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Viewpoint

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Recent Applications of Organic Dyes as Photoredox Catalysts in Organic Synthesis

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INTRODUCTION

Single electron redox pathways play a pivotal role in a vast array of processes integral to life on the planet. It is no surprise that organic chemists have been intrigued by the possibility that single-electron redox manifolds might be harnessed in the discovery and design of novel organic transformations. In particular, single-electron processes mediated by photoredox catalysis hold significant promise.

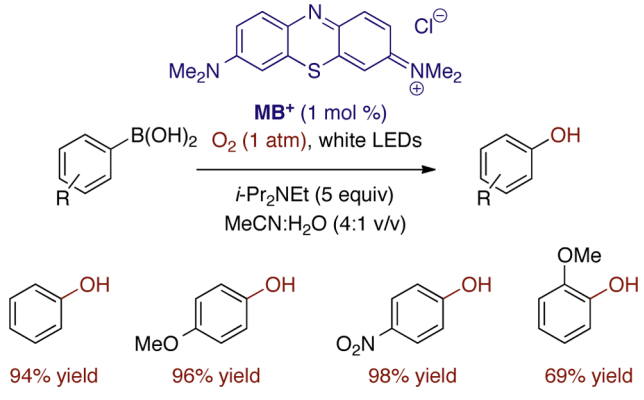
Recently, a surge of interest from the synthetic community has brought photoredox manifolds to the forefront of catalysis. Most of the activity in this field has centered on the use of Ru- and Ir-based polypyridyl photoredox catalysts to facilitate reactivity. Several reviews[1] and perspectives[2] cover this topic in great detail and are not the subject of this Viewpoint. Organic photoredox catalysts have been utilized in this context for several decades, so it is somewhat surprising that far fewer recent reports employ this class of catalysts, despite their relatively lower cost, their wide availability, and properties that can, in some cases, outperform their inorganic and organometallic counterparts.[3] This Viewpoint will give an account of recent selected advances in the use of purely organic photooxidants in synthetic transformations.

METHYLENE BLUE

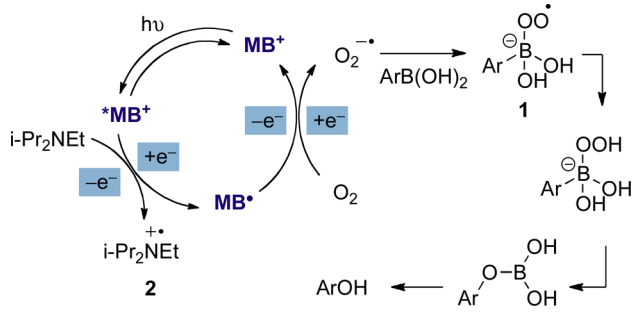
The Scaiano group recently reported an experimentally simple approach to aryl boronic acid oxidation.[4] This work builds on that of Xiao and co-workers, who previously disclosed the same reaction employing $[Ru(bpy)_3]^{2+}$ as the photoredox catalyst.[5] However, in the Scaiano work, 1 mol % of the common organic dye, methylene blue, is employed as the photooxidant under aerobic conditions with a sacrificial donor (Hünig's base) to effect the formation of phenols from the corresponding aryl boronic acids (Scheme 1). The scope of the reaction using Scaiano's conditions is not nearly as extensive as Xiao's; however, the yields of the phenol adducts are all quite high. Through a series of excited state quenching studies, the key observation in this work was that MB^+ was more efficient than $[Ru(bpy)_3]^{2+}$ at catalyzing the transformation.

Scaiano and co-workers were able to conclude that the intervention of methylene blue in the catalytic cycle likely involves reductive quenching of its triplet state ($*MB^+$) via single electron transfer from Hünig's base (Scheme 2). Further,

Scheme 1. Scaiano's Aryl Boronic Acid Oxidation



Scheme 2. Boronic Acid Oxidation Mechanistic Proposal



the researchers were able to determine through kinetic quenching data that *MB is nearly 40 times faster at this key event than $*[Ru(bpy)_3]^{2+}$. The reduced form of methylene blue ($MB^\bullet$) is proposed to act as an electron donor to the molecular oxygen present to form $O_2^{\bullet-}$. The mechanism from this point mirrors that of Xiao and co-workers, because the generated $O_2^{\bullet-}$ is presumed to add to the boron center, giving borate **1** and following hydrogen atom abstraction from the amine cation radical (**2**) and rearrangement, the desired phenol is formed following a hydrolytic workup. This method should find broad use in organic synthesis as a result of the mildness of the protocol.

EOSIN Y

In 2011, the Zeitler lab reported a method for the catalytic, organophotoredox asymmetric intermolecular α-alkylation of aldehydes.[6] The authors found success with conditions similar to those previously reported by the Macmillan lab,[7] replacing the $[Ru(bpy)_3]^{2+}$ catalyst with eosin Y, a simple organic dye. Eosin Y (EY) was identified after screening a number of dyes in the dehalogenation of α-bromoacetophenone and demonstrated efficiency in a small substrate scope (Scheme 3). These findings were applied to the main transformation, the α-alkylation reaction, employing 0.5 mol % of eosin Y, 20 mol %

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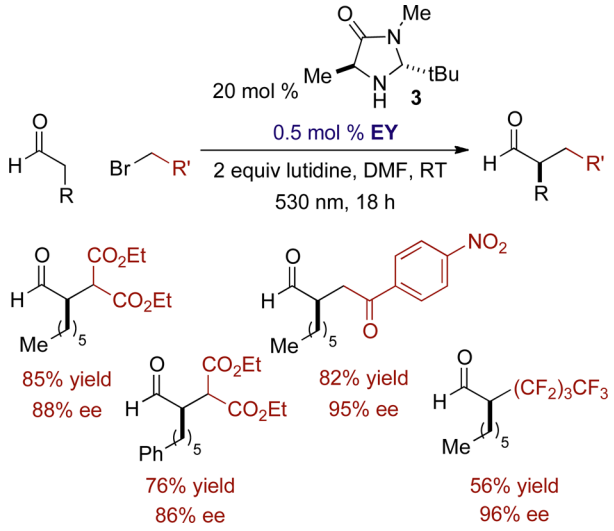
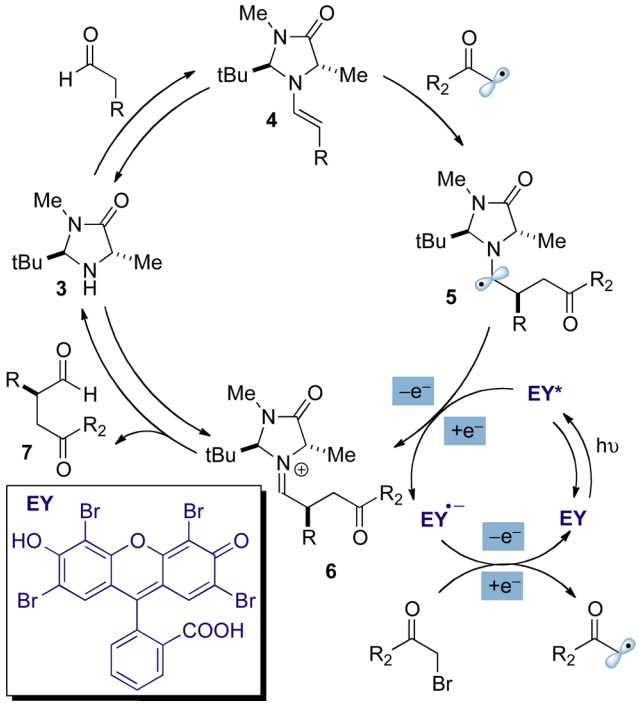
Scheme 3. α-Alkylation of Aldehydes Catalyzed by Eosin Y



of MacMillan's imidazolidinone (**3**), and 2 equiv of lutidine in the presence of 530 nm light. The desired products were obtained in good yields and high enantioselectivities.

Eosin Y can act as a reductant or oxidant in its excited state. In keeping with the mechanism proposed by MacMillan and co-workers, the authors propose that it acts as an oxidant (Scheme 4). Initially, a catalytic amount of enamine (**4**) is

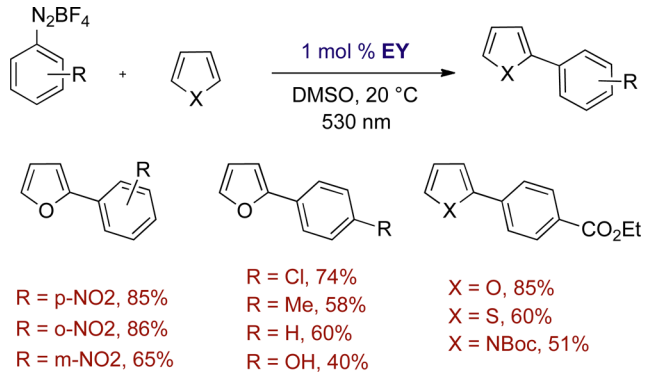
Scheme 4. Mechanism for the α-Alkylation of Aldehydes



oxidized, generating eosin Y radical anion ($EY^{\bullet-}$), which reduces the alkyl halide substrate to give the reactive α-carbonyl radical species. Enamine **4** undergoes reaction with the α-carbonyl radical to furnish α-amino radical **5**. Subsequent oxidation of **5** by the excited state catalyst (EY*) affords iminium **6**. This step propagates the catalytic cycle for both the photooxidant and the imidazolidinone catalysts. Finally, hydrolysis of the iminium intermediate (**6**) gives the desired aldehyde products (**7**).

A recent report by the König lab also takes advantage of eosin Y as a photoredox catalyst, in this case using it as a photoreductant to initiate catalysis.[8] They irradiate 1 mol % of eosin Y with visible light to catalyze the direct C−H bond arylation of heteroarenes using aryl diazonium salts (Scheme 5). Aryl diazonium salts are known for their high reduction

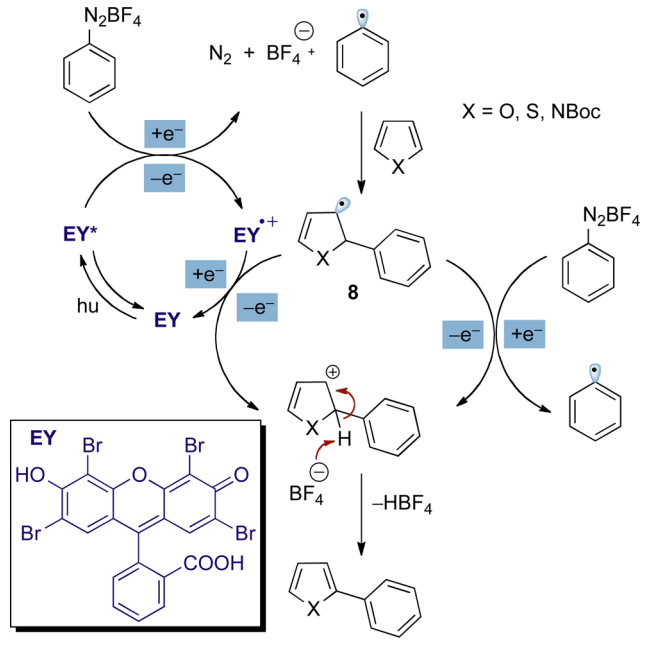
Scheme 5. König's Arylation of Heteroaromatics Catalyzed by Eosin Y



potentials and have found utility as oxidative quenchers in many transformations. This work provides a mild and effective alternative to transition metal- and copper-catalyzed or *t*-BuOK-assisted methods.

The reaction was tolerant to a number of functional group substitutions, including halides, alcohols, esters, nitro, and cyano groups as well as various heteroaromatic partners. The mechanism is proposed to proceed through reduction of the diazonium salt by the excited catalyst (EY*), followed by addition to the heteroarene (Scheme 6). The allyl radical (**8**) can then undergo oxidation by eosin Y radical cation ($EY^{\bullet+}$) or radical propagation by another species of aryl diazonium salt.

Scheme 6. König's Proposed Mechanism



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Subsequent deprotonation regenerates aromaticity and provides the desired arene-coupled product.

The König lab found that electron-deficient diazonium salts resulted in higher yields, likely because of their increased propensity toward reduction. Addition of 2,2,6,6-tetramethylpiperidinoxyl (TEMPO) to the reaction mixture halted the coupling reaction, and the TEMPO-trapped intermediate was detected. This supports the mechanistic hypothesis that the reaction follows a radical pathway.

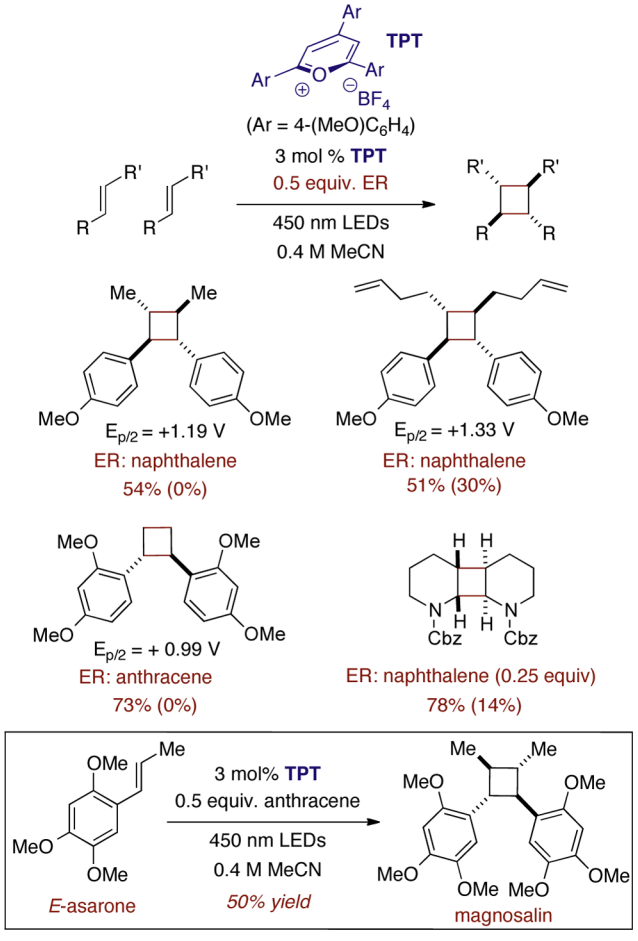
PYRYLIUM SALTS

Triarylpyrylium salts have been used for some time as powerful excited state oxidants.[3a] Their modular synthesis combined with easily tunable reduction potentials and absorption in the visible region makes this class of organic photooxidants particularly appealing for applications to single-electron catalytic manifolds.

We have recently applied the use of 2,4,6-tris(4-methoxyphenyl)pyrylium tetrafluoroborate (TPT) to the catalysis of [2 + 2] homocycloaddition reactions of alkenes (Scheme 7).[9] The reaction is presumed to proceed via the intermediacy of alkene cation radicals generated via the oxidation of the alkene substrates by the excited state of the TPT. We, as well as the Yoon group,[10] observed that cycloadditions proceeding through this mechanistic manifold are highly reversible due to competitive oxidation of the final cyclobutane adducts that initiate a retro-[2 + 2] cycloaddition. Importantly, the final cycloadducts typically have higher oxidation potentials than the starting alkenes. We hypothesized that inclusion of an oxidizable arene with an oxidation potential between the alkene substrate and cyclobutane products would function as an electron relay (ER). This strategy would permit the use of a single photooxidant with a carefully selected arene ER and thereby avoid oxidative cycloreversion. For this application, we selected arenes such as naphthalene and anthracene because these were marginally higher in oxidation potential of the alkene, yet lower than that of the corresponding cyclobutane adducts.

This strategy proved fruitful because a number of styrene and even enamides could be dimerized in this fashion (Scheme 7). In the absence of the ER, very little, if any, of the desired cyclobutane adducts was observed (parenthetical yields). It is worthy of mention that all the cyclobutane adducts gave a single diastereomer of product. As a demonstration of the utility of this method, we were able to accomplish the synthesis of the lignan magnosalin from naturally occurring (*E*)-asarone.

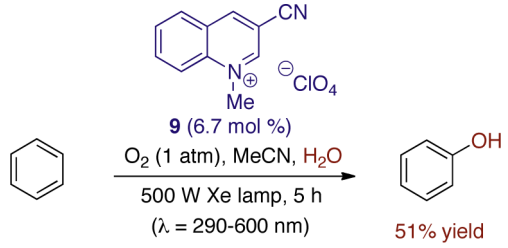
Scheme 7. Alkene [2 + 2] Homodimerization Catalyzed by Triaryloxopyrylium Salts; Nicewicz and Riener



QUINOLINIUM AND ACRIDINIUM OXIDANTS

Recently, the Fukuzumi laboratory has developed a direct protocol for the production of phenol from benzene using 3-cyano-1-methylquinolinium perchlorate (**9**) as the catalyst (Scheme 8).[11] This process relies on the strong oxidizing capabilities of **9** in the singlet excited state (E_{red} = +2.72 V vs SCE, MeCN) to oxidize benzene (E_{ox} = +2.32 V vs SCE, MeCN) and initiate a photoredox mechanism to ultimately produce phenol directly in 51% yield (t = 5 h). This protocol could be conducted on a gram scale, albeit with slightly diminished yields and requiring extended irradiation periods (41% yield, 48 h). This is a remarkable feat given that current metal catalysts furnish only a fraction of the yield of Fukuzumi's system and require elevated temperatures. In addition, chlorobenzene could also be oxidized to a mixture of *p*- and *o*-chlorophenol using the same catalyst system in yields of 27% and 3%, respectively.

Scheme 8. Fukuzumi's Benzene Oxidation to Phenol



Through isotopic labeling studies, the researchers were able to conclude that the source of oxygen incorporated in the phenol was not from O_2, but rather, the H_2O employed in the reaction. From the isotopic labeling and transient absorption spectroscopic studies, the Fukuzumi laboratory proposed that the mechanism of the reaction first proceeds via single-electron oxidation of benzene by the excited state of **9** (Scheme 9). Water then adds to the benzene cation radical (**10**) to give hydroxy arene radical **11** and, following hydrogen atom abstraction, affords phenol. It is worth noting that Fukuzumi does not observe further oxidation of phenol to dihydroquinones, despite the fact that phenol's oxidation potential is lower than that of benzene. A more recent report from the same

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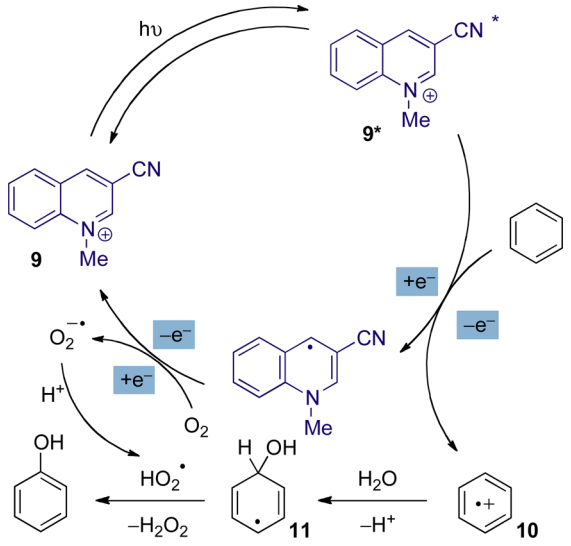
Scheme 9. Proposed Benzene Oxidation Mechanism

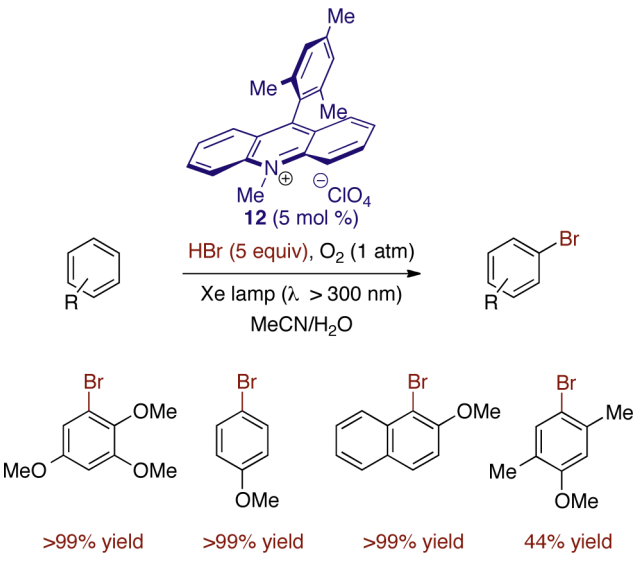


laboratory replaces **9** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the photooxidation catalyst and uses *tert*-butyl nitrite as a redox recycle reagent in a mechanism that bears similarity to the quinolinium-catalyzed reaction.[12]

Fukuzumi has also developed an intriguing acridinium-based organic salt (**12**) that has displayed remarkable redox properties in the excited state.[13] This catalyst has excellent oxidizing capabilities in the excited state (E_{red} = +2.06 V vs SCE, MeCN) while only requiring irradiation in the visible region (λ > 450 nm). This mesityl acridinium salt is believed to derive its strong oxidizing capabilities from a long-lived charge-shift state in which the mesityl group is oxidized by the excited state of the acridinium moiety in MeCN.

This organic photoredox catalyst has been employed in several organic transformations by Fukuzumi's laboratory.[14] In a recent example, the Fukuzumi group were able to brominate substituted arenes using HBr as the bromine source and O_2 as the terminal oxidant (Scheme 10).[15] Arenes with oxidation potentials within the range of the oxidizing abilities of the mesityl acridinium photooxidant were suitable candidates for

Scheme 10. Fukuzumi's Arene Bromination



the transformation. Typically, this required the presence of an electron releasing functionality on the aromatic ring, such as a methoxy group. Good to excellent yields for a number of substrates were reported with reasonable levels of regiocontrol. The mechanism for this transformation bears similarity to the benzene oxidation of phenol, in which an arene cation radical intermediate is intercepted by bromide, followed by H-atom abstraction to generate the aryl bromides.

Over the past year, our laboratory has introduced a general two-component organic photoredox catalyst system that enables a range of anti-Markovnikov alkene hydrofunctionalization reactions.[16] The catalyst system consists of the Fukuzumi acridinium salt and an organic redox-active hydrogen atom donor. Several different redox-active hydrogen atom donors have been identified and range from C−H donors such as 2-phenylmalononitrile and cyanofluorene to S−H donors such as benzene sulfinic acid and thiophenols. The hydrogen atom donors were selected on the basis of their homolytic bond dissociation energies as well as the oxidizing abilities of the subsequent radicals generated following hydrogen atom abstraction.

In general, these transformations all share a common mechanism (Scheme 11). On the basis of prior art and mechanistic studies, we propose that single-electron oxidation of the alkene substrates ($E_{1/2ox}$ < +2.0 V vs SCE) by the excited state acridinium photooxidant (**12***) furnishes the reactive cation radical species (**13**). The origin of the anti-Markovnikov selectivity in these reactions is likely the result of the formation of an initial three-membered nucleophile-cation radical adduct (**14**).[17] Homolysis of the weaker of the two bonds in this initial compound leads to the formation of the more stable radical intermediate (**15**), which is intercepted by the hydrogen atom donor (**16**), completing the transformations. We propose that the resultant radical (**17**) then acts as an oxidant for the long-lived acridine radical **19** to return the oxidant to its ground state (**12**) and reset the catalytic cycle. This two-component catalyst system is critical to maintain net redox neutrality.

By employing this generic catalytic protocol, we first published an anti-Markovnikov intramolecular hydroalkoxylation of alkenols (Scheme 12).[16a] This report made use of 2-phenylmalononitrile as the redox-active hydrogen atom donor. The scope of the reaction permitted the use of alkenols with oxidation potentials ranging up to E_{ox} ~ +2.0 V (vs SCE, MeCN). This included a range of substituted styrenes as well as trisubstituted aliphatic alkenes. It is worth noting that $[Ru(bpy)_3]^{2+}$ was ineffective as a catalyst for this reaction because it is not as powerful an oxidant, E_{ox} = +0.86 V (vs SCE, MeCN). Challenging cyclization modes such as 6-endo were observed to furnish cyclic ethers with complete anti-Markovnikov regioselectivity. The formation of 5−7 membered ethers was possible using this catalyst system.

Subsequent publications from our laboratory have expanded the versatility of this catalyst system in additional anti-Markovnikov hydrofunctionalization reactions. Employing thiophenol as the redox-active hydrogen atom donor, an anti-Markovnikov intramolecular hydroamination of unsaturated amines was described (Scheme 13).[16b] It was necessary to protect the amine with either a *p*-toluenesulfonyl (Ts) or *tert*-butoxycarbonyl (Boc) protecting group to isolate the desired hydroamination adducts in good yields, presumably to prevent oxidation of the amine. The scope with respect to the alkene component was similar to the anti-Markovnikov alkene hydroalkoxylation reaction and gave access to a variety of

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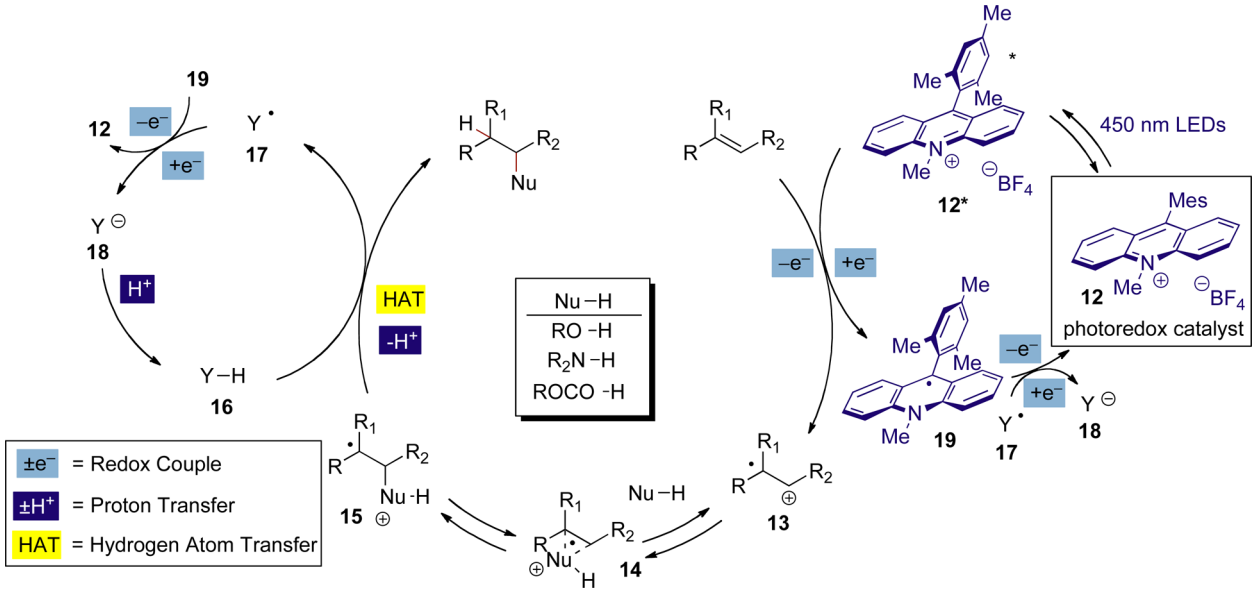
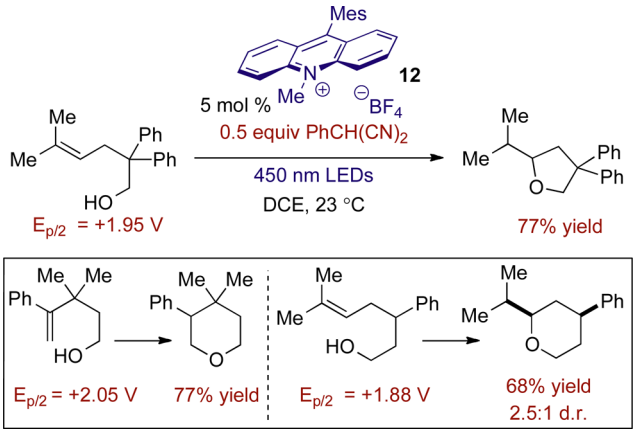
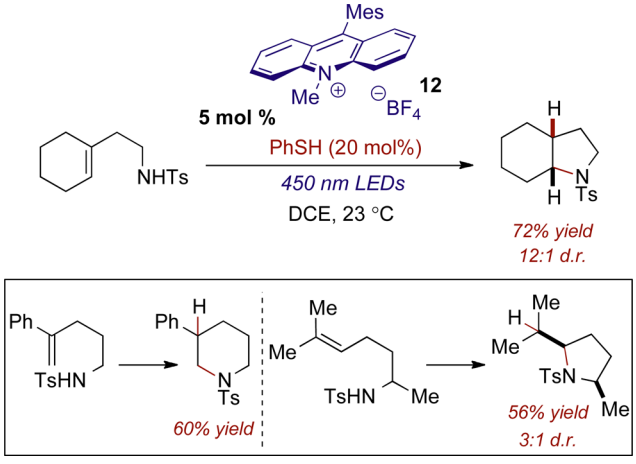
Scheme 11. General Mechanism of Anti-Markovnikov Hydrofunctionalization of Alkenes Proposed by Nicewicz



Scheme 12. Anti-Markovnikov Alkenol Hydroalkoxylation Reported by Nicewicz and Hamilton



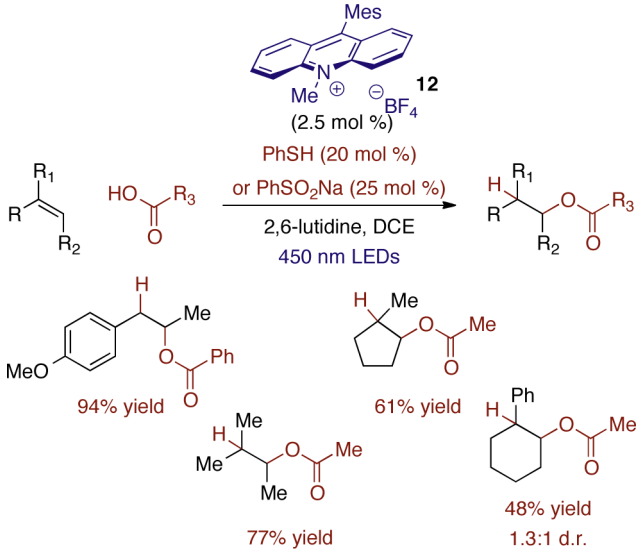
Scheme 13. Anti-Markovnikov Alkene Hydroamination of Alkenes Reported by Nicewicz and Nguyen



pyrrolidines and piperidines. In addition to the intramolecular examples, two intermolecular examples were also disclosed and displayed complete regiocontrol.

In addition, our laboratory also disclosed the use of this catalytic protocol for the anti-Markovnikov addition of carboxylic acids to alkenes (Scheme 14).[16c] In this report,

Scheme 14. Anti-Markovnikov Addition of Carboxylic Acids to Alkenes Reported by Nicewicz and Perkowski



either sodium benzene sulfinate or thiophenol were employed as cocatalysts. In the case of sodium benzene sulfinate, small quantities of benzene sulfinic acid, the proposed hydrogren atom donor, were presumably generated via an acid−base equilibrium with the carboxylic acid. This mechanistic proposal was supported by a deuterium-labeling experiment and also pointed to the hydrogen atom transfer step as rate-limiting for this process. The scope of this reaction with respect to the alkene is similar to the previous reactions in this series but also included the use of an enamide and enol ether as reaction partners. All of these reactions afforded the anti-Markovnikov adducts exclusively, save for acid-sensitive dihydropyran, which afforded a 2:1 ratio of Markovnikov to anti-Markovnikov adducts, underscoring the mildness of the reaction conditions.

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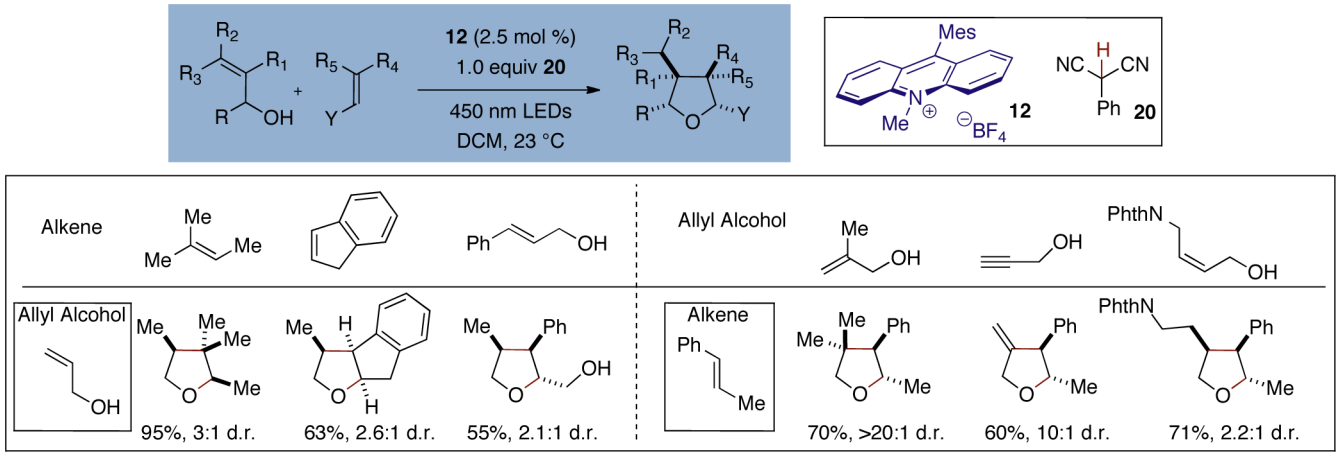
Scheme 15. Polar Radical Crossover Cycloaddition Reactions of Alkenols and Alkenes; Nicewicz



Given that the general mechanism of these transformations involves subsequent polar and radical sequences, we saw an opportunity to further expand the utility of this process by capitalizing on the radical intermediate. Now by using an allylic alcohol and an alkene, we envisioned a cycloaddition process to construct highly substituted tetrahydrofurans (Scheme 15).[18] We proposed that following addition of the unsaturated alcohol to the alkene cation radical, a radical cyclization would occur before hydrogen atom abstraction to allow for the direct formation of cyclic ethers.

We were pleased to find that this proposal could be put into practice. A number of complex tetrahydrofurans bearing a variety of functional groups, including free alcohols, protected amines, and aryl halides, could be formed from inexpensive allylic alcohols and alkenes. Moreover, propargyl alcohols could also be employed to forge cyclic ethers bearing exocyclic alkenes. Because of the tolerance of a variety of functional groups and the convergent nature of this transformation, this method promises to find utility in natural product synthesis.

SUMMARY AND FUTURE OUTLOOK

Although the seeds of organic photoredox catalysis were sown several decades ago, the recent surge in the use of this catalysis manifold shows that the synthetic organic community has taken serious notice and begun to realize the true potential of this method of catalysis. The promise for organic photoredox catalysis is great because it is able to deliver unique and valuable chemical reactivity under mild reaction conditions. In particular, it is not difficult to imagine the use of organic photoredox catalysis in key transformations in complex natural product synthesis. Challenges lie in store, however, particularly in the ability to render these processes enantioselective as well as developing new, more powerful organic photooxidation catalysts as well as organic photoreductants. It is clear, however, that this resurgent field has many opportunities for discovery.

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Notes

The authors declare no competing financial interest.

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