acidic than closed-shell hydrocarbons,[37] the radical **36**, in the presence of a suitable base, may be deprotonated to form a radical-anion (red pathway). The latter would be a reductant much stronger than its neutral radical precursor and should be able to reduce all three bromides **37a−c**. This mechanistic scenario would create SET-based chains (i.e., chains sustained via electron upconversion) that can be fully functional even for the relatively weak oxidants as long as a sufficiently strong base is present.[38] However, the scope of such scenarios is presently unclear, because the necessary data on the deprotonation of radicals are still scarce.

Hence, "chains" in photoredox can be of several types. One should distinguish between the classic radical (XAT) chains and the SET chains, which can be propagated by electron transfer from either neutral radicals or, after the redox-amplifying deprotonation, from radical-anions. Although the peculiar nature of photoredox allows both SET and XAT chains to operate, SET chains have an inherent advantage over X atom transfer chains. For X atom transfer, the interacting partners have to establish the radical···X−Y contact. In contrast, SET can propagate through much longer distances.[39,40] This advantage alleviates steric and entropic penalties characteristic for XAT!

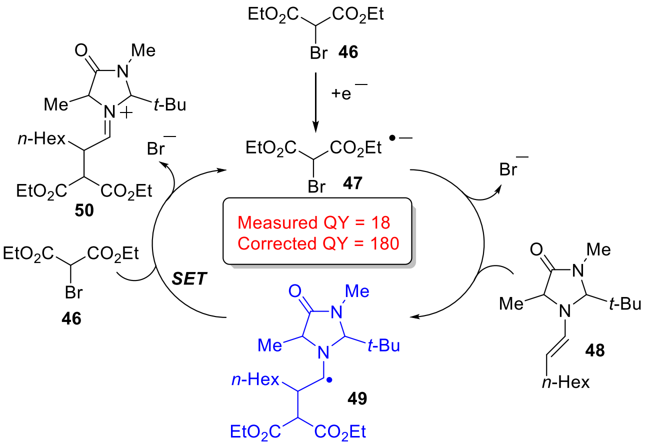
■ EXAMPLES OF REDOX (SET) CHAINS

Here, we use several examples of known SET chains in photoredox reactions to highlight the work that can illustrate important general points and guide our discussion in subsequent sections.

The importance of SET chains in photoredox catalysis is underscored in a number of examples.[10] For example, Cismesia and Yoon reported a QY of 18 in photoredox α-alkylation of aldehydes mediated by electron-rich α-amido radicals.[10] Furthermore, quantitative photophysical studies indicated that only 10% of the absorbed photons enter the photoredox path, indicating the effective QY (i.e., the chain length) to be as high as 180.

The mechanism starts with the usual SET from photoexcited $Ru(bpy)_3^{2+}$ to the alkyl bromide, creating a radical-anion that fragments into a bromide anion and an alkyl radical (Scheme 7). The radical adds to the enamine double bond to generate an α-amino radical. In a conventional mechanism, these species terminate the chain by ET to form the oxidized form of the photocatalyst. However, the authors provide convincing arguments that this species has a sufficiently high reduction potential to transfer an electron directly to another molecule of the alkyl bromide, i.e., to restart the catalytic cycle with SET. While it is yet unclear if the SET (upconverted) mechanism is the only path or whether XAT (common radical chain) contributes as well, there is no doubt that an efficient chain process plays an important role in assisting this complex multistage cascade.

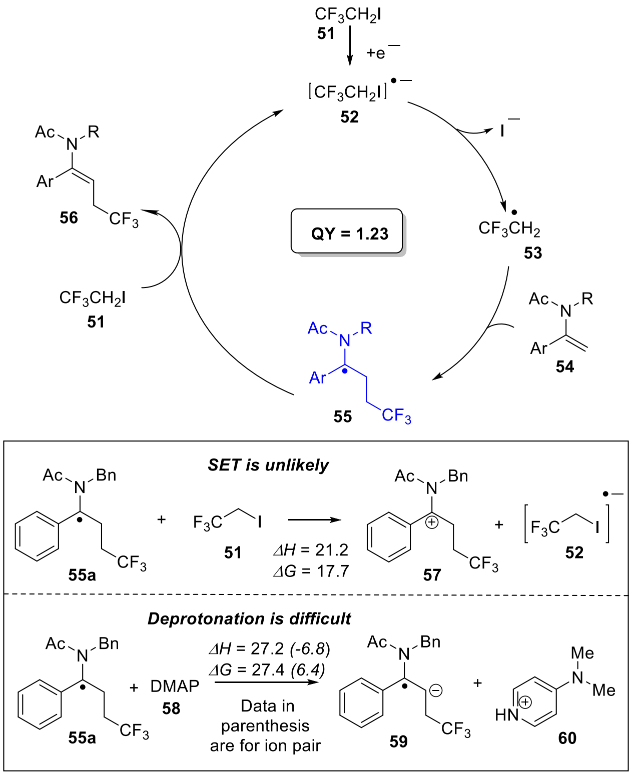
Scheme 7. Part of the Photoredox α-Alkylation of Aldehydes, Which Includes the Key Enamine Intermediate



A similar SET chain is likely in photochemical C−H trifluoroethylation of enamides reported by Loh et al.[41] which also proceeds with QY = 1.24 (Scheme 8). Although the authors cautiously state "the transformation was more likely to predominantly proceed through a photocatalytic process, whereas a short radical chain mechanism could not be completely ruled out", it is likely that, considering the multiple deactivation pathways for a multistep photoinitiated process, the chains can account for the majority of the product formed.

Without experimental redox potentials, the nature of the chain is unclear. To address this, we have calculated free energies (for computational details, see SI) for SET from the α-amido radical to a trifluoroethyl iodide, i.e., the step needed to establish the catalytic cycle, is possible. Interestingly, the oxidation for the *N,N*-Ac,Bn-substituted enamide is uphill (ΔG = 17.7 kcal/mol). Although the C−I scission in the concomitantly formed radical-anion is 3.9 kcal/mol exergonic and can partially compensate against this penalty for the overall process, the SET chains in this reaction encounter a considerable thermodynamic penalty of ~14 kcal/mol.

Scheme 8. (Top) Experimental Evidence for the SET Chains in Photochemical C−H Trifluoroethylation of Enamide; (Center) Computational Data for the Suggested SET Step; (Bottom) Thermodynamics of Radical Deprotonation with DMAP



(U)M06-2X/def2-TZVP/GD3/SMD=MeCN, ΔH and ΔG in kcal/mol

Interestingly, the reaction is sensitive to the nature of the external base. The yields varied from 85% (DMAP) to zero (pyridine). Despite these external base effects, DFT calculations predict deprotonation of this enamide radical with DMAP under concomitant formation of a super-reducing radical-anion (SET to trifluoroethyl iodide: ΔG = −34.2 kcal/mol) is uphill by 6.4 kcal/mol. Since the neutral radical is an inefficient donor and further upconversion via deprotonation is difficult, it is tempting to connect the inefficient electron upconversion with the relatively low QY. An XAT chain cannot be excluded either.

The third example of an anomalously high QY in a photoredox reaction mediated by α-amino radical is provided by a thorough study by Knowles and co-workers[42] who investigated the nature of chain processes in photocatalytic indoline dehydrogenation with *tert*-butyl peracetate (*t*BPA), Scheme 9. The presence of chains is apparent from the observed QY of 2. However, the nature of these processes remains unclear even though the authors used an impressive battery of tools from the arsenal of physical organic chemistry, including kinetic, isotope labeling, electrochemical, and

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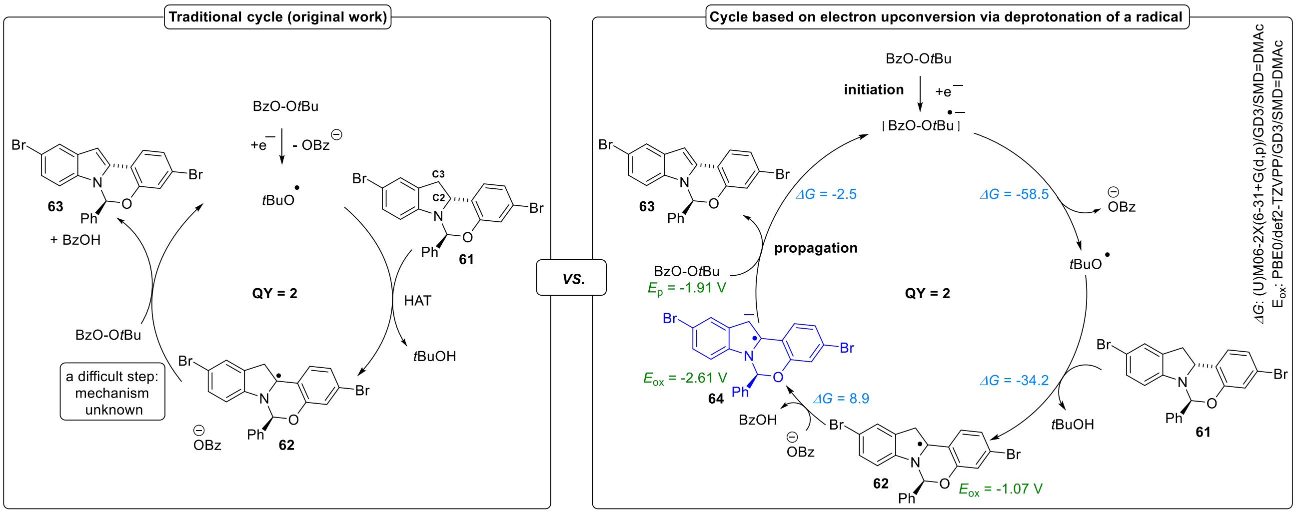
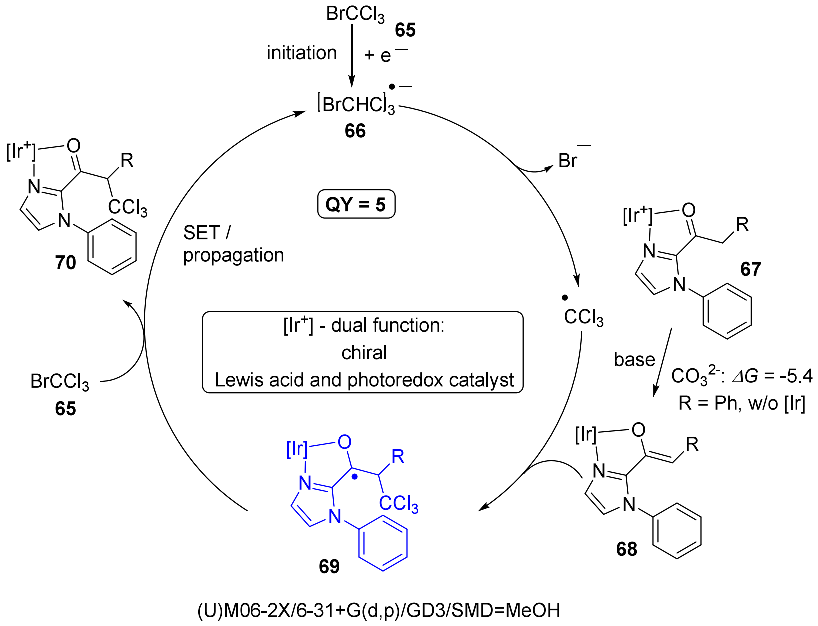
Scheme 9. Two Mechanistic Scenarios for Indoline Dehydrogenation: Without (Left) and With (Right) Radical Deprotonation Leading to Electron Upconversion



Scheme 10. Photoredox Trichloromethylation of Ketones



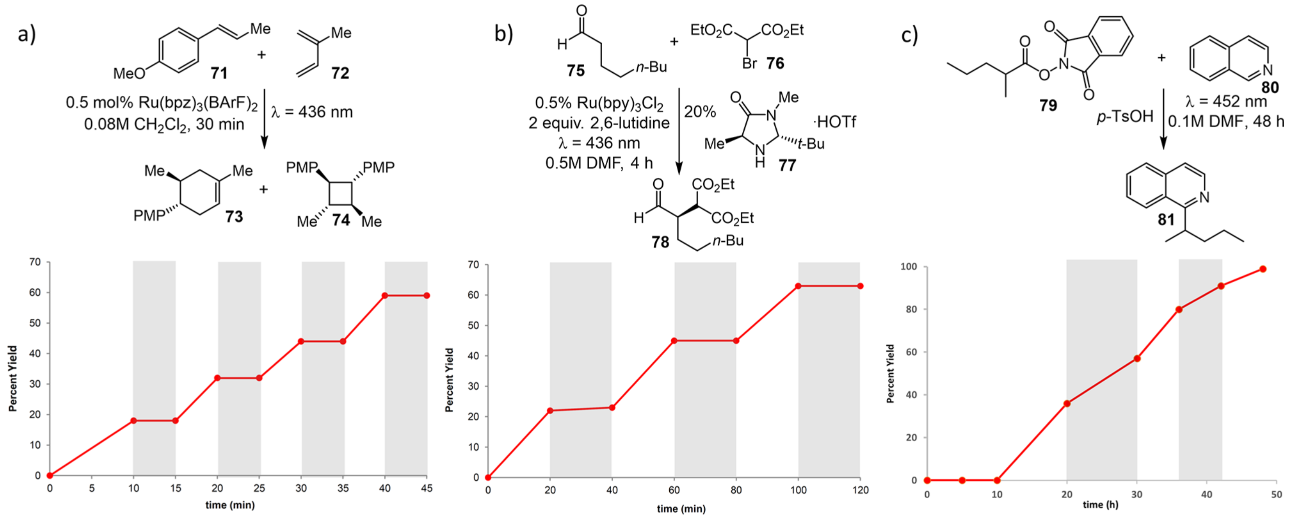
spectroscopic studies. In conclusion, the authors insightfully comment on the general importance of solving this difficult mechanistic puzzle: "As such, the exact nature of the perester activation step remains unclear, though we note that similar questions often surround propagation steps in related Minisci reactions...". We show below that electron upconversion via radical deprotonation may provide a key piece of this puzzle.

Parts of this photoredox cycle are well understood. Photoexcitation of the Ir catalyst initiates SET to *t*BPA with the formation of a *t*BPA radical-anion. Expectedly, this species dissociates into a benzoate anion and a *t*BuO radical. The latter reacts at the weakest C−H bond of the indoline precursor.

The ambiguity arises in the nature of the subsequent radical propagation. Although the propagation chain should start with the α-amino radical, it remains unclear how this radical restarts the catalytic chain. After considering a number of options, including direct HAT to *t*BPA, benzoyl transfer to the C2-radical center with subsequent elimination of benzoic acid, and a SET chain starting with the α-amino radical, the authors ruled out all of them. In particular, the oxidation potential of the α-amino radical of −1.07 V vs Fc/Fc$^+$ in MeCN (estimated by DFT) does not appear strong enough to reduce the perester (E_p = −1.91 V vs Fc/Fc$^+$ in DMA) via direct ET.

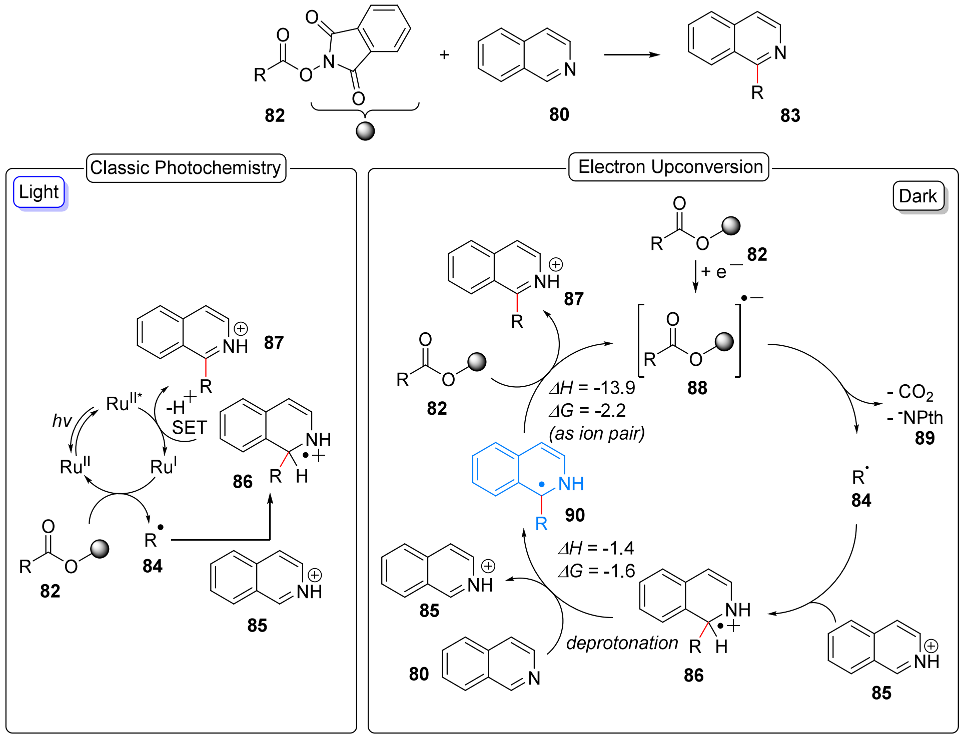
However, an alternative exists. If a benzoate anion can deprotonate the α-amino radical, it would form the upconverted radical-anion (E_{ox} = −2.61 V vs Fc/Fc$^+$ in DMA, by DFT) capable of simultaneously reducing BzO−O*t*Bu, forming the indole product and restarting the catalytic cycle. The calculated deprotonation free energy is small (8.9 kcal/mol) and can be decreased by acid−base ion pair formation. Considering that this process can be coupled with the very favorable (−58.5 kcal/mol) fragmentation of the *t*BPA radical-anion, such deprotonation-enhanced upconversion appears plausible.

Scheme 11. "Light/Dark" Experiments for (a) the Radical-Cation [4 + 2] Cycloaddition, (b) Photoredox Aldehyde Alkylation Reaction,[10] and (c) Catalyst-Free Minisci Reaction[47a]



[a]Plots are reconstructed from the published data.

Scheme 12. Proposed Classic Light-Induced Catalytic Cycle (Left) vs. Electron-Induced Catalytic Cycle via Electron Upconversion in the Dark (Right) in a Minisci Reaction[47]

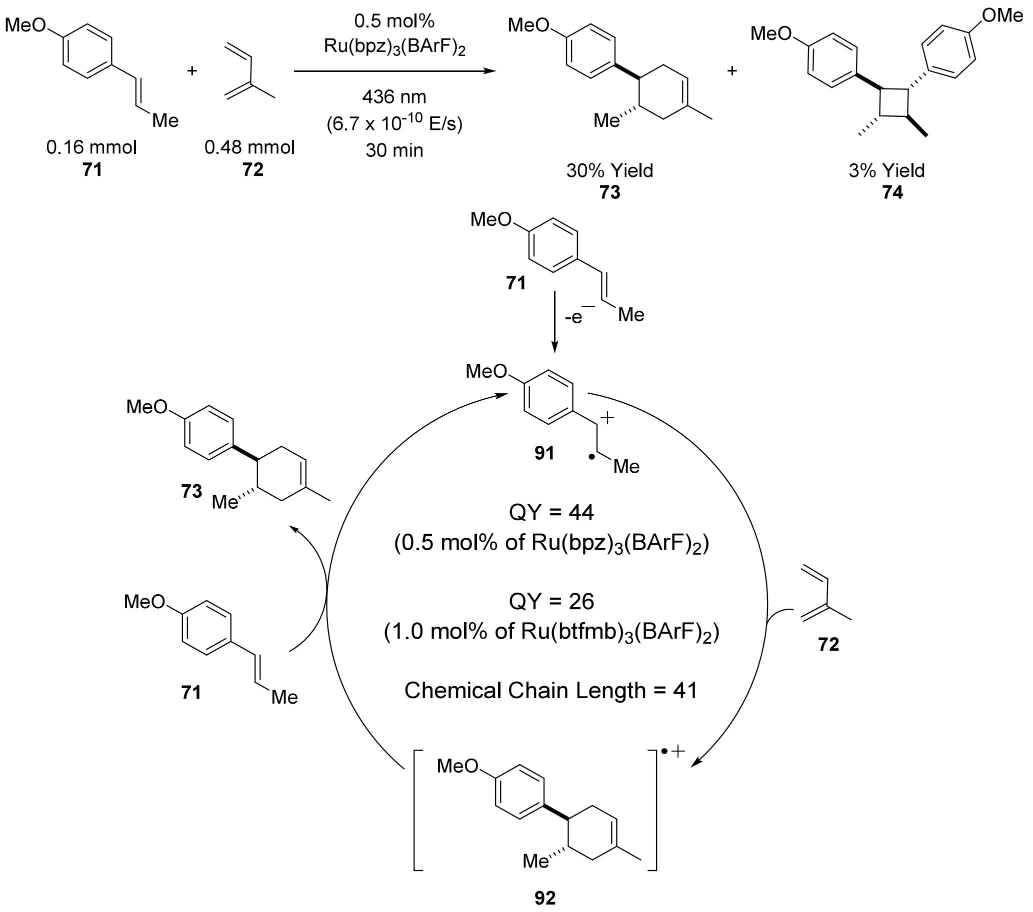


Interestingly, the inverse isotope effect for the C3-deuterated starting material suggests a shift toward sp^2-hybridization at C3 as the H−C3 bond is broken. This is also consistent with the formation of radical anion **64** via deprotonation.

α-Oxygen radicals can also propagate the SET chains as illustrated by trichloromethylation reported by Meggers et al. (Scheme 10).[43] In the presence of an Ir-photosensitizer/Lewis acid, the reaction proceeds in high yields. It is greatly assisted by the presence of a base (Na_2HPO_4 or $NaHCO_3$) and inhibited by the presence of air. The measured QY of 5 clearly implicates a chain process.

The SET nature of this catalytic chain is quite clear. The initial photoinduced SET to bromotrichloromethane results in a radical-anion that dissociates to form a trichloromethyl radical. The latter adds to an enolate, forming the upconverted ketyl radical-anion. Although no redox potentials were reported, SET from this radical-anion to a fresh $BrCCl_3$ molecule is quite likely to be efficient in restarting the catalytic cycle. Additionally, the suggested presence of this chain is supported by the beneficial effect of the base needed for the enolate formation and by the deleterious effect of air, which can intercept the chain-propagating ketyl anion.

Scheme 13. Selected Hole-Catalyzed Photoredox Cascades



DIRECT EVIDENCE FOR PERSISTENT NONPHOTOCHEMICAL CATALYTIC CYCLES: “LIGHT/DARK” EXPERIMENTS

Depending on the nature of reaction participants, the SET chains should have intrinsically different lifetimes—some are short, but others may persist without light. This led to many attempts to detect the presence of nonphotochemical chain reactions.

Many similar attempts have been futile. For example, in the “light/dark” experiments to test for the occurrence of chain processes in photoredox reactions, the product formation occurred only during periods of constant irradiation (Scheme 11). No reaction was observed in the dark, including the radical-cation, radical-anion, and neutral reactions with long catalytic chains.[10] Similar findings were reported for other “light/dark” experiments.[44−46] Based on these results, Yoon suggested the following: “we urge caution in drawing conclusions about chain propagation from “light/dark” experiments.”

We fully agree with this statement and support it with the following simple “numeric experiment” for a hypothetical but realistic situation. Suppose that there is an efficient SET chain that, according to the measured QY, persists for 100 turnovers. Let us also suppose that the overall rate constant k for this process is diffusion controlled ∼10^{10} M^{-1} s^{-1}. Let us consider mM concentrations of both reagents and that one of them (A) undergoes 1% conversion to the radical-anion. Assuming that the second reagent B concentration is constant, the pseudo-first order rate would be $k[B] = 10^2$ 1/s and half-life for A would be $\ln(2)/100 = 0.007$ s. Hence, even quite long chains (∼100 turnovers) will last only seconds. However, if the overall reaction is slower with a rate constant of $1-10^4$ M^{-1} s^{-1}, a TON = 100 chain may live longer and be detectable hours after irradiation has stopped (assuming that the concentration of upconverted species is sufficiently high). Thus, the outcome depends on the overall kinetics of a multistep cascade. Although the presence of a detectable dark reaction strongly supports light-independent chains, the absence of a noticeable dark reaction does not rule them out.[10]

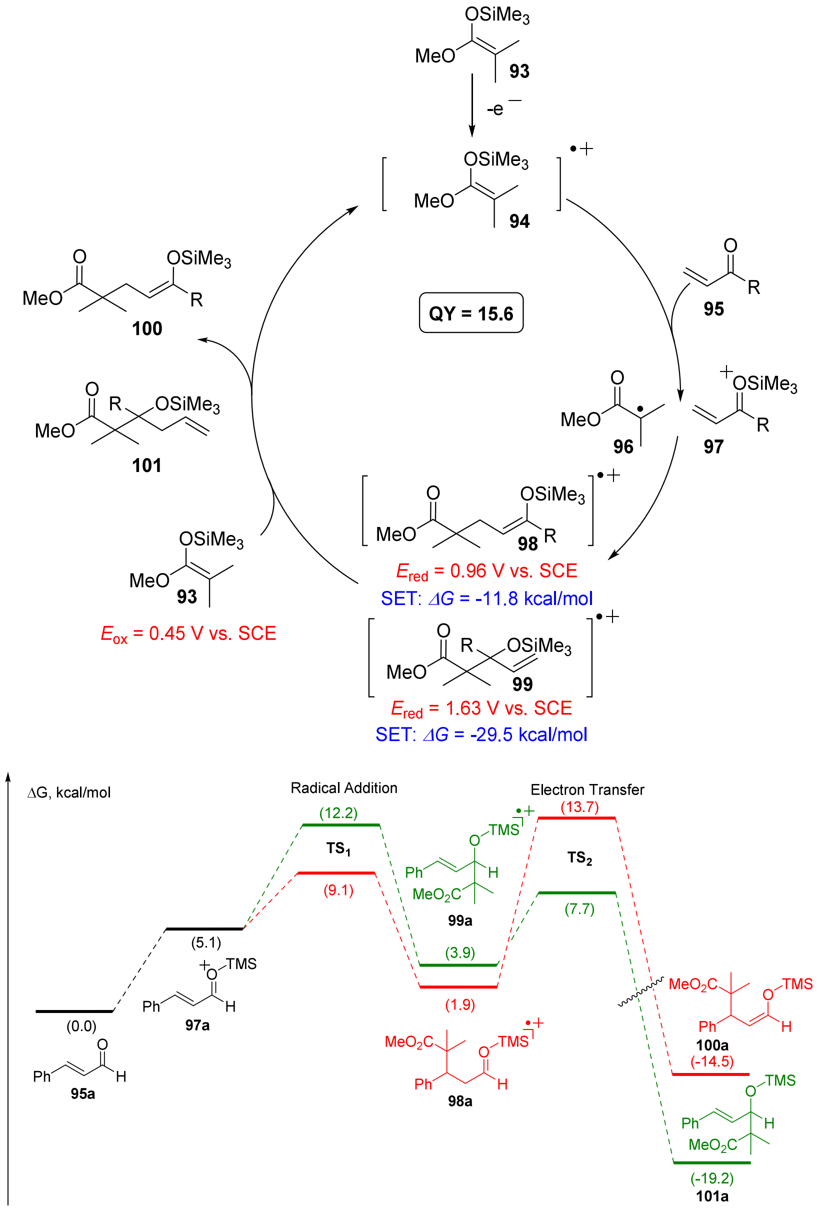
Three outcomes of literature light/dark experiments on photoredox reactions involving chains are listed in Scheme 11.

While dark reactivity remains invisible in examples a and b, example c clearly reveals a light-independent reaction progress. The latter process was reported in the studies of the light-driven Minisci reaction of NHP-esters of carboxylic acids with isoquinoline (Scheme 12).[47] In the absence of photocatalyst, the reaction has a long induction period.[48]

The clear self-sustained component points toward possible electron upconversion. Although radical-cation **86** is not a competent electron donor toward the NHP ester **82** (Scheme 12), the CH-acidity of **86** is sufficient for its deprotonation by both isoquinoline and by the phthalimide anion to be exergonic (−1.6 and −18.8 kcal/mol, respectively). The resulting upconverted neutral radical **90** is a sufficiently strong reductant to transfer an electron into **82** ($\Delta G = -2.2$ kcal/mol).

Calculations indicate that HAT from **86** to the imide carbonyl of **82** would be an alternative option (+0.0 kcal/mol).

Scheme 14. (Top) Hole Upconversion in a Catalytic Cycle for a 1,2- and 1,4-Addition of Silyl Ketene Acetals to *α,β*-Unsaturated Carbonyl Compounds; (Bottom) Energy Landscape for the 1,2- and 1,4-Addition[60]



It is not yet clear why the kinetics of the chain reaction is slow enough to be observable in this particular case but radical **90** is likely a persistent species,[49] in analogy to *α*-(arylamino)benzyl radicals.

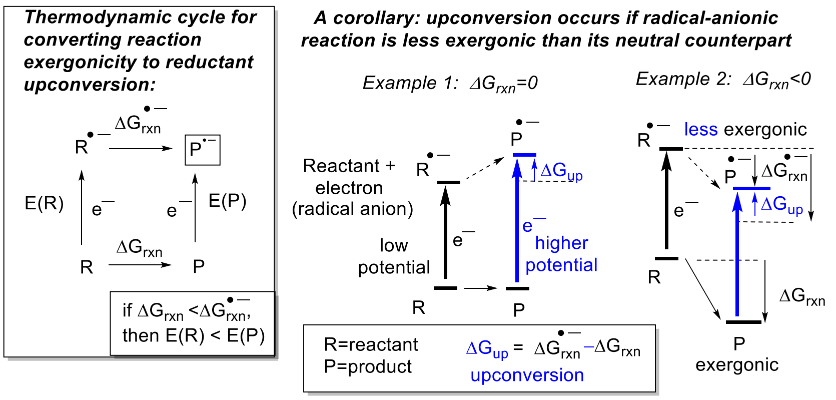
■ HOLE CHAINS: EXAMPLES

The prevalence of electron upconversion brings a question about its counterpart: is hole upconversion important for oxidative photoredox cascades? Indeed, similar to the known examples of chemical and electrochemical hole catalysis of cycloadditions,[50−55] hole-propagating chains are observed under photoredox conditions as well.[56,57] This is not surprising as similar chain processes have been well-documented in the chemistry of radical-cations.[58]

In this catalytic cycle (Scheme 13), the oxidizing Ru(II) photocatalyst injects a hole in the dienophile, producing a radical-cation, which then reacts with a diene to form the upconverted cyclic radical-cation. Hole transfer to a neutral dienophile produces the Diels−Alder product and reinitiates the catalytic cycle. The presence of catalytic chains is supported by a QY of 44.[10] A similar chain length (41) was found when the same reaction was promoted via chemical oxidation while electrocatalytic oxidation under optimized conditions gave current efficiencies of up to 8000%, corresponding to a chain length of 80.[52]

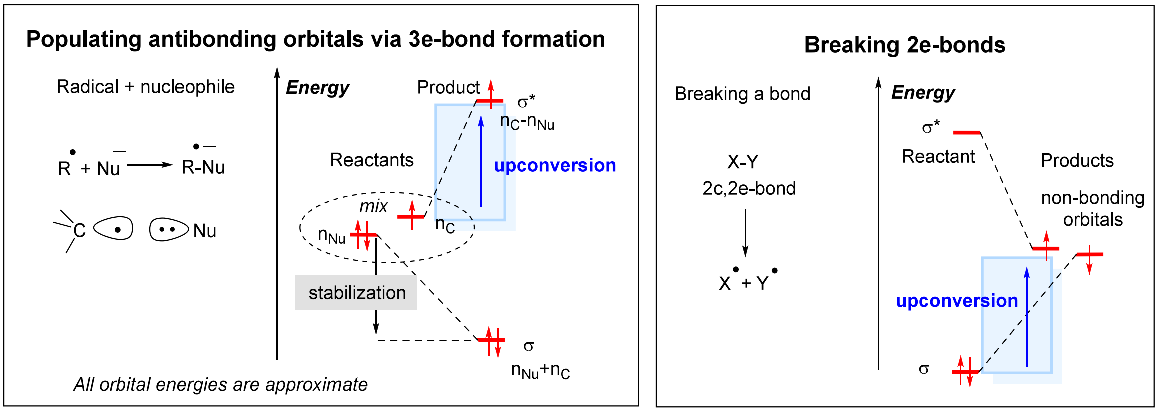
A striking difference was found for the QY of photoredox reactions mediated by the Ru cationic photocatalyst with different counterions: 26 for $BAr^F{}_4{}^-$ but only 0.35 for $Ar^FSO_3{}^-$. The data suggest a correlation between the noncoordinating nature of the catalyst counterions and the reaction rate. After detailed analysis, the authors concluded that "counteranion effects impact multiple aspects of the photocatalytic mechanism, including the energy of the reactive triplet excited state, the rate of the electron-transfer photoinitiation event, and the dynamics of nonphotochemical product-forming radical chain propagation events". This again illustrates the inherent

Scheme 15. Difference in Reaction Exergonicities is *the* Source of Redox Upconversion[a]



[a]The relationship is direct—100% of the free energy deficit (in comparison to the neutral process) becomes the redox potential increase (E_{red} for radical-anions and E_{ox} for radical-cations).

Scheme 16. Two Approaches to Electron Upconversion: (a) Formation of 2c,3e-Bonds; (b) Breaking a 2c,2e-Bond



complexity of photoredox reactions. As an appealingly simple hypothetical counterpoise, one can suggest the chain-propagating electron transfer which should greatly depend on the counterion, as the tightly coordinating counterion should inhibit the charge transfer in comparison to a noncoordinating counterion.

Another interesting observation comes from the comparison of QYs for different amounts of photocatalyst. The higher QY (44) is observed when using 0.5% of the photocatalyst compared to when using 1% (26). Although slightly different substitutions of the catalysts complicate the direct comparison, this is also consistent with the presence of SET chains. The oxidized photocatalyst can quench such chains, so one would expect lower catalyst loadings to increase chain length.[59]

Other types of hole-catalyzed transformation exist as well.[22,56,60−66] For example, Glorius et al.[60] reported photosensitized additions of silyl ketene acetals with methyl methacrylate and related Michael acceptors (Scheme 14). Not only did it have a high QY of 15.6, but it also provided an example where reaction regioselectivity was determined by SET chain propagation.

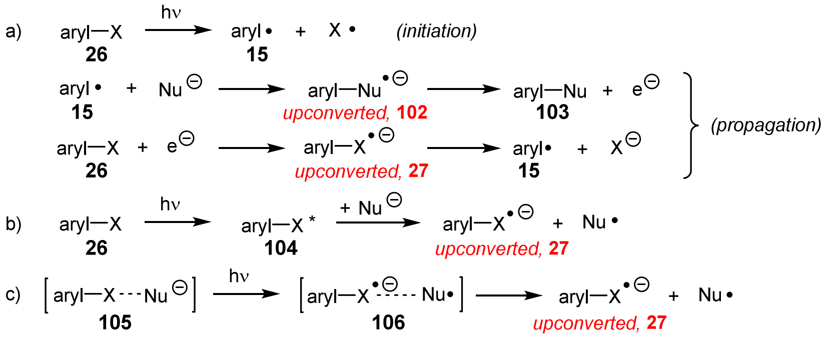
Photosensitization followed by SET from the silyl ketene acetal to the photocatalyst results in a radical-cation. This initial radical-cation then transfers the trimethylsilyl (TMS) cation to the partner, forming an oxonium enal cation and a methyl methacrylate α-radical. These species can react via either 1,2- or 1,4-fashion, both reactions resulting in new upconverted radical-cations with redox potentials higher than those of the initial radical-cation. In both cases, SET from another ketene acetal reactant can form the product and initiate the catalytic cycle. Interestingly, it is the SET chain propagation step, which is both faster and more exothermic for the formation of the 1,2-addition product, that determines the selectivity. The selectivity control through a catalytic redox chain is a rare[67] but a potentially impactful approach for reaction design.

It is clear that the scope of reactions involving SET chains will continue to expand. It is not our goal here to give an exhaustive discussion or a full list of such transformations. Instead, after illustrating that such processes are possible, we focus on the following fundamental questions: Where do the redox properties highlighted in the previous section come from? How can the redox potential go *up* when the total energy of the molecular system goes *down*?

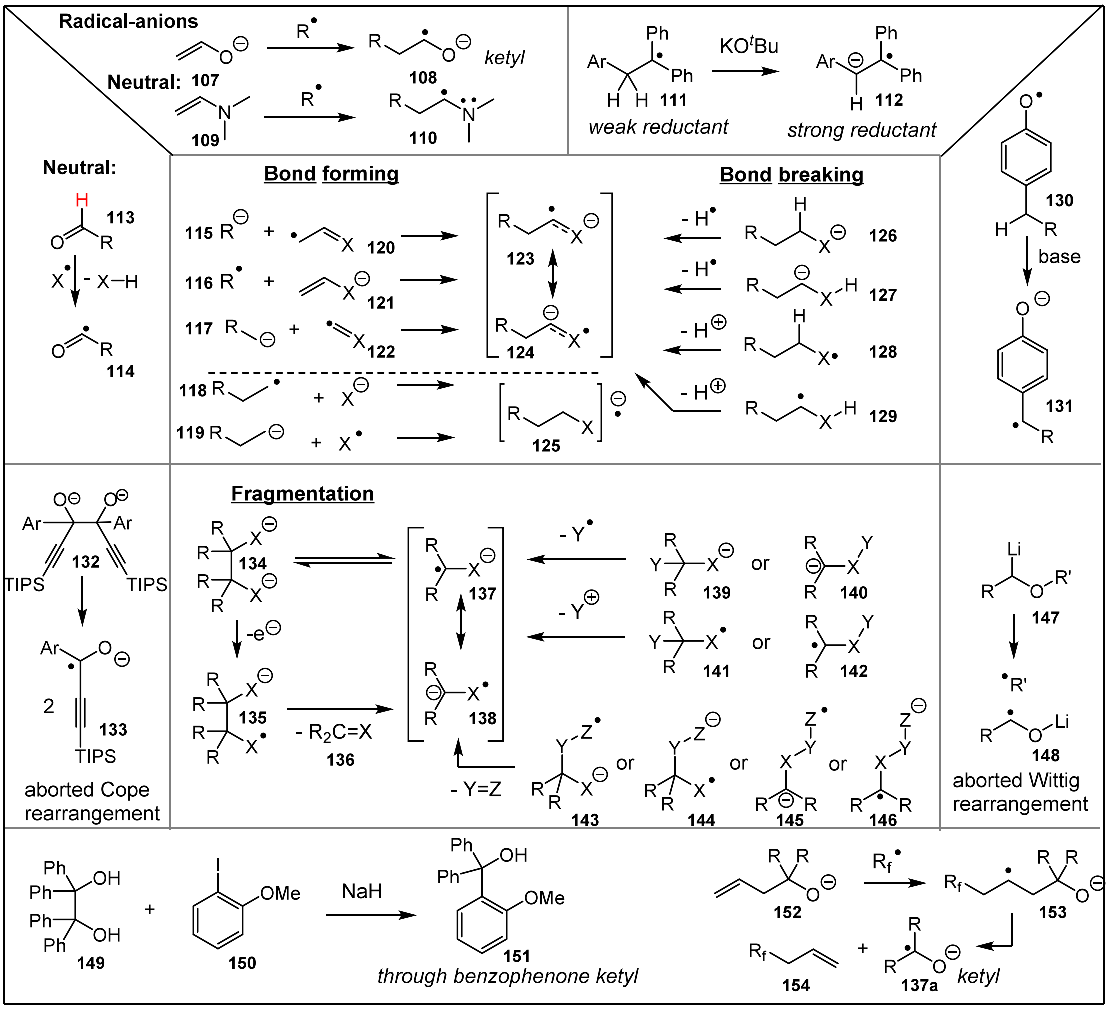
■ WHEN TO EXPECT UPCONVERSION? THE THERMODYNAMIC PERSPECTIVE

In short, redox upconversion can be thermodynamically favorable when the charge transfer is coupled with an exergonic chemical reaction. In such cases, reactions can be both downhill *and* produce strongly reducing/oxidizing species from weakly reducing/oxidizing reactants. In order to understand how reaction exergonicity can be converted into an increase in the redox potential, it is sufficient to consider the thermodynamic cycle in Scheme 15. This cycle shows how

Scheme 17. Light-Induced $S_{RN}1$ Reaction: (a) Standard Scenario through Direct Bond Homolysis and Propagation through Upconverted Radical-Anion Species; (b and c) Alternative Generation of the Upconverted Radical-Anion



Scheme 18. General Approaches to Electron Upconversion through the Formation of 2c,3e-Bonds in Anionic Systems



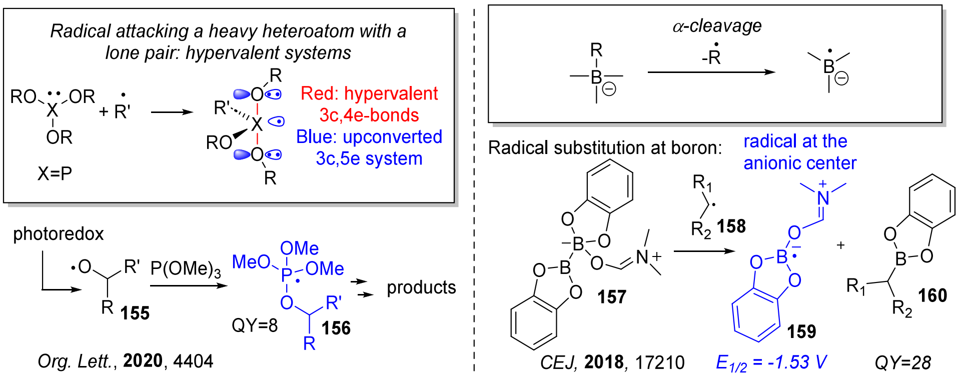
the *difference* in exergonicity of the neutral and radical ionic reaction *has to* translate directly into a change in the redox potential for the product radical-ion relative to the reactant radical-ion.

In summary, the secret to redox upconversion is simple: Any chemical reaction that becomes less exergonic upon one-electron reduction upconverts an electron. In the same way, any chemical reaction that becomes less exergonic upon one electron oxidation upconverts a hole.

■ WHEN TO EXPECT UPCONVERSION? THE MOLECULAR PERSPECTIVE

But what kind of reactions are expected to be less exergonic upon addition of an electron (or a hole)? Are there reactions where upconversion is expected? The answer is "Yes", and one does not need to look any further than the most important reaction of chemistry, i.e., the formation of a two-electron two-center bond. This reaction that serves as the basis of chemistry, becomes less favorable when an electron is either added or removed. For example, the BDE(H−H) is >100 kcal/mol but

Scheme 19. Examples of Upconversion without Population of Antibonding Orbitals



the 2c,3e or 2c,1e H−H bonds are much weaker (~52 and 64 kcal/mol, respectively[68]). Hence, any reaction of two nonbonding orbitals populated by a total of either three or one electron(s) can "upconvert" an electron or a hole (Scheme 16).

These expectations fully agree with the fundamentals of the MO theory, which provides another way to understand redox upconversion. For example, the formation of 2c,3e bonds "converts" two nonbonding atomic orbitals (AOs) into a bonding and an antibonding MO. Although the antibonding MO is raised relative to the starting AOs, Pauli's exclusion principle requires one of the three electrons to be forced into this higher energy orbital. Here, electron upconversion is inevitable as the formation of three-electron bonds "moves electrons" from *nonbonding* orbitals to *antibonding* orbitals.

This analysis provides further clues on where else to look for upconversion. For example, homolytic cleavage converts a covalent bond into two nonbonding atomic orbitals. In this process, two electrons move from a lower energy *bonding* orbital to the two higher energy *nonbonding* orbitals. A related but more subtle approach to upconversion stems from structural distortions that weaken bonds and raise energy of the HOMO. Bond stretching, alkyne bending, alkene twisting, breaking conjugation in an amide, etc. provide examples of such processes.[68,69]

The first of the two above approaches is "associative" (i.e., a bond is formed), while the second one is "dissociative" (i.e., a bond is broken). From a practical point of view, one would expect that making a bond, even a 3-electron one, is intrinsically thermodynamically favorable while breaking a bond is generally thermodynamically unfavorable. However, both processes move electrons from lower energy orbitals to higher energy orbitals. Furthermore, both types of reactions can be either uphill or downhill, depending on the specific bonding situation, charge, substitution, etc.[70] Importantly, both types of processes are common in photoredox reactions, which by their nature include both radical and ionic processes, sometimes transitioning ("crossing over") into each other.

Reactions of aryl radicals with anionic nucleophiles are quite fast. For example, the reaction between a phenyl radical and Ph_2P^- is only ~10 times slower than the diffusion limit. Even the reactions with more stabilized nucleophiles are still sufficiently fast to be useful ($Ph^\bullet + PhS^-$, $k_2 = 2.6 \times 10^7$ M^{-1} s^{-1}; $Ph^\bullet + CN^-$, $k_2 = 4 \times 10^5$ M^{-1} s^{-1}).[71,72]

Combining this process with the reductive breaking of an aryl−X bond can establish the chains of $S_{RN}1$ reactions proceeding through aryl−X radical-anions. Furthermore, the direct photolysis of the aryl−X bond is not the only option for initiating the chain process, and other scenarios are possible (Scheme 17) including SET to the photoexcited aryl halide or a preformed EDA complex. The combination of the reactants and the excitation wavelength determines the exact mechanistic path.[73]

Guided by the general considerations in Scheme 16, one can find that other reactions leading to upconversion generally follow the same logic. For example, electron upconversion associated with population of antibonding orbitals is observed not only when a radical and an anion form a σ bond but also in processes where radical and anion interact indirectly, e.g., when radicals are deprotonated,[74] when radicals add to enolates,[10,26] or when anions undergo homolytic cleavage.

Homolytic cleavage of a C−C bond near an anionic center is another route to upconverted 2c,3e-based radical-anions. Such fragmentations occur outside of the photoredox realm too, for example, in retro-pinacol reactions,[75] Wittig rearrangement analogs,[76−78] and the dissociative dianionic Cope rearrangement.[79]

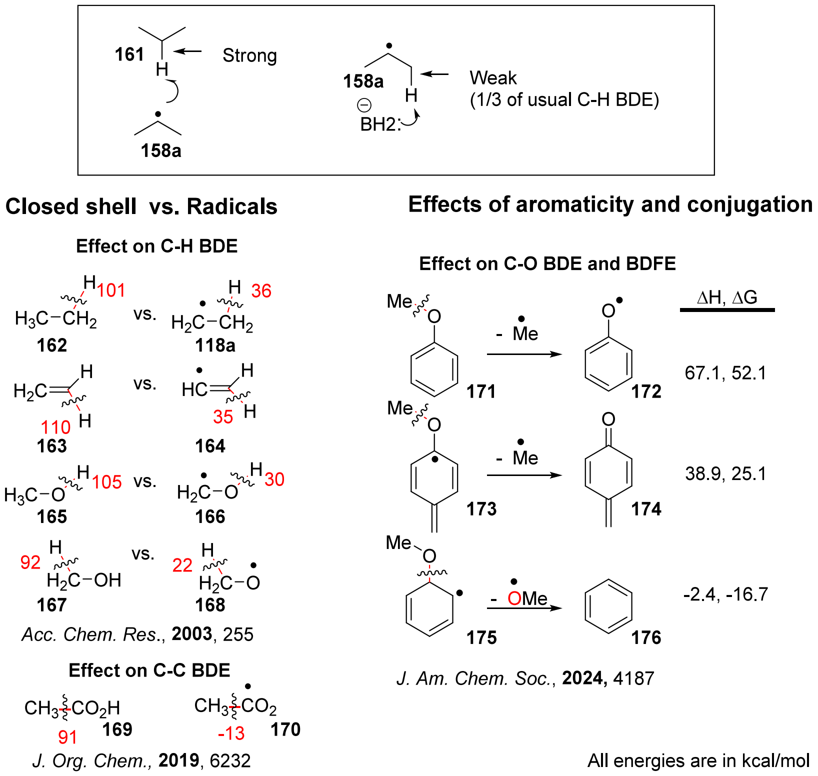
Scheme 18 presents a selection of upconverting reactions associated with the formation of 2c,3e-bonds. While there are only two C−X bond forming approaches for injecting an electron into a σ^* C−X orbital, there are many ways to make upconverted radical-anions where the extra electron populates an antibonding π^* C═X orbital: three based on C−C bond formation and four based on either C−H or X−H bond breaking (Scheme 18, top). The bottom part of Scheme 18 extends the list of reactions for making ketyl-like radical-anions via fragmentations and eliminations where C−C, C−X, or X−Y bonds are broken in anionic or radical-anionic species.

The upconverted species do not have to be anionic. For example, addition of alkyl and aryl radicals to enamines is also clearly an upconversion. If the radical center in the addition product is adjacent to a lone pair of a neutral heteroatom, this is still an upconverted 2c,3e-system with one electron in a higher energy antibonding orbital.

However, formation of 3e-bonds (or the avoided crossing version where the extra electron goes into a lower energy π^* orbitals instead of the σ^* orbitals)[80] is not the only mechanistic scenario for upconversion. Two additional possibilities where the radical center populates a nonbonding orbital are shown in Scheme 19.

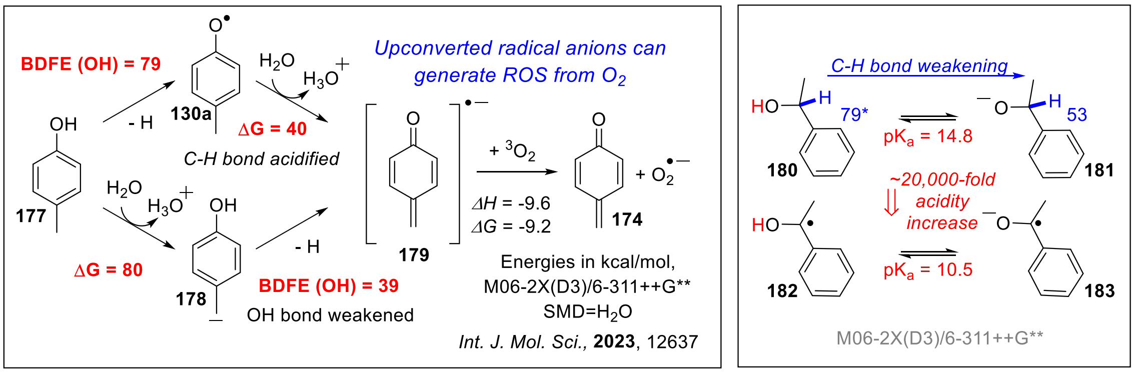
An interesting situation is observed when a radical interacts with a lone pair of a third period heteroatom (e.g., phosphorus[81] or sulfur[82]). In analogy with the earlier examples, one would expect this reaction to create a 2c,3e-bond and populate an antibonding orbital, but the situation here is

Scheme 20. Role of Thermodynamics of Radical C−O Bond Fragmentation in Different Conjugated Systems[a]



[a]Radical center in a molecule can be considered "a hot spot" which weakens adjacent C−H, C−C and C−O bonds.

Scheme 21. Acidification of C−H Bonds by Radical Centers



different in an intriguing way. The heavy atoms are capable of hypervalency that involves a change from "normal" 2c,2e-bonds to 3c,4e-bonds that "free" a nonbonding orbital for the unpaired electron.[83]

Structures of such radicals are diverse and substituent-dependent, but EPR data for phosphoranyl radicals suggest a trigonal-bipyramidal structure, with the odd electron in an equatorial site.[84] If the apical substituents have lone pairs, they can stabilize and simultaneously upconvert the P-centered electron (2c,3e-bond for one heteroatom or 3c,5e-bond for two apical heteroatoms (Scheme 19)). Such species has been shown to initiate SET chain reactions with QY = 8.[85]

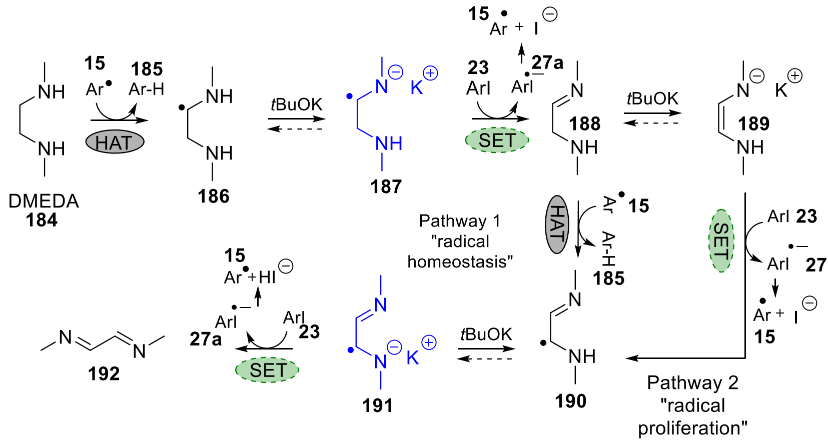
Radical substitution at an anion can also produce upconverted radical-anions as illustrated by reaction of the $R_2B{-}B(^{-})\ R_3$ unit with a C-centered radical (Scheme 19, right).[86] As the B−B bond is broken to form the C−B bond, the leaving group gets both the negative charge and the unpaired electron allocated to a nonbonding orbital at boron. The SET chain in borylation mediated by such radicals is supported by a QY of 28 and a highly negative calculated redox potential.

■ WHY DEPROTONATION OF RADICALS IS A GOOD ALTERNATIVE TO ATOM TRANSFER REACTIONS?

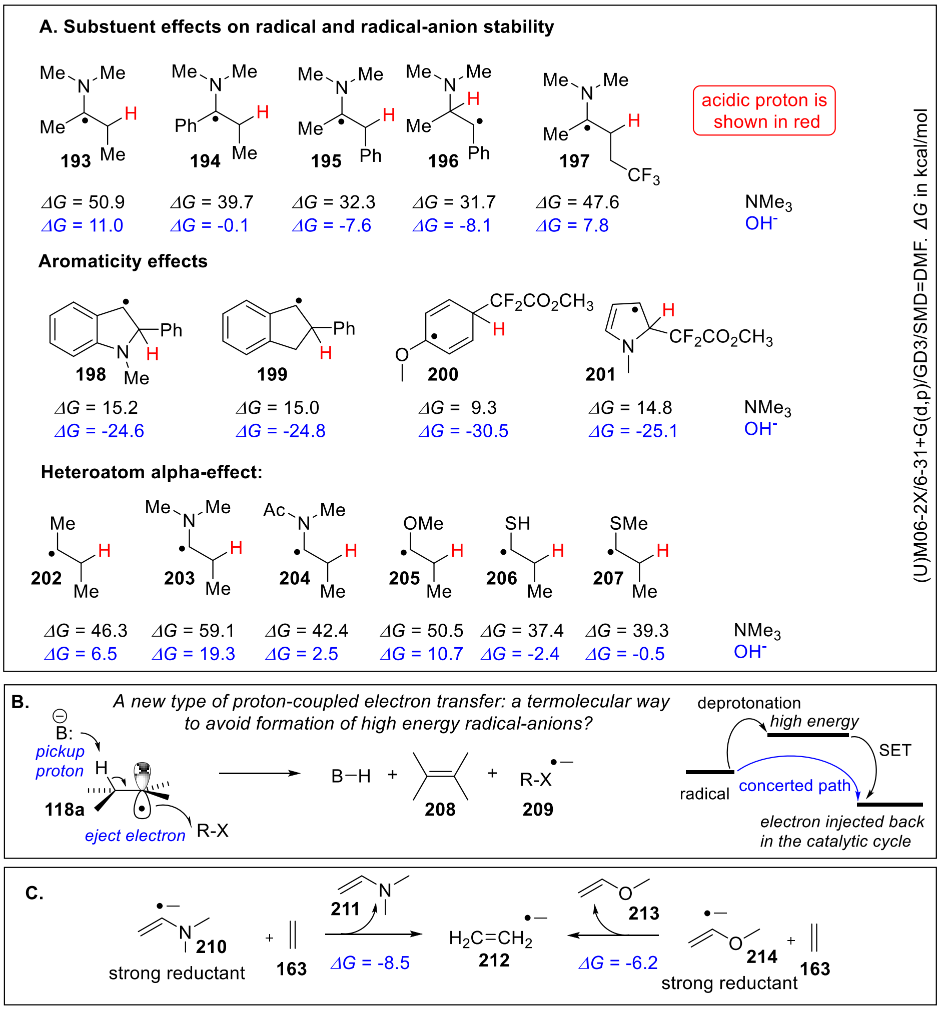
In this section, we want to highlight a common path to electron upconversion, i.e., the deprotonation of radicals. This is not a reaction that first comes to mind when one thinks of radical chemistry. In the collective mind of organic chemists, radicals generally do one-electron chemistry, which includes atom transfer, addition to π-bonds, fragmentations into a closed shell molecule and a radical, or one-electron oxidation/reduction.

However, the importance of such steps is recognized in ground state radical reactions (Scheme 5).[24] In the photoredox

Scheme 22. Evolution of Secondary Amines under Basic Conditions Can Lead to the Formation of Several Upconverted Electron Donors



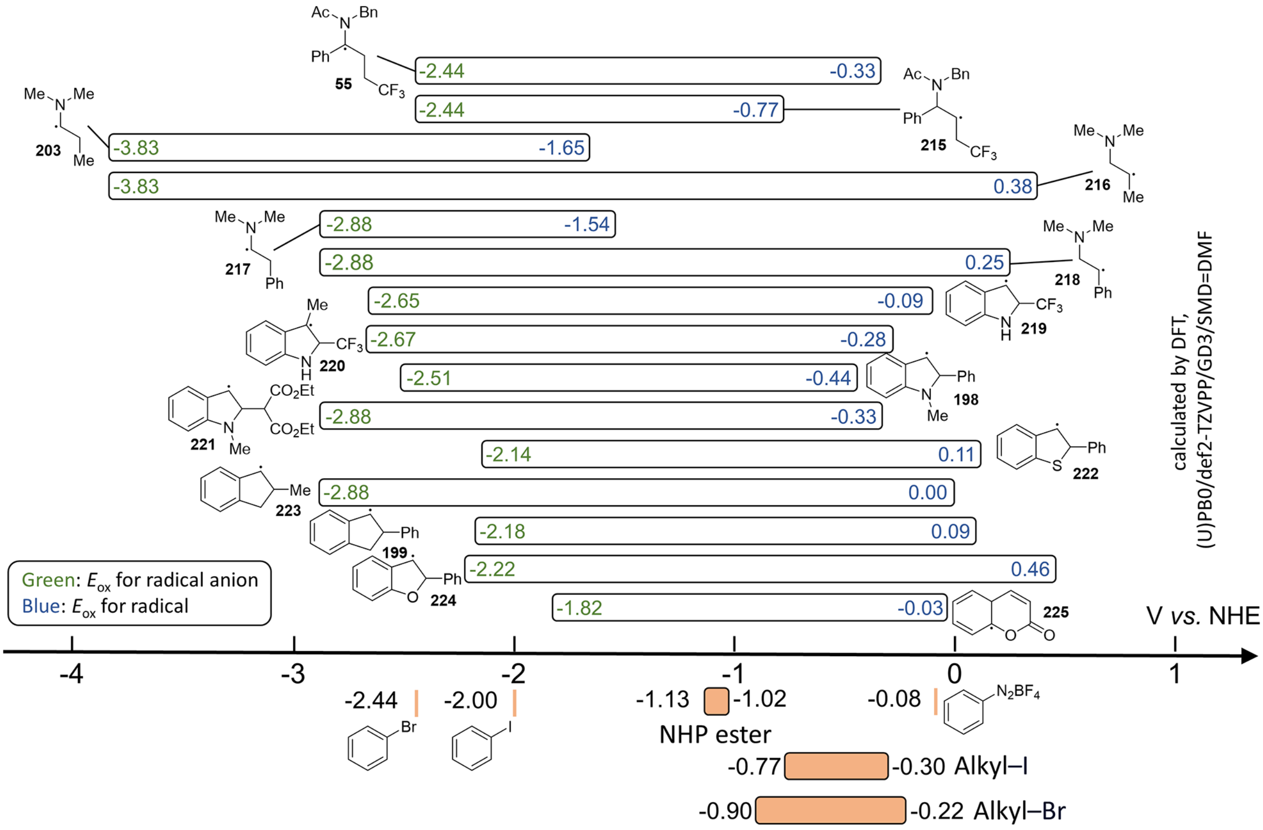
Scheme 23. (A) Structural Effects on Deprotonation Exergonicity for Typical Radical Intermediates of Photoredox Reactions; (B) A Possible Way To Avoid the High Energy Intermediates Where Deprotonation Is Coupled with Electron Transfer; (C) Heteroatom-Substituted Radical-Anions Can Be Stronger Reductants than Their Hydrocarbon Analogues



realm, transient radicals often cross to the radical ionic regime via two-electron processes. In the presence of bases, deprotonation is one example. Conspicuously, bases are known to have significant effect on photoredox reactions.[9]

This is not surprising because radical centers have two related effects on vicinal C−H bonds: bond-weakening and an acidity increase (Scheme 20). Even in neutral radicals, the *β*-C−H bonds are weakened so much (BDE ~ 35 kcal/mol) that it becomes much weaker than the C−Br bond that needs to be

Scheme 24. Oxidation Potentials vs. NHE for Various Radical Species (Blue) and Their Conjugate Radical-Anions (Green)[47,95−97]



broken for the competing XAT (~70 kcal/mol).[87] This activating influence is also observed for the C−C[88] and C−O bonds.[89] The effect of BDE lowering is amplified by the acceptor nature of radicals,[74,90,91] leading to considerable acidification of C−H bonds aligned with the partially occupied orbital.[74]

Radical acidity has many consequences. One of them is the chameleonic nature of antioxidant phenols (Scheme 21). Typically, they break radical chains by forming a relatively stable ArO radical. However, this radical has an unexpected weak spot at a remote position as the *para*-benzylic C−H bonds are acidified. The calculated C−H free energy for deprotonation of C−H bond in *p*-cresol with water decreases from 80 to 40 kcal/mol.[74] Electron acceptor and aryl groups further increase the C−H acidity (×10^{13} for phosphonates or ×10^9 for a phenyl group) and render C−H deprotonation important.[74] Such double C−H/O−H activation leads to the formation of quinone methide radical anions, which can transfer an electron to molecular oxygen with the simultaneous formation of two reactive species (the quinone methide and superoxide). In this sequence, phenols change from antioxidants to cytotoxic agents under the oxidative stress conditions typical for tumors.

Deprotonation of relatively acidic N−H bonds in *α*-amino radicals is facile.[92,93] The combination of *N,N*′-dimethylethylenediamine (DMEDA) and *t*BuOK was investigated by Murphy, Tuttle, and co-workers[94] who, through D-labeling, found that cleavage of the C−H bond on the ethylene group played a critical role in the radical initiation process. Jiao and co-workers[92] thoroughly analyzed the initiation and propagation steps for this system. Although *t*BuOK does not deprotonate the secondary amine, the N−H of the subsequently formed DMEDA *α*-amino radical is greatly acidified. Its deprotonation creates an upconverted radical-anion (**187**), which can serve as an SET-propagating donor (Scheme 22). Its oxidation gives a new intermediate with a more acidic N−H bond, so deprotonation is now even more likely, setting up facile H atom transfer that would create yet another strongly reducing agent.

This example shows how a well-designed reagent can engage in multiple SET cycles. Interestingly, the authors identified two distinctly different radical initiation networks. In one of them, the "radical homeostasis" pathway, two aryl radicals are consumed and two are regenerated, so there is no net change in the aryl radical count. In the alternative "radical proliferation" pathway, a sequence of steps mediated by two rounds of electron upconversion consumes one radical but generates three new radicals.

It is important to note a common drawback of ground state upconversion in these systems. Generally, they involve induction periods for generating the critical mass of the redox initiators. However, the photoredox version does not need to have such induction periods as long as the flux of photons is sufficient.

Considering the generality of deprotonation for radical reactions under basic conditions, the nature of the base should be important for photoredox processes. Ideally, the base should not interfere with the photocatalyst but should be able to turn acidified radicals into highly upconverted radical-anions.

Scheme 23 illustrates that these deprotonations should not always be taken for granted and can be quite endergonic. In these situations, finding a base that is sufficiently strong for initiating a beneficial SET chain (but not too strong to interfere with other steps of the reaction) becomes an important part of reaction optimization.

Computational data offer useful guidelines for future investigations. For example, the effect of conjugation is very large—compare the effects of phenyl substituents at both the α- and the β-positions relative to the radical center in the reactant (top row in Scheme 23A). As discussed earlier, if deprotonation is coupled to partial rearomatization, the process is greatly facilitated (middle row). On the other hand, in the absence of conjugation and aromaticity, deprotonations are less favorable. Although donor heteroatoms introduce an additional penalty (bottom row), this penalty can be lowered when acceptor groups are added to the heteroatom (NMe vs NAc).

For the endergonic deprotonations, one can suggest the possibility of avoiding the formation of high-energy radical-anion bonds via a termolecular reaction where deprotonation is coupled with electron transfer in a concerted manner (Scheme 23B). Nature often finds ways to avoid a high energy path, especially when the final product is way downhill in energy.

The degree of upconversion achievable through deprotonation of a radical to a radical-anion bond can be expressed as the difference between the oxidation potentials of these two species. Results for a series of radicals are shown in Scheme 24.

Clearly, upconversion through deprotonation transforms radicals to better reductants. The highly negative E_{ox}-values for the upconverted radical-anions indicate a strong reducing power, comparable to photoexcited anions or radical-anions of photosensitizers.[98,99] Remarkably, such extremely reducing species were successfully used even in protic solvents.[100] As expected, the most negative potentials are predicted for radical-anions of unconjugated enamines (a 3c,5e situation). Although both conjugation and the absence of strong donor substituents diminish the reductive power, in many cases, it is still sufficient to cleave the C−X bonds in aryl iodides or even aryl bromides.

CONCLUSIONS

Photoredox originates from the marriage of one-electron transfer with two-electron chemistry. What happens at the intersection of these two chemical paradigms? Although the mechanistic complexity of photoredox catalysis does not prevent it from being versatile and efficient, it also leads to hidden secrets and underappreciated mechanistic scenarios. In this Perspective, we discussed how redox upconversion, a paradoxical increase in redox potentials that can be associated with exergonic reactions, can be the hidden secret of the surprising efficiency of photoredox catalysis.

We present experimental and computational data to illustrate how redox upconversion serves as one of the conceptual cornerstones of photoredox catalysis. The key advantage of upconversion is that it provides a thermodynamic foundation for SET chains where electrons (or holes) can serve as the true catalysts.

Although chain processes have been identified in a large number of photoredox reactions, the nature of the chain processes is not always well-defined. In this Perspective, we appeal for differentiating atom-transfer-based radical chains from chains propagated via SET. The importance of the SET chains highlights the pervasive role of electron and hole upconversion in photoredox catalysis.

Measured QYs[101] alone can reveal only a small part of the SET chains. In fact, since such chains can be masked by the inefficiency of other steps of the cascade, most chain reactions likely evade detection, especially because they can be quite short-lived. However, upconversion (evaluated through CV voltammetry or computations) can reliably identify a broader selection of cascades in which SET chains can persist.

Hence, it is important to understand the fundamental effects associated with upconversion. To do so, we highlight the most common mechanistic steps, which can lead to considerable increase of redox potential, permitting the upconverted electron or hole to be reinjected in the catalytic cycle. In particular, deprotonation of radicals should be taken into consideration in the presence of a base.

Understanding the mechanistic pathways of photoredox reactions is essential for optimizing the catalyst performance. We hope that this general understanding will contribute meaningfully to practical reaction design. One key practical outcome would be in revealing the nature of the base as one of the key parameters in the design of a photoredox reaction. Currently, the focus is on the photocatalyst, especially its absorption and redox properties. But if the real catalyst is in fact an electron, upconverted by reaction of a base and a radical intermediate, then the nature of the base becomes crucial. The right choice can help to engineer catalytic chains where SET is always exergonic and where the reducing power is restored (upconverted) at the end of each catalytic cycle.

Another intriguing question is how to make the SET-chains longer—currently, most examples show that there is no reactivity in the dark, so the chains are mostly short-lived. This is a design element that has not been directly optimized so far but could be an underutilized reserve of photoredox catalysis.

In those cases, when the inefficiencies in a photoredox reaction stem from short chain lengths, understanding the nature of the chain processes can guide the rational optimization of the method. When electron (reductant) upconversion operates, the electron serves as a true catalyst, multiplying the power of photoredox activation by the length of the electrocatalytic chain.

Finally, redox upconversion is not limited to photoredox reactions. It can also serve to control selectivity[60,67,80,102] and increase efficiency of electrochemical[93] and redox[103,104] reactions. Upconversion also participates in a range of biochemical processes[21]—from firefly luminescence[105] to radical enzymes,[106] to reductive repair of DNA photo-damage.[107−115]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c10422.

Computational details and optimized geometries (DFT) of all computed molecules (PDF)

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Notes

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