nature portfolio

Peer Review File

Selectivity Emerges from Indiscriminate Photoreduction

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This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Referee #1

(Remarks to the Author)
This paper describes the deliberate use of exceptionally high redox potentials that significantly exceed those minimally required for the reaction. As a result, selectivity is shifted away from control by the initial electron-transfer event and the intrinsic redox potentials of the substrates, toward control by the kinetic stability of the reduced intermediates that are generated. This conceptual advance enables an unprecedented transformation that would not be accessible by conventional approaches, as the reaction requires selective reduction of a cyclopropyl ketone in the presence of a more readily reducible olefin. The work convincingly demonstrates that long-standing paradigms governing redox-mediated chemistry can be broken and represents a significant conceptual contribution that is likely to influence how synthesis enabled by electron-transfer reactions are designed in the future. In my view, this is an outstanding study that merits publication in this journal following the minor revisions detailed below.

Given the overall high quality and rigor of the study, the majority of my comments focus on data presentation rather than scientific concerns.

1) On page 3, lines 61–69, the explanation for why a photoredox catalyst is required is unclear as written, particularly for a non-specialist audience that may reasonably be expected to read this paper. I recommend rewriting this paragraph to improve clarity. Two key points would benefit from explicit clarification:
(i) In photoredox catalysis, the forward SET and the back electron transfer (BET) correspond to different redox couples (PC^*/PC^+ vs PC^+/PC), which do not share the same potential. This asymmetry is precisely why the process can be productive and why a photocatalyst is necessary. Although the authors allude to this point, the current wording is confusing, and even as an expert reader I had to reread the section multiple times to infer this interpretation.
(ii) In line 69, the manuscript states that both SET and BET must occur at the diffusion limit. I do not believe this is correct. The essential requirement is that forward SET occurs at the diffusion limit, while BET must be selectively suppressed for one of the reduced species through a competing pathway. This allows only one partner to progress to product formation, whereas the other undergoes rapid BET to regenerate itself. This distinction is not equivalent to the statement: “this new selectivity profile emerges from capping the rate of both SET and BET at the diffusion limit.” While I believe this is what the authors intend, rewriting this paragraph would greatly improve reader comprehension.

2) In the same paragraph (line 67), the manuscript states: “Herein, we show that super-potent photoreductants elicit selectivity solely from reactivity differences following SET.” Should this instead refer to differences following BET? Please clarify.

3) In the paragraph spanning lines 140–150, the authors show that both substrates are reduced at similar rates, likely due to the involvement of solvated electrons. As additional support for the proposed mechanism, could the authors repeat these experiments using a different photocatalyst that reaches similarly high reducing potentials but does not promote the desired chemistry, presumably due to differences in BET behavior? Such a comparison would provide strong evidence that diffusion-limited forward SET is necessary but not sufficient for the observed selectivity.

4) In lines 211–212, the authors write: “our initial hypothesis that only reductants that render SET and BET both rapid and unselective could elicit the desired selectivity.” Is this statement accurate? Wouldn’t selectivity instead require BET to be

faster for one substrate than the other? Please clarify this point.

5) Suggestion: Since the manuscript ultimately demonstrates that forward SET is driven by solvated electrons, could similar reactivity be achieved using a broader range of photocatalysts if an additional molecule—one with a lower reduction potential than the more easily reduced substrate—were introduced to control BET selectivity? In principle, this strategy could extend the scope and tunability of this approach by decoupling the SET and BET events, and it may be worth discussing briefly.

Referee #2

(Remarks to the Author)
Paton, Damrauer, Wickens & team in this manuscript describe a strategy to overcome redox potential control allowing to reduce organic substrates with deep potentials than those with shallower ones. Central to the claim of this strategic discovery is use of pyrene radical anion photocatalysts that photoionize solvated electrons as diffusion limited indiscriminate photoreductants, kinetically competitive back electron transfer such that the 'easier' substrate is protected, and irreversible bond cleavage of an alpha cycloproylated ketyl radicals. The concept is intriguing and the authors are to be commended for the comprehensive concert of experimental, spectroscopic and theoretical efforts in the SI file. The experiments in S23 to determine in concert with TA data the quenching of solvated electrons, as well as the computational comparison of theoretical photoreductants, were particular highlights.
However, in its current form, I do not find the manuscript suitable for further consideration at *Nature*. The current manuscript seems to falls short in multiple aspects; broadness of interest/sufficient demonstration of generality, synthetic utility, and the mechanistic support is not developed enough to rule out other possibilities. While I find the manuscript premature for publication in any journal in its current form, I would be open to considering a substantially revised manuscript in a more specialized Springer Nature journal (e.g. *Nature Chem*).
1) The concept of capitalizing an irreversible bond cleavage post SET to compete with BET is not a new concept. The viability of such an approach was known since the 1970s (Kornblum, Kochi, Bunnett, among others): *J. Am. Chem. Soc.* **142**, 5461 (2020), has been commonly applied with deprotonatable amines as reductive quenchers for decades and more recently to strain relief driven cleavages.
2) It is questionable how this strategy can be general (if truly in operation?) and this is not sufficiently demonstrated in the current manuscript. If true- the strategy relies heavily on a delicate interplay of substrate engineering and interplay/co-incidence of multiple rate phenomena. The 'harder' substrate must have an in built irreversible bond cleavage that happens to be competitive in rate with ET from the 'easier' substrate back to catalyst. It is not intuitive nor clearly demonstrated how this strategy can be applied in a synthesis - practitioners would require to substantial resource and expertise to estimate such rates and could easily do so only computationally; direct quantification of back-ET requires non-routine transient spectroscopy.
As a strategic concept, I am yet to be convinced this is as elegant as more established concepts such as catalyst control / use of catalyst-substrate interactions. Pg2 asserts there are 'no general strategy to promote reactions that require SET to the harder-to-reduce of two reactants'. This claim of novelty feels overbloated. It is well known that metal co-ordination can modulate redox properties in situ (*J. Am. Chem. Soc.* **133**, 1162 (2011), Ref21), allowing selective SET to the partner which is ‘harder’ when uncomplexed. Moreover, photocatalyst design has overtunred redox chemoselectivity in the literature, either between two redox labile substrates (e.g. Pospech & team: kinetic favored, selective oxidation of ‘harder’ stilbene in presence of ‘easier’ benzylamine (ΔE 0.25 V); *ACS Catal.* **11**, 4862 (2021) or within one substrate containing two redox labile groups (e.g. König & team: selective reduction of ‘harder’ OPAr2 in presence of ‘easier’ ArBr; *Angew. Chem.*, **60**, 20817 (2021).
3) Further to generality: The concept should be agnostic as to the types of ‘easier/harder’ substrates so long as radical anion of one has an irreversible cleavage, but authors particular model system herein is heavily biased due to cycloproyl ring strain relief. The current manuscript does not go far enough to demonstrate the concept over any other substrate class combination. Instead of a substrate scope involving mostly incremental changes to the same two partners, it would have been much more convincing if the concept would apply to other substrate class combinations/competitions. Solvated electrons can reduce fluoroarenes and alkyl chlorides (Fig.1A), reactions should be designed examining these as ‘harder’ substrates in presence of some ‘easier’ - e.g. can authors couple a fluoroarene to any radical trap in the presence of bromo- or chloroarene due to protective back-ET from the radical anion?
4) The manuscript structure is a 'self-fulfilling prophecy’. A proposed concept is accompanied by carefully designed mechanistic experiments considering only the initial hypothesis. While such a structure is in principle OK/not un-common. The severe drawback is it overlooks alternative explanations for observations (i,ii).
For example, mechanism for radical anion cycloadditions are well-established as chain reactions (Φ>>1), where product radical anion reduces starting ketone in propagation. This has not been considered as explanation for chemoselectivity and is particularly worrying, in light of highly related prior literature (e.g. Krische, Bauld, Simonet & teams show similar polyarene radical anion and electrochemical systems can effect such chain reactions: *J. Am. Chem. Soc.* **126**, 1634 (2004); *Tetrahedron Lett.* **31**, 667 (1990): It is likely **Per** radical anion is a simple initiator. In Scheme S37 authors suggest the neutral **Per** accepts the product radical anion’s electron, however, the rate of cycloaddition process is not beyond diffusion control (reaction with styrene, then rotation to allow trans-diastereoselectivity). Concentration of ketone acceptor will far outweigh that of neutral **Per** Chain does not require photoexcitation per turnover, may dominate product formation. Sub-stoichiometric F/mol cannot tell anything on chain reactivity in redox neutral case. Quantification of the quantum yield of the reaction is truly essential.
Alternatively, ring opening of cyclopropyl ketones by photoexcitation (Zimmerman & Flechtner: *J. Am. Chem. Soc.* **92**, 6931 (1970) and photosensitization to give biradicals is known (e.g. Waser, Bach & teams: *J. Am. Chem. Soc.* **145**, 25411 (2023); *Angew. Chemi* **59**, 21640 (2020). The polyaromatic catalysts examined (SI file Section 3) are all known as classical energy

transfer photosensitizers. While reasonable clear the neutral polyarene singlet states (absorbing <400) are not responsible for reactivity, doublet-to-triplet energy transfer (DTET) is an established, efficient concept (*J. Am. Chem. Soc.*, **147**, 43013 (2025); *J. Phys. Chem. Lett.* **8**, 5865 (2017); *J. Am. Chem. Soc.* **147**, 1017 (2025); *Chem. Sci.* **13**, 6732 (2021) and this should be investigated via similar methods used in aforementioned studies. Piperylene should be added as redox inert energy transfer quencher, known to quench triplet of cyclopropylated ketone within an order of magnitude of the diffusion rate (Zimmerman).
Finally and most critically, the Marcus inverted region has not been considered as a factor in redox chemoselectivity. While clear the styrene's reduction is at diffusion limit (ketone is ~6x below it), the back-ET falls below diffusion limit at which point the driving force for the ketyl radical anion's reduction of **Per** pushes it into Marcus inverted. This exact phenomenon is previously reported for both excited state oxidants (*J. Photochem. Photobiol. A* **107**, (1997) and radical anion reductants (*ACS Catal.* **12**, 6047 (2022); it most likely underpins the selectivity herein. Authors should measure more BET rate constants to examine if an inverse dependence on driving force in the inverted region occurs. Leveraging the Marcus inverted region in photocatalysis is a strategy previously exploited (*Science* **382**, 191 (2023).
5) The authors attribute signatures to solvated electrons in the TA studies, but do not correlate the quenching with any detection of the ketyl radical anion to show this is a productive pathway, although this should be observable in the TA (Tanko & team: *J. Org. Chem.* **70**, 4170 (2005). Authors should detect the ketyl radical anion.
6) To comment on synthetic utility, reductive activation of these cyclopropylated ketones and their (3+2)-radial cycloadditions to olefins is well precedented in multiple papers, with much more simple, predictable chemoselectivity control factors (Sm/Ti/Mn as reductant and/or L.A.; H-bonding catalyst). In many cases with much broader scopes: Ref21 (includes non-aromatic ketones, including alkyne partners, more diversity on geminal position): *J. Am. Chem. Soc.* **146**, 12799 (2024) (reductively labile functions ArX, C-F bond are tolerated); *J. Am. Chem. Soc.* **140**, 3514 (2018) - see 14,23,24,27,29; almost identical scope stressing, the vinyl pyridine and acrylate are 'easier' than the ketone); *Angew. Chemie* **63**, e202406845 (2024); *Angew. Chemie* **57**, 5454 (2018). *ChemSusChem* **18**, e202500521 (2025); *ACS Catal.* **13**, 11277 (2023). In fact, the transformation is already reported using a radical anion photocatalyst (Qiao, Jiang & team: *Angew. Chem.* **63**, e202406845 (2024), not cited), where pyrene was added as a energy transfer quencher. It was already investigated by TA by Ceroni & team (Ref28) and solvated electrons already found as the active reductant, so much of the mechanistic study herein is unsurprising. While the use of non-aromatic ketones is less represented in the above studies and is commended, this emphasizes the need to address point (3) and step outside the comfort zone of these cyclopropylated ketones.
7) It is claimed products could be made 'with a range of steric profiles', this is not true of gem substituents on the cyclopropane, only Me and pyran. Different gem substitutions should be included.
8) Table S1, it is very surprising that Cor vs Pyr radical anions react with same redox properties and similar photochromic properties (*Chemistry Eur. J.* **18**, 15753 (2012); Ref22) give such different performances. Photo-ionization at shorter wavelengths should afford solvated electrons in each case, it seems to follow for Cor but not for Pyr? Why this discrepancy?
9) Pg5: It is mentioned the quenching of solvated electrons by styrene is only 1 order of magnitude faster than by ketone, despite a 650 mV difference predicting ~20 orders magnitude. Why? Does this speak to a favourable interaction between **Per** radical anion and ketone that renders a higher local concentration of ketone?
10) Comparisons with other methods are not always fair. Fig2: Mediated electrolysis done with CPE and compared to direct electrolysis and electrophoto with CCE. PTH ($*E_{1/2}$ –2.10 V) was doomed to fail for both substrates. A photoredox catalyst that can actually reach the potentials of the two substrates must be tested ($*E_{1/2}$ > -3 V, e.g. Melchiorre, Xia & teams thiolate or phenolate: *Angew. Chem.* **62**, e202306364 (2023); *Chem. Sci.* **11**, 6996 (2020). ConPET conditions should be done using perylene, since excited acridinium can likely oxidize the styrene in competition with the amine reductive quencher. Acridinium should be used under electrophoto reductive conditions as acridinyl is potent enough and also known to photo-ionize solvated electrons.
11) Authors mention protonation of styrene radical anion by water at multiple points, but it is not obvious why this is relevant under the reaction conditions. No water is explicitly added, to model reaction or most of the scope reactions apart from certain cases Fig.4 superscript 'f'. Therefore in Fig2/3/5, it seems somewhat disingenuous to compare the cyclopropane opening with protonation when there is no clear proton/water source in the reaction. According to the SI file, reactions were prepared under strict conditions with thoroughly degassed, anhydrous solvents and purged with N2. Particularly, the T.S. for protonation is assuming water/cleavage of a strong O-H bond, and is likely to be lower in energy for whatever is the true proton source under relevant reaction conditions (DMF?..).
12) While the visible TA data for **Per** radical anion used both 520 and 460 nm pumps, the NIR monitoring used only the 460 nm pump. The longest wavelength absorption of **Per** radical anion peaks at ~575 nm. As an obvious missing control experiment, green pump should be used as a control to monitor the NIR and rule out photo-ionization from its first excited state.
13) Fig3D: The 'photocurrent' CV experiments are too superficial. Different scan rates and different substrate concentrations are needed to demonstrate this is a true trend and not due to experimental artefacts.
14) Many compounds in the scope are not isolated, about half in Fig.4 are 1H NMR yields. This is insufficient for *Nature*. For this method to be a synthetically meaningful access to cycloadducts from non-aromatic cyclopropyl ketones which is a pillar of its novelty, authors need to demonstrate proper isolation.
Manuscript:
Fig1B seems misleading, suggesting visually the quenching rate of solvated electrons by both substrates is at the diffusion limit. In fact the ketone (4 x 10^9) lies ~6x below the diffusion limit (2.5 x 10^10).
Figure 5A shows a barrier of ~10 kcal mol-1 for the BET from styrene radical anion. However, the barrier is ~8 kcal mol-1 for BET from ketyl radical, so the red arrow 'BET' should be added here also.
Fig.4 reaction scheme: Pery? ; Fig.4 title: 'c' 1.5 equiv w.r.t. ???
Reference 30: Should be expanded to earlier reports important contributions including authors' own: Ref27; *ACS Catal.* **14**, 2252 (2024); Reference 33: Should be expanded to earlier reports important contributions: König & team (2021); *ACS Catal.* **12**, 6047 (2022)

Pg5: ‘marginally’ is not the correct word for an order of magnitude difference.
Role of TEABr and a speculated proton source for forming hydrogenated product ‘A’ should be mentioned somewhere.
SI file:
Although SI file is data rich, the authors have not taken good care checking the SI file for type-o and formatting. Some of these issues were somewhat surprising for a manuscript submitted to Nature: The word ‘sorry’ appears in the SI file (S21). 5 mutes should be 5 minutes (S21). Lazy formatting (S23, most of section 9, format of S3-S7 differs in font size). Beta Greek symbol missing (S29, S81). Missing word in a sentence (S26). Invalid compound/procedure number ‘XX’ (S89,93).
Table S5, put equivs of reductants, it implies stoichiometric. e.g. entry 3, terminal reductant is DIPEA not Fukuzumi acridinium.
Table S6-S10 titles: ‘Stern-Volmer plot’ is incorrect, refers exclusively to emission. Solvated electrons being quenched are ground state species.

Referee #3

(Remarks to the Author)
This work aims to establish a previously unrecognized paradigm in which highly potent reductants, specifically solvated electrons, evade the conventional thermodynamic selectivity criteria for substrate single-electron transfer (SET) based on redox potential differences. Instead, the authors propose that selectivity is determined after SET, governed by the competition between back electron transfer (BET) and annulation pathways. To validate this hypothesis, the authors employ a combination of femtosecond-TA (fsTA) and nanosecond-TA (nsTA) spectroscopy, cyclic voltammetry, Stern-Volmer analysis, and steady-state UV/Vis absorption studies coupled with computational chemistry within an electro-photochemical framework.
Overall, this paper is novel while inspired by recent works on the generation of solvated electrons and closed shell Meisenheimer species and it has the potential to provide insight into photocatalyst excited state dynamics and how they influence reactions. This manuscript should be published after major outlined suggested below.
A hypothesis of the work is that electrochemically generated Per•–, when excited at 570 nm, is incapable of substrate activation due to its reported picosecond-scale excited-state lifetime observed by fsTA. While the short lifetime is clearly demonstrated, the conclusion that substrate activation is precluded is not directly validated on lines 126-127, as quenching experiments with relevant substrates were not performed under these conditions. As such, it remains unclear whether ultrafast SET events could still occur with the pico-seconds lifetime or if pre-association might facilitate that. Authors should evaluate for the possibility of pre-association.
Another central hypothesis is that diffusion-limited BET enables selective substrate reduction. The introduction ignores decades of photocatalysis research in which charge recombination is often faster than diffusion and occurs before the electron donor and acceptor escape the solvent shell. It is important that BET is slower with a solvated electron than with an excited state reductant.
Upon shorter-wavelength excitation (390-460 nm), the formation of neutral Per is observed, which the authors attribute to photoionization and the generation of solvated electrons. This assignment is supported by NIR transient absorption measurements (1100-1600 nm) showing a characteristic absorption band centered near 1450 nm, consistent with solvated electrons in MeCN. Stern-Volmer analysis using two substrates further reveals nearly identical quenching rates approaching solvent diffusion limits, supporting the assertion that electron transfer occurs independently of substrate redox potentials.
The authors further support their post-SET selectivity argument through nsTA studies using pyrene as a substrate, proposing that pyrene rapidly traps solvated electrons to form Pyr•–, followed by fast BET to regenerate Per•–. While transient features assigned to Pyr•– and Per-derived species are presented, the evidence for BET remains largely qualitative. A more direct and compelling validation would involve correlating the decay of Pyr•– with the simultaneous decay of Per based transients on identical timescales, thereby establishing kinetic coupling consistent with BET. Showing decay of the neutral Per would provide additional evidence of BET between Pyr•– and Per.
A paper that was cited in the article titled, ‘P. Organic Super-Reducing Photocatalysts Generate Solvated Electrons via Two Consecutive Photon Induced Processes’ by Paola Ceroni stated that recombination of the solvated electrons with the parent molecule is forbidden in the computation they carried out. To show that there is recombination of the solvated electron with the parent molecule, Per, juxtaposing the kinetic of the solvated electrons against the decay of the neutral Per and having similar lifetimes would go a long way to make the argument on the recombination compelling.
I realized the authors were unable to achieve a pure Per•– and some amount of neutral Per was present in the experiments at all times. When doing quenching studies, the authors subtracted the quenching rate by the neutral Per from the quenching by the reactants, which is a convoluted approach to obtain an electron transfer rate constant. Is it not possible to generate a pure Per•– instead of the mixture?
The UV/Vis for the sample after the TA was not re-taken to confirm that degradation is not happening. The concentration of neutral Per is high at the onset of the TA experiment and changes as a function of time with ketone reduction. A UV-vis spectrum before and after TA is important to show that the electron transfer is cyclical and the relative concentrations of reduced and neutral Per does not change during the TA experiment. It needs to be clearly stated that recombination is not necessarily between the solvated electron and neutral Per from recently oxidized Per•– because the starting [Per] is high. Further, how does high [Per] affect the BET rate and competition with annulation?
Cyclic voltammetry was used to argue that BET dominates in the presence of styrene, as evidenced by reversible voltammograms upon substrate addition, whereas the authors state that ketone substrates induce increased cathodic currents and diminished anodic return, consistent with catalytic turnover. However, the ia/ic ratios are nearly identical in dark and light with ketone. This is not catalytic current (see Nicholson and Shain Analytical Chemistry, 1964, 36, 707-723). The lack of catalytic current may result from low excited state concentration at the electrode surface.
The kinetics for ketone bond cleavage and protonation of the reduced alkene are important for the selectivity argument regarding kinetic competition with BET. Although the manuscript acknowledges the importance of evaluating these kinetic parameters with a section titled “Kinetic Model for Emergent Selectivity,” only thermodynamic properties are discussed in

that section. Can the calculations provide an approximation of the relevant rate constants, particularly scission and protonation?
The thermal control reaction using Na^0 results in extensive ketone reduction but no formation of product B. While this observation is consistent with the authors' assertion that SET alone is insufficient for productive chemistry, the manuscript does not adequately address why thermally generated ketone radical anions fail to access the annulation pathway observed under electro-photocatalytic conditions. A more explicit discussion of this discrepancy would strengthen the mechanistic framework and clarify the role of post-SET dynamics in influencing selectivity.
A constant current of 1mA was applied during electro-photocatalytic reactions. Please provide evidence that the voltage is not shifting to more negative values, thereby resulting in competing direct electrolysis of the substrates.

Minor typo noted: "Rapid Substrate Reduciton" on line 169.
Rate constants for annulation

Referee #4

(Remarks to the Author)
I co-reviewed this manuscript with one of the reviewers who provided the listed reports.

Version 1:

Reviewer comments:

Referee #2

(Remarks to the Author)
The revise manuscript of Paton, Damrauer, Wickens & team has incorporated additional experiments and discourse that addresses some of the concerns raised in previous round of review. The prose and clarity of the manuscript has risen and mechanistic alternatives are at least dissected. The authors are thanked for clearing up some misunderstandings and improving presentation of the SI file.
Regreattably, the key requests for a synthetic demonstration that the concept applies to any pair beyond a cyclopropyl ketone and a styrene are rebutted with the phrases 'distract from the central conclusion', 'out of scope of this current manuscript'. The suggestions made are facile to try and to disclose, even if, only to the reviewers and Editor due to the existing density of the manuscript, to convince that this is a conceptual step change in selectivity control rather than a delicately tuned system confined to those two specific partners. The phrasings: "The use of the relative ability of two substrates to outcompete BET to induce selectivity for a harder-to-reduce but faster-to-fragment substrate encounters major impediments as the mismatch in reduction potentials increases." "While this unambiguously relies on substrate features (e.g., fragmentation rates)"
confirm this reviewer's retained concerns about generality of the approach, which indeed requires careful substrate engineering and a delicate co-incidence of multiple rate phenomena to succedd. The improvements to the manuscript and considerations of alternative mechanistic explanations are duly noted, however the central concern remains that the concept has not been applied to any other combinations of two competing reducible substrates. Showing that the concept holds true for a few different combinations of different competitors, would be way more compelling than the currently (incremental) advance of being able to fragment these strained cyclopropanes derived from alkyl, rather than arylketones – for the latter of which synthetic methods are heavily reported and for the former of which examples do exist. In the end, what is sold as a potentially fascinating selectivity mode has only translated into an ability to engage aliphatic ketone reduction of these cyclopropylated species. This an incremental advance that seems to fall short of the kind of paradigm shift expected at this journal; there is no new bond formation or cleavage being disclosed here. The concept being described, if true, seems is not being done justice by the current application of the manuscript.
How many synthetic scenarios exist, where two separate reducible molecules with such specific requirements (harder-to-reduce but faster-to-fragment) are put into a reaction to be able to establish such a requirement? So far I fail to see the broader synthetic problem that can be addressed by this conceptual demonstration. The way more relevant context would be, to apply the method to a single molecule with multiple reductive sites. Such a context would be much more useful for generality in academic and industrial settings, such as late stage selectiv functionalization. But this has also not been attempted.
While the authors' line of argument about confining the study sharply to the mechanistic studies of these strained cyclopropanes and their reluctance to assess other combinations at a superficial level is acknowledged: this same current specificity underpins the concerns raised above and impression that a more specialized journal such as *Nat. Chem.* would be appropriate.
Specific responses:
1) In responding to the possibility of a chain mechanism, the authors have computed Marcus barriers for SET (Figure S2.30) between various combinations to substantiate that even in the operation of a chain the general concept holds at the point of re-initiation. Authors need to confirm if these calculations were done using proper DFT or through approximations (DFAs). Specifically, whether any interaction exists between the ketyl radical and the C=O pi star that could direct selectivity but may habe been missed.
2) Authors raised the generation of ZnBr2, which can be seen visually in copious amounts in the electrochemical cell on Figure 1.3 of SI, even particles in the cathodic chamber can be seen between the stirrer and carbon cathode (which seem not to be gas bubbles from HER as it is coming up from the stirrer even not just around the cathode). It should be noted that these cells are not truly divided, the porosity reflects a pore size diameter of hundreds of microns allowing ZnBr2 to pass

through to the cathodic chamber.
The Lewis acidity of M(II) salts to activate carbonyl groups including aliphatic carbonyls to reduction is well known (*Science* **362**, 225 (2018); *J. Am. Chem. Soc.* **43**, 651 (1921); reaction rate accelerated adding zinc chloride). It is known to accelerate migratory insertion of Ni complex carbon moiteies to aliphatic carbonyls: e.g. *J. Am. Chem. Soc.* **141**, 1823 (2019) (Scheme 4 therein and the proposed mechanism).
There seems to be a severe risk that all the unconventional selectivity behaviours may not be down to the proposed promiscuous reduction and selective BET and be simply down to in-situ generation of a M(II) Lewis acid, that migrates over to the cathodic chamber, lower redox potential of the carbonyl into a normal redox potential regime, probably in a controlled chain mechanism?
There could be other reasons why a chain would continue to engage the ketone vs the styrene upon re-initiation, e.g. if metal(II) salts are around. E.g. well known Pinacol coupling involves such an interaction and similar interaction modes could direct ET to the ketone.

This concern over presence of M(II) salts in cathodic chamber is a critical concern to address. Authors should examine the contents of the 'cathodic chamber' by ICP-OES for presence of Zn before and then after the reaction to see if a substantial increase.
Authors should run the reaction with a proper membrane separator eg Nafion or Celgard, to completely preventing Zn from migrating.
What is by CV the redox potential of the ketone in presence of ZnBr2?

In the case of the consecutive photoinduced ET reactions the radical cation of the amine or a protonated amine byproduct can act as an acid activator of the carbonyl: *J. Org. Chem.* **81**, 6959 (2016). Although authors show conPET did not work.

3) In authors response re-simulating the selectivity with the calculated Marcus barriers, then vs arbitrarily assuming same barrier, for both they claim no difference but there is a difference in S2.32 vs S2.31. The selectivity starts to blurr in bottom right quadrant. It is possible that all it takes is some adventitions Zn(II) salts to bring the barrier below that of the styrene reduction and disrupt completely the selectivity profile, meaning point (2) is of utmost importance. This is another reason why the concept should be demonstrated for another hard-to-reduce vs easy-to-reduce couple, where the risk of traditional activations modes of carbonyls is completely eliminated (eg. ArF vs ArBr/Cl)
4) The use of Melchiorre thiolate catalyst is intriguing, but the conditions are biased as there is no proton source(?) so the formation of the hydrogenated styrene is inherently chemically not possible. This is a corollary to the main electrophotocatalytical experiments that need to be confirmed not to be due to M(II) carbonyl activation as in point (2).

Referee #3

(Remarks to the Author)
The authors responded to questions thoughtfully and with appropriate data. The revised manuscript provides a more clear mechanistic description. A few minor concerns/suggestions remain and are listed below.

The cyclic voltammetry data now show irreversible current in the presence of Ket-1 with light, consistent with reduction of the ketone. In agreement with this, the UV-vis before and after transient absorption with Ket-1 are not identical, pointing to an incomplete cycle. It would strengthen the argument to add a TA spectrum to the SI showing incomplete recovery of the ground state bleach with Ket-1.

In agreement with Reviewer 2 regarding figure 2, it does not seem fair to compare constant current to constant potential and the reducing environment should be sufficient to reduce both ketone and styrene substrates. In the case of mediated electrolysis, the -2.5 V vs Ag/AgNO3 applied potential is sufficient to reduce styrene but not the ketone. For the conventional photoredox system, the redox potential of excited PTH has been shown to have a potential of just over -2 V vs SCE, which is inadequate for reduction of either substrate. It would be helpful to compare selectivity with reducing systems that are capable of reducing either substrate.

The diffusion limitation argument should be distinct from the potency of a reductant. Solvated electrons are shown to have high diffusivity usually limited by the solvent diffusivity coefficient. To make synthetic comparisons with other photocatalysts, they should be potent enough to reduce either substrate (thermodynamically possible) but have kinetics that are much less than the solvent limit to demonstrate this. It is distracting to compare systems that are thermodynamically impossible to thermodynamically possible systems.

Referee #4

(Remarks to the Author)
I co-reviewed this manuscript with one of the reviewers who provided the listed reports.

Version 2:

Reviewer comments:

Referee #2

(Remarks to the Author)

The revise manuscript of Paton, Damrauer, Wickens & team thoroughly addressed concerns raised in the previous round of review.

In particular:

1) The authors have clarified ambiguities around the calculations done and have probed for specific C=O pi star interaction, which was found to be marginally uphill (8 kcal/mol) and can be excluded.

2) The successful reaction with a Nafion membrane is sufficient to completely preventing any sacrifised Zn from migrating. This excludes a critical concern about some ZnX2 salt being a Lewis acid activator of the substrates carbonyl groups.

3) The authors have clarified their motivation and purpose of testing the Melchiorre thiolate catalyst and this rationale is now available to readers.

While I continue to regret the non-extension to other substrate combinations that would have convinced of the generality of interest for Nature, the efforts made by the authors to exclude prior concerns have convinced me that the manuscript is now ready for publication from the scientific side. Congratulations on the authors for this curious discovery.

Referee #3

(Remarks to the Author)
In the most recent revision, the authors clarified control reactions to investigate the Curtin-Hammett scenario. It is still not clear why a different photocatalyst was selected for the classic conPET while assuming that the amine used was the reason for the lack of yield when they could have used the same perylene they used in the electron primed system for the classic conPET instead of mesityl acridine. This would have made the sacrificial electron donors only variable, which would move the speculative argument of the role of sacrificial electron donors influencing reaction to a more factual statement. Additionally, spectroscopic evidence for the perylene radical formation is preferred over a statement of visible color change.

Referee #4

(Remarks to the Author)
I co-reviewed this manuscript with one of the reviewers who provided the listed reports.

Prof. Zachary K. Wickens
Associate Professor, Department of Chemistry
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February 26, 2026

[redacted]

[redacted]

[redacted]

We believe this revised article addresses each of the reviewers' concerns and that it is now appropriate for publication in *Nature*. In the point-by-point response, reviewer comments are denoted with blue text, our responses are denoted with black text, and specific manuscript changes are denoted with red text.

To jump right to responses to each individual reviewer, we have provided links with a note regarding what we saw the core critiques.

Response to referee 1 (pinpointed the role of BET as unclear and offered suggestions regarding clarity of the introduction)
Response to referee 2 (identified a range of alternative mechanistic scenarios that must be excluded and expressed concerns about the overall novelty of our study that revealed that we failed to properly contextualize our initial study in prior work)
Response to referee 3 (identified necessary supporting mechanistic studies and clarifying revisions to the discussion of these studies)

Referee #1 (Remarks to the Author):

This paper describes the deliberate use of exceptionally high redox potentials that significantly exceed those minimally required for the reaction. As a result, selectivity is shifted away from control by the initial electron-transfer event and the intrinsic redox potentials of the substrates, toward control by the kinetic stability of the reduced intermediates that are generated. This conceptual advance enables an unprecedented transformation that would not be accessible by conventional approaches, as the reaction requires selective reduction of a cyclopropyl ketone in the presence of a more readily reducible olefin. The work convincingly demonstrates that long-standing paradigms governing redox-mediated chemistry can be broken and represents a significant conceptual contribution that is likely to influence how synthesis enabled by electron-transfer reactions are designed in the future. In my view, this is an outstanding study that merits publication in this journal following the minor revisions detailed below.

We thank the reviewer for their careful reading and suggestions to clarify our manuscript. We have addressed each of their suggestions as detailed below. Since points 1 and 2 both provide feedback on the same section of text, we have elected to respond to these comments together.

1) On page 3, lines 61–69, the explanation for why a photoredox catalyst is required is unclear as written, particularly for a non-specialist audience that may reasonably be expected to read this paper. I recommend rewriting this paragraph to improve clarity. Two key points would benefit from explicit clarification:
(i) In photoredox catalysis, the forward SET and the back electron transfer (BET) correspond to different redox couples (PC/PC$^+$ vs PC$^+$/PC), which do not share the same potential. This asymmetry is precisely why the process can be productive and why a photocatalyst is necessary. Although the authors allude to this point, the current wording is confusing, and even as an expert reader I had to reread the section multiple times to infer this interpretation.*
(ii) In line 69, the manuscript states that both SET and BET must occur at the diffusion limit. I do not believe this is correct. The essential requirement is that forward SET occurs at the diffusion limit, while BET must be selectively suppressed for one of the reduced species through a competing pathway. This allows only one partner to progress to product formation, whereas the other undergoes rapid BET to regenerate itself. This distinction is not equivalent to the statement: "this new selectivity profile emerges from capping the rate of both SET and BET at the diffusion limit." While I believe this is what the authors intend, rewriting this paragraph would greatly improve reader comprehension.

2) In the same paragraph (line 67), the manuscript states: "Herein, we show that super-potent photoreductants elicit selectivity solely from reactivity differences following SET." Should this instead refer to differences following BET? Please clarify.

We appreciate this constructive feedback and have completely rewritten this portion of the third paragraph of the intro to clarify these incisive comments. We have reproduced the entire paragraph here and highlighted changes with red text.

Revisions to the manuscript:

We envisioned a fundamentally distinct approach to subverting redox potentials in SET processes. We were inspired by observations that SET from exceptionally strong reductants becomes limited by diffusion rather than following Marcus kinetics (Fig. 1b).[19] Thus, a sufficiently potent reductant reduces all substrates at roughly the same rate, since diffusion coefficients vary minimally across small molecules. We suspected that a unique selectivity profile would emerge if we coupled this indiscriminate SET to fast and favorable back electron transfer (BET). In principle, if all substrates are reduced regardless of their relative redox potentials then only substrates that can outcompete BET with an irreversible step would react.[20–22] While detailed balance precludes such a scenario for ground-state reductants where favorable SET entails unfavorable BET, photoreductants promote these steps through distinct redox couples (e.g., PC•+/PC* and PC•+/PC), which allows both steps to be thermodynamically favorable. Herein, we show that super-potent photoreductants render substrate redox potentials irrelevant and instead elicit selectivity from the relative ability of reduced substrates to outcompete BET.

3) In the paragraph spanning lines 140–150, the authors show that both substrates are reduced at similar rates, likely due to the involvement of solvated electrons. As additional support for the proposed mechanism, could the authors repeat these experiments using a different photocatalyst that reaches similarly high reducing potentials but does not promote the desired chemistry, presumably due to differences in BET behavior? Such a comparison would provide strong evidence that diffusion-limited forward SET is necessary but not sufficient for the observed selectivity.

Indeed, photogenerated solvated electrons are expected to be particularly effective for this new selectivity manifold due to the unusual BET kinetics of our photocatalytic system since BET occurs through a bimolecular process that cannot proceed faster than diffusion. The broader point, however, is simpler. We envision that this selectivity profile should emerge from any redox catalysts with sufficiently large rate constants for both SET and BET. While high BET rate constants are unambiguously required to protect the easier-to-reduce coupling partner, our kinetic model actually indicates that limiting BET rates to the diffusion limit is not a strict requirement for our model reaction due to the rapid β-scission pathway (though imposing a diffusion limit on BET will likely prove important in future reactions with slower fragmentations). As a result, our kinetic model predicts that the new selectivity phenomenon will be general across super-potent photoreductants for this model reaction. As a part of our revision, we have expanded our evaluation of other photoreductants and have provided support for this conclusion. Specifically, Melchiorre's thiolate photocatalyst, which has a highly reducing excited state ($^*E_{1/2}$ = –3.4 V), promotes the desired [3+2] annulation with moderate efficiency (44% yield, 6% styrene hydrogenation and full conversion of both coupling partners).

We have revised the discussion of our catalyst evaluation studies to clarify the generality of the phenomenon across super-potent photoreductants, studies that also expose the crucial role of terminal reductants in these processes. Additionally, we have added discussion of the potential broader role of diffusion-limited BET with photogenerated solvated electrons both in the main text and SI. This illustrates that as we reduce the fragmentation rate constant of our cyclopropyl ketone, diffusion-capped BET is predicted to become increasingly important.

These changes are reproduced below:

Discussion of Figure 2

These investigations revealed that, under electrophotocatalytic conditions, diverse PAHs promote the desired reaction with dramatically suppressed hydrogenation (see Table S1.1 for full optimization data). Conventional strong photocatalytic reductants, such as phenothiazine (PTH), are insufficiently potent and led to low ketone conversion and no annulation. However, we also tested several of the recently reported potent photoreductant systems (see Table S1.5 for details). These studies revealed that Melchiorre's thiolate photocatalyst,[30] a super-potent single-photon reductant ($^*E_{1/2}$ = –3.4 V), promotes the [3+2] annulation, albeit in diminished yield. Intriguingly, established potent consecutive photoinduced electron transfer (conPET) systems were found to be ineffective despite, in principle, offering comparably potent reduction potentials.[31] Rather than illustrating specific catalyst limitations, however, we suspect this observation reflects the problematic byproducts derived from the amines used as reductants (see SI Section 1 for details).[32] Overall, these data are consistent with our proposal that redox-potential-independent selectivity can emerge from diverse super-potent photoreductants.

Discussion of Figure 5b

The electrophotocatalytic conditions we have used exemplify this phenomenon: solvated electrons are photogenerated concomitantly with perylene, providing a mechanism for both SET and BET to proceed at the diffusion limit. Indeed, this system is ideally suited to exploit diffusion-limited electron transfer processes because conventional excited state reductants often undergo in-cage BET,[54,55] which can occur faster than diffusion and imposes an additional bias against productive ketone reduction. While high BET rate constants are unambiguously required, our kinetic model indicates that capping BET at the diffusion limit is not a strict requirement for this reaction due to the rapid β-scission pathway but will likely facilitate implementation in processes involving slower downstream steps (for detailed discussion of BET rates, see SI Section 7).

SI Section 7:

Impact of Diffusive BET

We questioned whether the photogeneration of solvated electrons is uniquely well suited to promote radical formation since BET is a bimolecular process that cannot proceed faster than the diffusion limit. In contrast, substrate reduction from an excited state can undergo BET via in-cage charge recombination that will not be limited by diffusion. To probe this hypothesis, we modified our kinetic model in Figure 5b to mimic the effects of in-cage charge recombination by removing the diffusion limit on BET (Figure S2.27). However, this change only leads to minor differences in the photocatalyst driving forces needed to elicit the desired selectivity profile, indicating that the diffusive nature of BET is likely not a major origin of selectivity for the model annulation reaction. We suspect that this insensitivity to faster-than-diffusion BET is a consequence of the large

differential in rates between styrene radical anion protonation and ketyl β-scission in the present reaction. When we re-evaluate our kinetic model using a slower rate constant for fragmentation, the impact of capping the rate of BET at diffusion becomes far more significant (Figure S2.28 and S2.29).

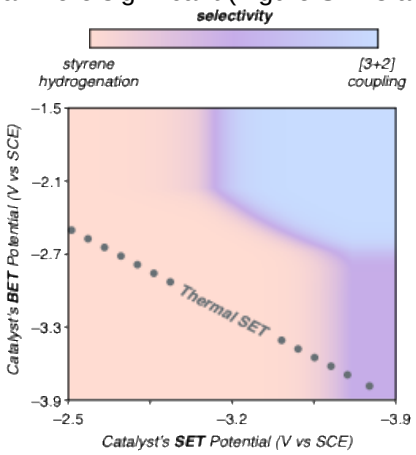


Figure 5c: Kinetic Selectivity model as a function of driving force for SET and BET.

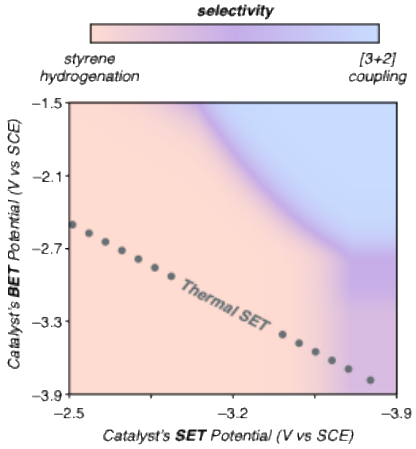


Figure S2.27: Reproduced from Figure 5c but with no diffusion cap on the rate of BET to mimic the impact of in-cage charge recombination

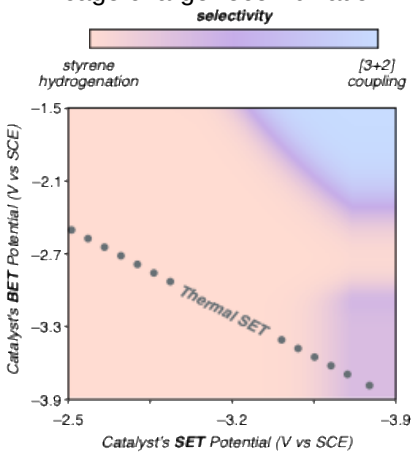


Figure S2.28: Reproduced from Figure 5c but with no diffusion cap on the rate of BET to mimic the impact of in-cage charge recombination and the rate of the radical formation is 100 times slower

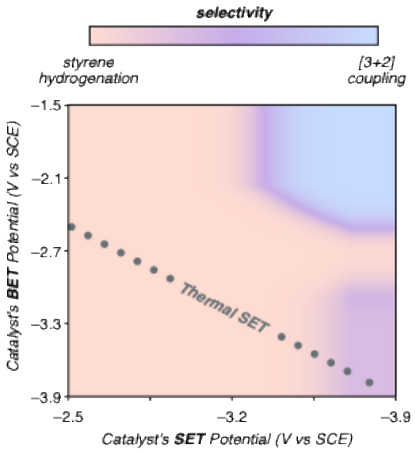


Figure S2.29: Reproduced from Figure 5c but the rate of the radical formation is 100 times slower

4) In lines 211–212, the authors write: "our initial hypothesis that only reductants that render SET and BET both rapid and unselective could elicit the desired selectivity." Is this statement accurate? Wouldn't selectivity instead require BET to be faster for one substrate than the other? Please clarify this point.

This is a subtle but crucial point that we need to clarify. Thank you for catching this. Below we clarify our thinking since our initial version was certainly ambiguous. Further, we have meaningfully revised this specific passage in this paragraph to adjust flow and address comments from another reviewer. This revised paragraph removed this sentence entirely and is reproduced at the end of our clarifying response.

We intended 'rate constant' with this statement, but we recognize that rate more traditionally refers to flux through a step. Moreover, we were implicitly assuming a Marcus normal kinetic regime where the best-case scenario for the harder-to-reduce substrate would be that BET rate would be diffusion-limited for both. To fully remove the influence of redox potentials, we require that we neither promote SET to the easier-to-reduce substrate faster nor BET from the harder-to-reduce substrate faster. Since β-scission is sufficiently fast to outcompete diffusion-limited BET, this enables selective radical coupling and very low flux of that substrate through BET pathways. However, if the rate constant were much higher for BET from the ketyl than styrene radical anion (as predicted by Marcus kinetics), this would erode selectivity.

Revised paragraph:

To assess the specific catalyst properties required to elicit the observed selectivity profile, we constructed a detailed kinetic model using a series of steady-state approximations (see SI Section 7 for derivation). Using the computationally derived barriers for protonation, β-scission and radical coupling to estimate rate constants for the kinetic model, we evaluated the selectivity predictions across a wide range of theoretical reductants with independently varied rates of SET and BET (Fig. 5b). As expected, the vast majority of this landscape of theoretical reductants results in exquisite selectivity for styrene hydrogenation. Only as the initial SET rates become exceptionally fast (electron donor strengths <–3.5 V vs. SCE) does this dominant selectivity begin to erode. However, a super-potent reductant alone is insufficient to induce selective radical coupling; BET must also be highly favorable. Of note, these requirements remain regardless of whether the product forms through a closed catalytic cycle or a photoinduced chain mechanism[48–50], because styrene is expected to inhibit both chain initiation and propagation using aliphatic ketone substrates (see SI Section 8 for a detailed discussion).

5) Suggestion: Since the manuscript ultimately demonstrates that forward SET is driven by solvated electrons, could similar reactivity be achieved using a broader range of photocatalysts if an additional molecule—one with a lower reduction potential than the more easily reduced substrate—were introduced to control BET selectivity? In principle, this strategy could extend the scope and tunability of this approach by decoupling the SET and BET events, and it may be worth discussing briefly.

Thanks for this interesting suggestion! The idea that SET and BET can be decoupled via the addition of an exogenous mediator is compelling and likely well suited with the use of solvated electrons to drive SET. Relatedly, we are currently exploring how BET kinetics can be further tuned by adjusting the concentration of

neutral catalyst with both chemical and electrochemical parameters. Though we think these ideas are more appropriate for follow up work where we can clearly outline the new reactivity they enable, we are excited to explore your suggestion.

Referee #2 (Remarks to the Author):

Paton, Damrauer, Wickens & team in this manuscript describe a strategy to overcome redox potential control allowing to reduce organic substrates with deep potentials than those with shallower ones. Central to the claim of this strategic discovery is use of pyrene radical anion photocatalysts that photoionize solvated electrons as diffusion limited indiscriminate photoreductants, kinetically competitive back electron transfer such that the 'easier' substrate is protected, and irreversible bond cleavage of an alpha cycloproylated ketyl radicals. The concept is intriguing and the authors are to be commended for the comprehensive concert of experimental, spectroscopic and theoretical efforts in the SI file. The experiments in S23 to determine in concert with TA data the quenching of solvated electrons, as well as the computational comparison of theoretical photoreductants, were particular highlights. However, in its current form, I do not find the manuscript suitable for further consideration at Nature. The current manuscript seems to falls short in multiple aspects; broadness of interest/sufficient demonstration of generality, synthetic utility, and the mechanistic support is not developed enough to rule out other possibilities. While I find the manuscript premature for publication in any journal in its current form, I would be open to considering a substantially revised manuscript in a more specialized Springer Nature journal (e.g. Nature Chem).

We appreciate the detailed and balanced comments throughout this referee's response. In responding to your incisive points as well as those of the other two referees, we have substantially revised the manuscript. Our assessment is that this has led to a substantially improved manuscript and we are optimistic you will agree, regardless of whether you ultimately conclude that the novelty is sufficient for publication in Nature.

To clarify our response to your comments, we have broken down our revisions into two distinct categories. *First,* we will present responses to your mechanistic concerns (points 4, 5, 8–13). Your comments identified specific mechanistic alternatives that we had not adequately considered in our initial submission. We felt our revisions in this domain were most clearly presented together, as the core question raised was whether the explanations we proposed were adequately supported by the data presented. *Second,* we will respond to the comments on novelty, broad interest and synthetic utility (points 1, 2, 3, 6, 7, and 14). We felt our responses to these more subjective assessments were best considered together.

Integrated Response to Mechanistic Concerns

In addition to addressing each mechanistic comment below, we have added a section to the supporting information **(Section 8)** that explicitly considers alternative hypotheses and provides data to evaluate each. This new section includes: contribution of chain mechanisms, Marcus Inverted BET, sensitization of the ketone *via* doublet-to-triplet energy transfer, and pre-association of the catalysts to the ketone to confer selectivity via an EDA complex. Having evaluated each alternative possibility, only our original proposal based on indiscriminate photoreduction via the intermediacy of a solvated electron remains consistent with this more complete body of mechanistic work.

4) The manuscript structure is a 'self-fulfilling prophecy'. A proposed concept is accompanied by carefully designed mechanistic experiments considering only the initial hypothesis. While such a structure is in principle OK/not un-common. The severe drawback is it overlooks alternative explanations for observations (i,ii). For example, mechanism for radical anion cycloadditions are well-established as chain reactions (Φ>>1), where product radical anion reduces starting ketone in propagation. This has not been considered as explanation for chemoselectivity and is particularly worrying, in light of highly related prior literature (e.g. Krische, Bauld, Simonet & teams show similar polyarene radical anion and electrochemical systems can effect such chain reactions: J. Am. Chem. Soc. 126, 1634 (2004); Tetrahedron Lett. 31, 667 (1990): It is likely Per radical anion is a simple initiator. In Scheme S37 authors suggest the neutral Per accepts the product radical anion's electron, however, the rate of cycloaddition process is not beyond diffusion control (reaction with styrene, then rotation to allow trans-diastereoselectivity). Concentration of ketone acceptor will far outweigh that of neutral Per Chain does not require photoexcitation per turnover, may dominate product formation. Sub-stoichiometric F/mol cannot tell anything on chain reactivity in redox neutral case. Quantification of the quantum yield of the reaction is truly essential.

Based on this prior literature, we think it is reasonable that chain mechanisms may contribute to product formation to some degree. However, crucially, even a chain mechanism would require the unusual mechanistic scenario we outlined to be productive for substrates with such severely mismatched redox potentials. Nonetheless, we completely agree that the lack of discussion of chain mechanisms was a critical omission in our original submission. Both because this is a reasonable question given what is known about the reaction and because many of the other important photoredox reactions are chain processes. How this unusual selectivity paradigm interfaces with different mechanistic scenarios (e.g., chain, non-chain) is now explicitly handled. In our response, first we will present a detailed explanation for our claim that a chain mechanism does not impact our central claims alongside kinetic modeling that is consistent with this analysis. Next, we will present specific changes made to the manuscript to clarify this important issue.

Why a chain would still require the proposed selectivity model: Initiation of the chain requires reducing the harder-to-reduce ketone in the presence of the easier-to-reduce styrene. This would simply not occur to any appreciable extent under a regime controlled by redox potentials. Even if styrene hydrogenation rates are very slow due to low proton availability, the desired 3+2 product would still not be observed since styrene would inhibit initiation (SET to styrene is many orders of magnitude faster than to ketone). This issue is then compounded because, during chain propagation, the 3+2 product radical anion can transfer an electron to styrene as readily as to ketone. So, while direct SET back to perylene is likely slow due to low concentration, SET to styrene (present in roughly equal concentration to ketone) is sufficiently favorable to be both diffusion-limited and irreversible. This introduces a facile termination pathway. So, like many photoredox chain reactions, we anticipate persistent 'smart initiation' (Studer and Curran, Angew. Chem. Int. Ed. 2016, 55, 58 – 102) will be crucial. And then each reinitiation requires reduction of the far harder to reduce ketone over styrene. As a result, participation of chain propagation is not relevant to the central conclusions of our manuscript. Even if $\Phi > 1$, selectivity for our observed products would be lost under conventional SET conditions.

Kinetic modeling to integrate chain propagation events: Our assessment above outlines why the question is not whether this reaction occurs via a chain mechanism but, rather, is whether a chain mechanism is a plausible explanation for the observed selectivity profile. To answer this question, we have introduced new terms into our kinetic models: 1) SET from product•– to styrene; 2) SET from product•– to cyclopropyl ketone; 3) SET from styrene•– to cyclopropyl ketone. We computed the (Marcus) barriers for each of these steps (Figure S2.30):

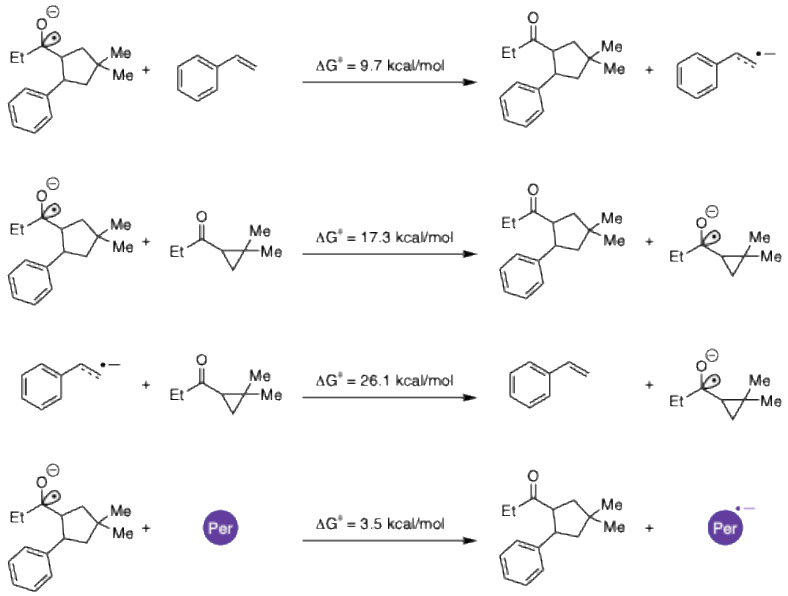


Figure S2.30: Computed barriers for chain termination (top); chain propagation (second); ketone reduction via SET from styrene (third); SET to perylene (bottom)

Addition of these terms results in a more complete model that allows for both chain propagation and termination events (Figure S2.31, shown below). We find that introducing these terms has almost no impact on the overall predicted selectivity profile. This is because propagation involves a roughly thermoneutral SET and significant reorganization energy, whereas SET from product•– to styrene is highly exergonic and results in lower reorganization energy (SET to styrene is predicted to be irreversible and occur 6 orders of magnitude faster than

propagation). This indicates that styrene poses a persistent termination pathway that is a direct consequence of its less negative potential.

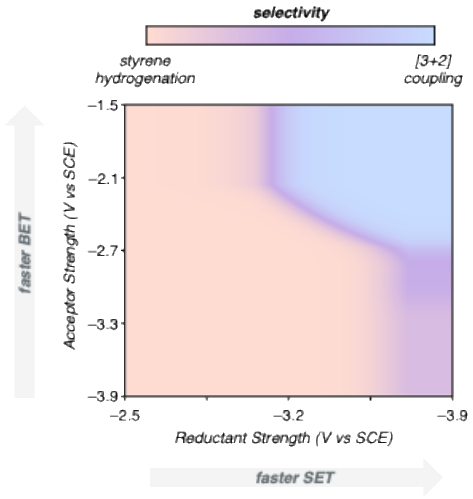


Figure S2.31: Kinetic selectivity model as a function of driving force for SET and BET, accounting for chain propagation and inhibition as predicted computationally

Importantly, however, the mechanistic logic that we outlined at the outset of this discussion would hold even if the propagation step were significantly faster than our calculations suggest. To evaluate that supposition, we arbitrarily set the barrier to SET from product•– to cyclopropyl ketone as *equivalent* to SET to styrene (which is a 9.7 kcal/mol decrease in barrier relative to the calculated values and thus represents a vast overestimate of the likely rate; Figure S2.32, reproduced below). When that change is made, without changing anything about the influence of substrate redox potential on other steps, *the kinetic performance still remains essentially unchanged*.

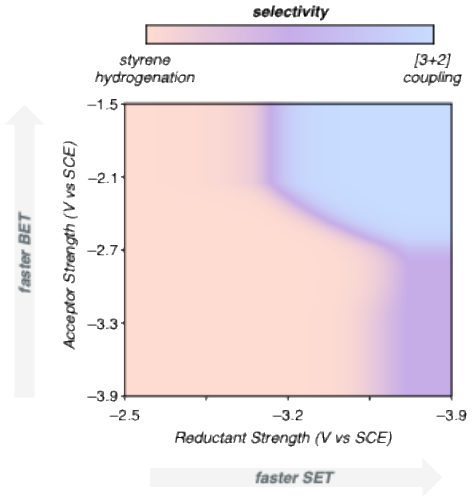


Figure S2.32: Kinetic selectivity model as a function of driving force for SET and BET, accounting for chain propagation and inhibition where propagation rate is intentionally overestimated

Unfortunately, quantum yield determination in electrophotocatalytic systems presents technical challenges distinct from conventional photoredox: the absorbing species (Per•–) is generated electrochemically at dynamic concentrations that vary spatially between electrode and bulk, both Per•– and Per absorb at the excitation wavelengths, and light attenuation through a divided cell is non-trivial. However, we hope that you will agree with us that this measurement is beyond the scope of the present study given that even a chain mechanism would still require our proposed selectivity model.

Changes to the manuscript and supporting information: We have added a brief mention of chain reactions, as well as relevant citations, to the main text when the kinetic model is discussed. This addition also refers

interested readers to an extensive discussion of chain pathways in the SI that mirror the response provided above, discussing the varied mechanistic scenarios and their kinetic implications.

Alternatively, ring opening of cyclopropyl ketones by photoexcitation (Zimmerman & Flechtner: J. Am. Chem. Soc. 92, 6931 (1970) and photosensitization to give biradicals is known (e.g. Waser, Bach & teams: J. Am. Chem. Soc. 145, 25411 (2023); Angew. Chemi 59, 21640 (2020). The polyaromatic catalysts examined (SI file Section 3) are all known as classical energy transfer photosensitizers. While reasonable clear the neutral polyarene singlet states (absorbing <400) are not responsible for reactivity, doublet-to-triplet energy transfer (DTET) is an established, efficient concept (J. Am. Chem. Soc., 147, 43013 (2025); J. Phys. Chem. Lett. 8, 5865 (2017); J. Am. Chem. Soc. 147, 1017 (2025); Chem. Sci. 13, 6732 (2021) and this should be investigated via similar methods used in aforementioned studies. Piperylene should be added as redox inert energy transfer quencher, known to quench triplet of cyclopropylated ketone within an order of magnitude of the diffusion rate (Zimmerman).

We appreciate the reviewer raising the possibility of DTET as a distinct selectivity mechanism. This is a pathway we hadn't considered in detail as we assumed initially that we could preclude bimolecular processes on the basis of the short doublet excited state lifetimes. Nonetheless, since doublet-to-triplet energy transfer (DTET) from perylene radical anion could be a pathway to bypass the proposed SET mechanism entirely, we agree it must be more explicitly ruled out.

Our assessment was that the most direct way to probe this hypothesis was to directly measure quenching of the short-lived doublet excited states (obtained at 520 nm irradiation) by the ketone, as a DTET pathway would induce measurable quenching. Transient absorption spectroscopy on the ps timescale found no detectable quenching of perylene radical anion doublet features upon addition of the ketone (Figure S2.35, reproduced below). These findings are inconsistent with productive energy transfer to the ketone.

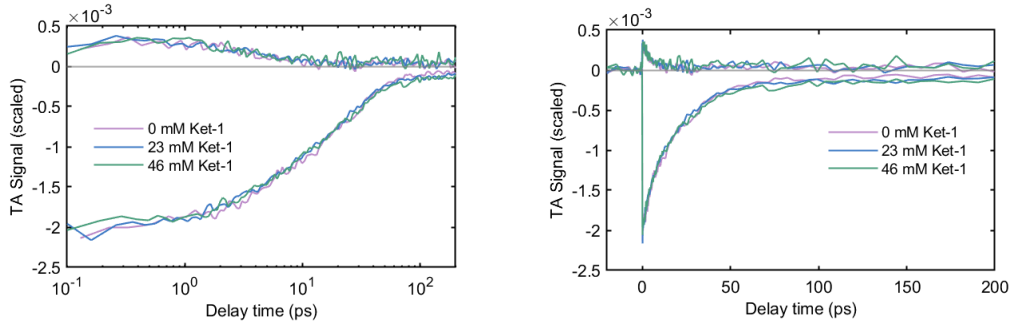
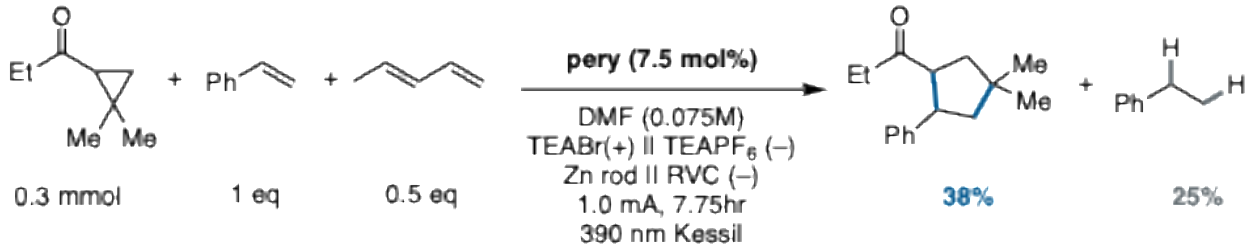


Figure S2.35. Excited state absorption decay and ground-state bleach recovery of Per•– monitored at 505 and 575 nm, respectively, following 520 nm excitation (500 nJ pulse energy). Addition of Ket-1 leads to small changes in the Per•– concentration; transient traces were therefore normalized by the peak Per•– absorption to enable direct comparison of the amplitudes of the decay traces. Data are plotted on a log scale (left) and linear scale (right)

Since the short doublet lifetime (of order 20 ps) dictates that DTET would require the substrate to pre-associate with the catalyst, we supplemented these spectroscopic data with a computational investigation into complexation between the radical anion photocatalyst and the substrates. This analysis indicates that EDA complex formation is endergonic for both styrene (ΔG = +4.1 kcal/mol, $K_{eq} = 10^{-3}$) and the ketone (ΔG = +4.2 kcal/mol, $K_{eq} = 10^{-3}$), while productive doublet reactivity typically requires strong association ($K_{eq} > 100$, Wegner Nat. Comm. 15, 4738, 2024).

As a third orthogonal probe for this mechanism, we also tested the suggested addition of piperylene. While some product inhibition occurs (38% yield vs. 70% without piperylene), this result is difficult to interpret unambiguously as piperylene is a diene that can also competitively trap the radical intermediates formed after ring opening or be reduced itself by a solvated electron. However, when combined with both the spectroscopic and computational evidence, we think the lack of complete suppression of the desired reactivity is consistent with our conclusion that we can exclude DTET as a likely pathway.



Placing these observations into the full context of the provided reports of DTET, we can rationalize the lack of DTET activity as a consequence of the short excited state lifetimes of our perylene radical anion and bimolecular nature of our system, conditions which are not in place in the past reports of this phenomenon.

Changes to the supporting information: A discussion of DTET pathways, which mirrors what is described above, has been added to the alternative mechanistic hypotheses portion of the SI.

Finally and most critically, the Marcus inverted region has not been considered as a factor in redox chemoselectivity. While clear the styrene's reduction is at diffusion limit (ketone is ~6x below it), the back-ET falls below diffusion limit at which point the driving force for the ketyl radical anion's reduction of Per pushes it into Marcus inverted. This exact phenomenon is previously reported for both excited state oxidants (J. Photochem. Photobiol. A 107, (1997) and radical anion reductants (ACS Catal. 12, 6047 (2022); it most likely underpins the selectivity herein. Authors should measure more BET rate constants to examine if an inverse dependence on driving force in the inverted region occurs. Leveraging the Marcus inverted region in photocatalysis is a strategy previously exploited (Science 382, 191 (2023).

We agree that Marcus inversion could, in principle, attenuate BET from the ketyl radical anion to perylene, enabling selective ketone activation even without indiscriminate SET. However, influence from the inverted region for bimolecular electron transfer requires not only that the driving force exceed the reorganization energy ($\Delta G > \lambda$), but also that BET is slower than diffusion ($k_{BET} < k_{diff}$) to be kinetically relevant. Literature precedents for Marcus inversion in bimolecular systems require driving forces approximately 1 eV larger than λ (ACS Catal. 12, 6047 (2022); JACS 142, 17997 (2020) where in both examples BET is about 2 eV favorable). For these reasons, we initially discounted the contributions of Marcus inverted BET on our observations. However, we agree this should be more carefully treated given the mechanistic focus of this project. Please find this more complete treatment below.

Theoretical evaluation of the possibility of Marcus inverted BET: Marcus theory calculations quantitatively indicate that these processes occur in the normal region because the reorganization energy for BET from the ketyl radical to perylene (λ = 2.7 eV) far exceeds the driving force (ΔG = –1.4 eV). Moreover, even if uncertainty in the computations did allow for BET in the inverted region (ΔG > λ), we observe that BET rates are computed to be comparable with the diffusion limit even for values of λ as low as 0.7 eV, well beyond the margin of error (Figure S2.33, reproduced below). Additionally, SET from the ketyl radical to styrene, which is present in approximately equimolar concentrations, only has a driving force of about –0.6 eV, and would unambiguously occur at diffusion-limited rates. Thus, while these findings strongly indicate that BET is not inverted, SET from the ketyl radical anion to styrene would kinetically mask any impact of Marcus inverted kinetics.

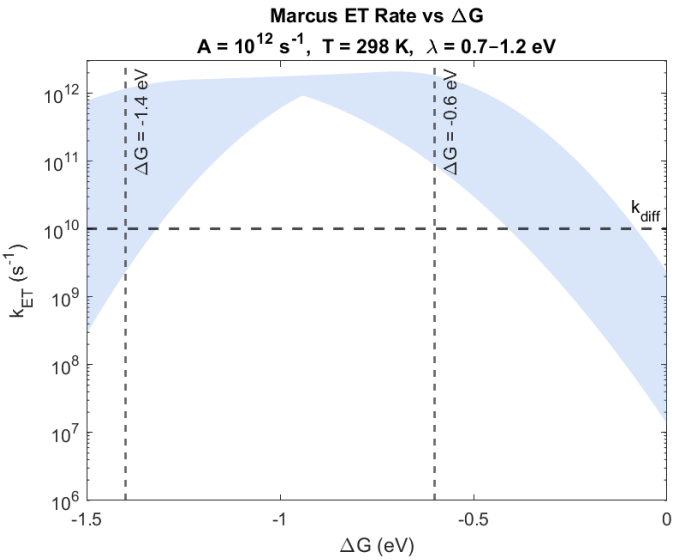


Figure S2.33. Kinetic simulations for the rates of BET and SET from the ketyl radical to perylene (–1.4 eV) and styrene (–0.6 eV) for a range of reorganization energies (λ).

Experimental evaluation of the possibility of Marcus inverted BET: To experimentally decouple driving force effects from post-SET fragmentation, we examined cyclic voltammograms of perylene under irradiation with an acyclic dialkyl ketone (1-cyclopentylethan-1-one). This structural analogue maintains the same driving force for BET as the cyclopropyl ketone but does not undergo ring opening upon SET reduction. Under identical conditions, the cyclopropyl ketone induces photocatalytic current whereas the acyclic analogue does not. These data are consistent with our model that catalysis arises from rapid fragmentation outcompeting BET, not from attenuated BET rates in the Marcus inverted region. Further detail regarding our CV experiments examining BET can be found below as well in our reply to your feedback about our preliminary CV data in the initial submission.

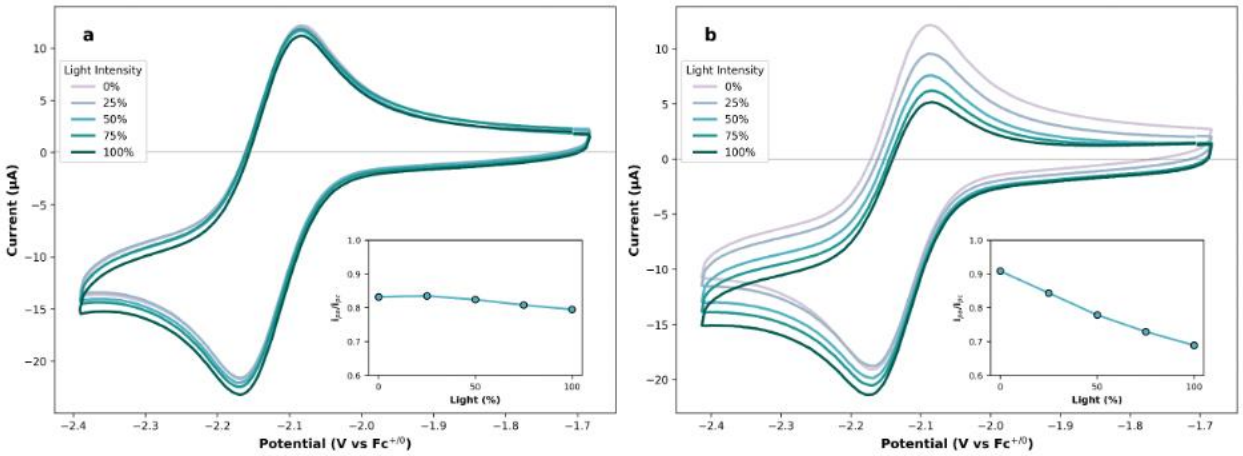


Figure S1.17 CV of Per (1 mM) in DMF containing 100 mM ketone substrate and 0.1 M $TEAPF_6$ at 100 mV/s with various light intensities (0%, 25%, 50%, 75%, 100%). (a) Cyclohexylmethyl ketone; (b) Ket-1. Insets show the impact of light intensity on the ratio of peak anodic to peak cathodic current (i_pa/i_pc). Lines are drawn to guide the eyes.

Changes to the supporting information: A discussion of the possibility of Marcus inverted BET as a mode of selectivity, which mirrors what is described above, has been added to the alternative mechanistic hypotheses portion of the SI.

5) The authors attribute signatures to solvated electrons in the TA studies, but do not correlate the quenching with any detection of the ketyl radical anion to show this is a productive pathway, although this should be observable in the TA (Tanko & team: J. Org. Chem. 70, 4170 (2005). Authors should detect the ketyl radical anion.

Unfortunately, the precedent cited (Tanko, J. Org. Chem. 2005) employs aromatic ketones whose ketyl radical anions absorb at 480-530 nm due to phenyl-carbonyl conjugation. Our aliphatic ketones lack this chromophore and their ketyl radicals are expected to absorb at significantly blue shifted wavelengths (in the UV/near-visible regions). These will be dwarfed by perylene absorbance features, which have a far higher molar absorptivity and preclude unambiguous detection. Since aromatic ketones are easier to reduce than styrene and well-precedented in this formal 3+2 process, they are not diagnostic model compounds.

However, in our revision, we present multiple lines of evidence to establish that the measured solvated electron quenching by ketones productively generates ketyl radicals:

1. Cyclic voltammetry under irradiation demonstrates unambiguous catalytic current with the cyclopropyl ketone. No catalytic current is observed in the dark or in the presence of an analogous aliphatic ketone without a cyclopropane. Like the TA solvated electron quenching experiments, the response magnitude is dependent on ketone concentration. These data are fully consistent with irradiation inducing SET to the ketone, which is rendered irreversible by fragmentation.
2. Our kinetic modeling, which is parameterized with computed barriers for all relevant SET, BET, and fragmentation steps, reproduces the observed selectivity only when accounting for ketyl formation and subsequent ring opening.
3. The solvated electron is quenched at diffusion-limited rates by perylene ($\approx 8 \times 10^{10}$ M^{-1} s^{-1}), pyrene ($\approx 5 \times 10^{10}$ M^{-1} s^{-1}), and styrene ($\approx 3 \times 10^{10}$ M^{-1} s^{-1}). Quenching by cyclopropyl ketone Ket-1 occurs at a reduced rate ($\approx 4 \times 10^{9}$ M^{-1} s^{-1}), consistent with SET to a harder to reduce substrate that approaches but does not reach the diffusion limit.
4. TA experiments with pyrene as a model compound clearly demonstrate quenching via SET. Although these measurements were primarily designed to quantify back-electron-transfer kinetics, the transient absorption data clearly show the growth of the pyrene radical anion, directly demonstrating reduction of a neutral substrate by the solvated electron under identical experimental conditions.

Changes to the supporting information: We have added a comment to our discussion of the quenching data in the SI to clarify that direct observation of the ketyl is not feasible, but we infer it based on ketone-dependent quenching as well as the CV measurements.

8) Table S1, it is very surprising that Cor vs Pyr radical anions react with same redox properties and similar photochromic properties (Chemistry Eur. J. 18, 15753 (2012); Ref22) give such different performances. Photo-ionization at shorter wavelengths should afford solvated electrons in each case, it seems to follow for Cor but not for Pyr? Why this discrepancy?

We were surprised by the differential performance of coronene and pyrene radical anions as well! However, photoejection of solvated electrons from radical anions is a rapidly emerging area of photocatalyst design that currently lacks any in-depth catalyst structure-activity relationships. Indeed, many phenomena could contribute to the poor performance with Cor. We suspect the difference reflects excited state dynamics (e.g., lower photoionization quantum yields) or reduced catalyst stability (e.g., decomposition by organic radicals). While interesting, an extensive study into these catalyst structure-activity relationships is not necessary to evaluate the proposed selectivity mechanism that is the central focus of our manuscript and we consider it beyond the scope of this report. We are currently examining the roles of photocatalyst structure on the generation of solvated electrons, but we would prefer to report a complete set of design principles by drawing systematic comparisons across many members of this catalyst family in a follow up study.

9) Pg5: It is mentioned the quenching of solvated electrons by styrene is only 1 order of magnitude faster than by ketone, despite a 650 mV difference predicting ~20 orders magnitude. Why? Does this speak to a favourable interaction between Per radical anion and ketone that renders a higher local concentration of ketone?

This observation is central to our proposed mechanism: once SET becomes diffusion-limited, further increases in driving force will not accelerate that rate. This means that once SET to the easier-to-reduce substrate becomes diffusion-limited, the kinetic bias favoring reduction of that substrate becomes compressed as further increases in driving force only impact SET to the harder-to-reduce substrate. Thus, the apparent disconnect between the 650 mV redox potential difference and the 8-fold rate difference arises from the influence of this diffusion limit. Under this regime, the influence from the intrinsic Marcus barriers is dramatically reduced because the rate of diffusion has capped the rate of SET to styrene.

We do not think that pre-association contributes to the observed rate similarity. The measured quenching rate for styrene ($k = 3 \times 10^{10}$ $M^{-1}s^{-1}$) matches the expected diffusion limit, while the ketone quenching rate ($k = 4 \times 10^{9}$ $M^{-1}s^{-1}$) is consistent with a modest residual Marcus barrier given the lower driving force, precisely as predicted for near-diffusion-limited kinetics. Additionally, transient absorption measurements find no doublet quenching by either substrate and calculations indicate that complexation of the radical anion with the ketone is endergonic.

We have revised lines 140-150 to clarify that the "predicted" rates are with weaker reductants that would not result in diffusion-limited SET and that these measurements are fully consistent with predictions of diffusion-limited SET. The change is reflected in red text with accompanying black text for context.

Changes to the manuscript:

These data starkly contrast the kinetic profile predicted for less potent SET reductants (–0.8 to –2.2 V vs. SCE) that operate soundly in the Marcus normal region where this 650 mV difference in redox potentials is expected to induce a massive kinetic bias, favoring olefin reduction by 10 to 20 orders of magnitude (Fig. 3c, bottom).

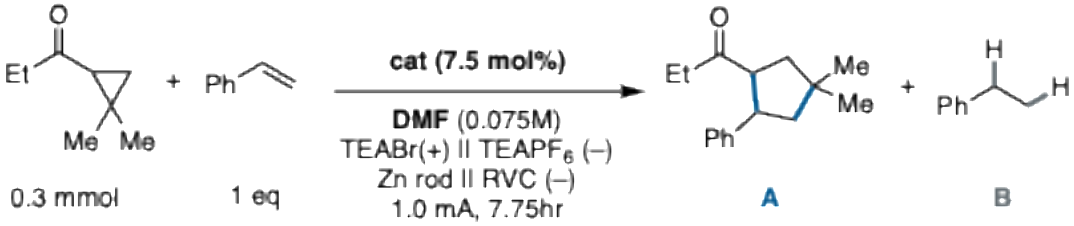
*10) Comparisons with other methods are not always fair. Fig2: Mediated electrolysis done with CPE and compared to direct electrolysis and electrophoto with CCE. PTH (*E1/2 −2.10 V) was doomed to fail for both substrates. A photoredox catalyst that can actually reach the potentials of the two substrates must be tested (*E1/2 > -3 V, e.g. Melchiorre, Xia & teams thiolate or phenolate: Angew. Chem.* ***62****, e202306364 (2023); Chem. Sci.* ***11****, 6996 (2020). ConPET conditions should be done using perylene, since excited acridinium can likely oxidize the styrene in competition with the amine reductive quencher. Acridinium should be used under electrophoto reductive conditions as acridinyl is potent enough and also known to photo-ionize solvated electrons.*

In our initial submission, we provided a limited set of comparisons since our initial focus was on identifying *any* potent photoreductant system that induced the predicted behavior. However, upon reflection, we agree that a more complete comparison is merited and that illustrating other super-potent photoreductants can engage the same selectivity manifold would strengthen the claims of the manuscript. Given the extensive experiments added, we have broken down our response by class of reductants.

Electrolysis comparisons:

We have now included CCE results with a range of mediators to enable direct comparison. Under constant current conditions, all mediators (including perylene) result in exclusive styrene hydrogenation with no desired product formation:

Electrochemistry



Entry	Catalyst	variation	Remaining Ketone	Remaining Styrene	A	B
1	none	constant current	93	55	0	38
2	Rub	constant current	98	54	0	47
3	DPAIPN	constant current	96	57	0	38
4	Per	constant current	96	84	0	12
5	Cor	constant current	95	57	0	37
6	Pyr	constant current	92	52	0	42
7	Pyr	constant potential	82	32	0	55

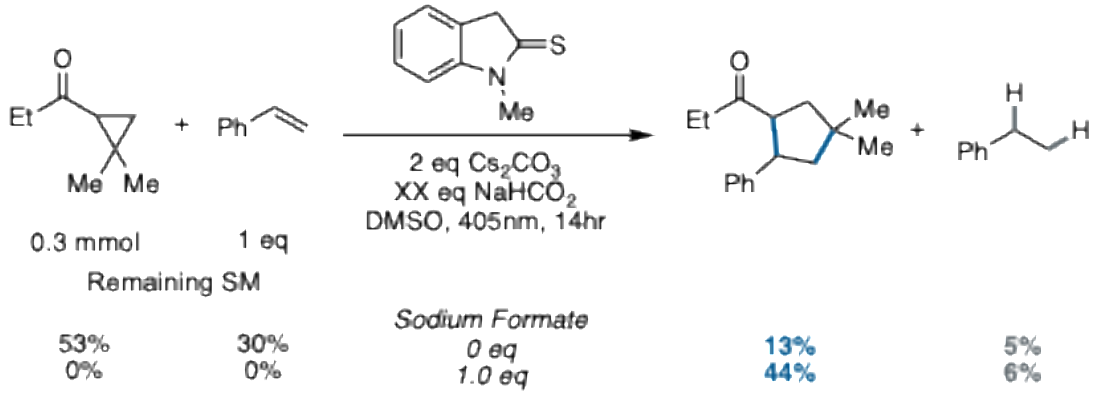
Table S4. Probing the efficacy of direct and mediated electrolysis Reactions are conducted according to general procedure 1, with the following modification: The reactions were performed in the dark, wrapped in foil and heated to 40 °C to recapitulate the heat from irradiation. Yields determined by GC with mesitylene (1 eq) as an internal standard. Constant potential experiments performed at –2.5 V vs. $Ag/AgNO_3$, a potential sufficient to reduce pyrene.

The earlier constant potential experiments with pyrene were performed to ensure selective mediator reduction without direct substrate electrolysis; constant current could provide cathodic potentials that induce competing direct electrolysis, convoluting the comparison. The CCE data presented here reinforce the conclusion that thermal SET from electrochemically generated mediators cannot overcome redox potential control.

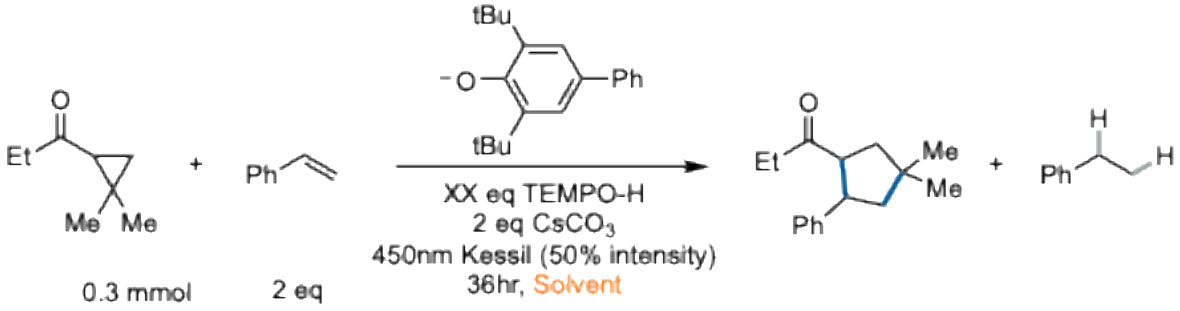
Comparison to stronger single photon photoreductants:

In our initial submission, we chose to not prepare any photocatalysts that were not commercially available, as our intent was to illustrate that the proposed redox-potential-independent selectivity paradigm is *possible*. However, we now realize the initial submission implied that this was somehow an electrochemically-unique phenomenon rather than that electrophotocatalysis is an ideal way to probe the behavior. Thus, we agree that the potent photoreductants/modified conditions you suggested were within the scope of this study, as they could clarify whether the redox-potential-independent selectivity is general across super-potent photoreductants and provide insight into the expected challenges in exploiting this reactivity in other catalytic systems.

We first synthesized and tested the thiolate photocatalysts reported by the Melchiorre group. Excitingly, under photoredox conditions, the thiolate system promotes the desired [3+2] annulation with moderate efficiency (44% yield, 6% styrene hydrogenation and full conversion of both coupling partners). This reactivity is consistent with our proposal of emergent selectivity from super-potent photoreductants. Melchiorre's thiolate photocatalyst is sufficiently potent ($*E_{1/2}$ = –3.4 V) to fall into the 3+2 selective regime of our kinetic modeling (see Fig 5c), overcoming the 650 mV redox potential mismatch.



We also synthesized the phenolate photocatalyst reported by Liang and coworkers. We tested this catalyst both with the TEMPO-H from the authors' original conditions as well as without since the role of this additive was not clear for our system. However, we observed no annulation product or hydrogenation under these conditions.

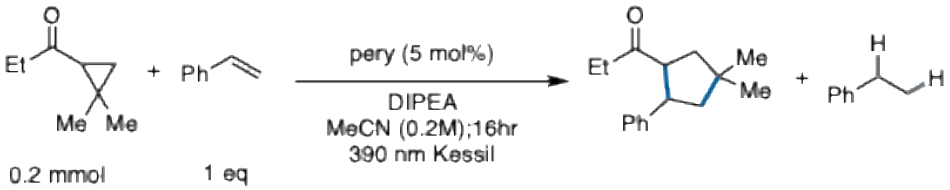


0.3 mmol 2 eq

Remaining SM		*TEMPO-H eq*	*Solvent*		
92%	1.4 eq	1.2 eq	DMSO	**0%**	0%
65%	0.9 eq	0 eq	DMSO	**0%**	0%
0%	1.2 eq	0 eq	MeCN	**0%**	0%

Investigation of switching terminal reductants in our system/reported systems:

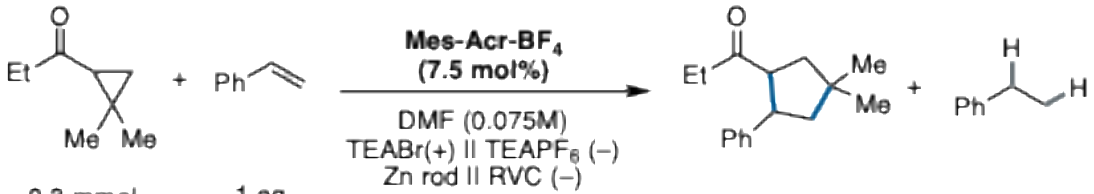
We attempted to recapitulate our electrophotocatalytic system with classic conPET approaches. Given that this is a redox neutral reaction, we tested this at both a substoichiometric and stoichiometric loading of the amine reductant. Neither provided meaningful amounts of the desired 3+2 product.



0.2 mmol 1 eq

Remaining SM				
100%	65%	0.1 eq DIPEA	**0%**	1%
73%	0%	1.0 eq DIPEA	**1%**	1%

The suggestion of using acridinium salts under electrochemical conditions is a great idea. While we found acridine radical photocatalysis was not productive at constant working potential, driving these catalysts with constant current electrolysis did provide 3+2 product in 23% yield. Of note, the conPET conditions we used originally followed Nicewicz's precedent for styrene reduction, which mitigates the concern that photooxidation of styrene is inherently problematic under these conditions. As a result, these electrophotocatalytic studies should complement (not replace) our initial use of conPET conditions with these catalysts.



0.3 mmol 1 eq

Remaining SM				
87%	2%	*constant potential* -1.14 V vs Fc	**0%**	0%
40%	10%	*constant current* 1.0mA, 7.75hr	**23%**	10%

Taken together, these experiments illustrate that multiple potent photoreductants can access the kinetic regime that underpins the distinct selectivity profile outlined in this manuscript. Moreover, they provide evidence that the terminal reductants are a crucial parameter that modulates the performance of such systems.

Revisions to the manuscript:

We have revised the discussion of other conditions to emphasize that redox-potential-independent selectivity is expected to emerge from any super-potent photochemically-driven reductant. We also note the importance of terminal reductants and present the full dataset in the supporting information.

We also revised the figure to include the Melchiorre thiolate result as a representative super-potent photoreductant that is not driven by electrochemistry. Please note, we left the PTH comparison in the Figure, as we felt the comparison to a more "conventional" strong photoreductant was important for a general audience, but we also adjusted the corresponding text to be clear that it is not expected to provide product.

Specific revised text (black text for context, red text substantially revised):

Conventional strong photocatalytic reductants, such as phenothiazine (PTH), are insufficiently potent and led to low ketone conversion and no annulation. However, we also tested several of the recently reported potent photoreductant systems (see SI Section 1 for details). These studies revealed that Melchiorre's thiolate photocatalyst,[30] a super-potent single-photon reductant ($*E_1/_2 = -3.4$ V), promotes the [3+2] annulation, albeit in diminished yield. Intriguingly, established potent consecutive photoinduced electron transfer (conPET) systems were found to be ineffective despite, in principle, offering comparably potent reduction potentials.[31] Rather than illustrating specific catalyst limitations, however, we suspect this observation reflects the problematic byproducts derived from the amines used as reductants (see SI for details).[32] Overall, these data are consistent with our proposal that redox-potential-independent selectivity can emerge from diverse super-potent photoreductants.

Revised figure 2 reproduced below:

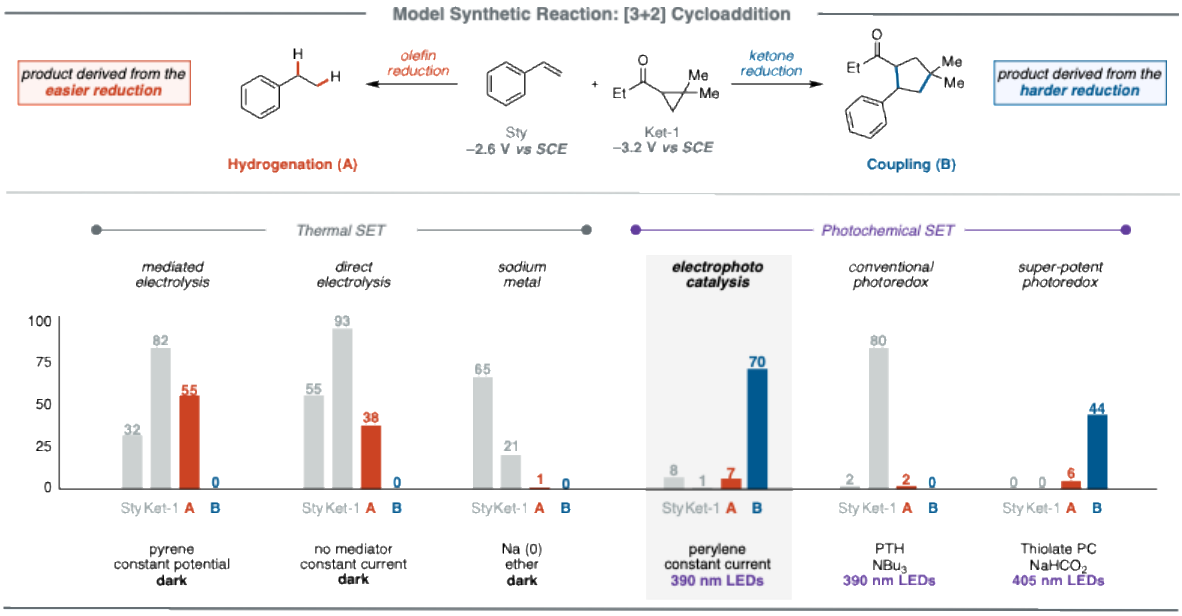


Fig. 2. Model Synthetic Reaction. Performance of various methods to drive SET in a synthetic context that requires violation of redox potential control. See SI (section 1) for full set of experimental conditions and procedures. PTH = 10-phenylphenothiazine, Thiolate PC = 1-methylindoline-2-thione

11) Authors mention protonation of styrene radical anion by water at multiple points, but it is not obvious why this is relevant under the reaction conditions. No water is explicitly, to model reaction or most of the scope reactions apart from certain cases Fig.4 superscript 'f'. Therefore in Fig2/3/5, it seems somewhat disingenuous to compare the cyclopropane opening with protonation when there is no clear proton/water source in the reaction. According to the SI file, reactions were prepared under strict conditions with thoroughly degassed, anhydrous solvents and purged with N2. Particularly, the T.S. for protonation is assuming water/cleavage of a

strong O-H bond, and is likely to be lower in energy for whatever is the true proton source under relevant reaction conditions (DMF?..).

The precise proton source in the system is, indeed, ambiguous. The reaction was intentionally designed to minimize proton availability, as this should limit the rate of hydrogenation pathways and maximize the protective effect of BET for styrene. Accordingly, when modeling the system, we wanted the most conservative model for protonation rates (fastest plausible protonation). While we employ “anhydrous” DMF and maintain strict exclusion of atmospheric moisture, complete removal of water from polar aprotic solvents is practically challenging, and residual water can persist even after significant effort to dry such solvents. However, we agree that the protonation rate is a potentially important aspect of this study and merits a rigorous treatment. To provide a more complete picture, we have now evaluated how alternative proton sources would affect the kinetic competition between BET and protonation. We computed barriers for styrene radical anion protonation by both acetonitrile and DMF (both solvents found to be effective), as well as tetraethylammonium cation (the electrolyte).

These data establish that if the actual proton source is solvent or residual ammonium salts, protonation becomes even slower relative to BET. Accordingly, modeling the reaction with water as the proton donor provides the most demanding test of our mechanistic framework: if BET successfully competes even with the fastest plausible protonation pathway, it will certainly dominate with any less acidic proton source present under reaction conditions. We have made this reasoning explicit in the revised SI and added an expanded discussion to include these alternative proton transfer pathways and their implications for the kinetic model. Of note, even with these slower rates our mechanism is still required because styrene would act as a competitive inhibitor if its reduction is not diffusion-limited (for details, see discussion of chain mechanisms in comment 4, first in this subsection).

12) While the visible TA data for Per radical anion used both 520 and 460 nm pumps, the NIR monitoring used only the 460 nm pump. The longest wavelength absorption of Per radical anion peaks at ~575 nm. As an obvious missing control experiment, green pump should be used as a control to monitor the NIR and rule out photo-ionization from its first excited state.

We have examined the effect of excitation wavelength on photoionization of the perylene radical anion. As shown in Fig. S2.5 (reproduced below), the measurements reveal a pronounced attenuation of solvated-electron generation with increasing excitation wavelength. As the pump is shifted to the red, the near-infrared signal assigned to solvated electrons diminishes substantially, consistent with either increasingly rapid geminate recombination or decreased quantum yield (470–480 nm), and becomes negligible at 494 nm. We have now more clearly outlined this phenomenon in the main text and referred readers to the relevant section of the supporting information for more details.

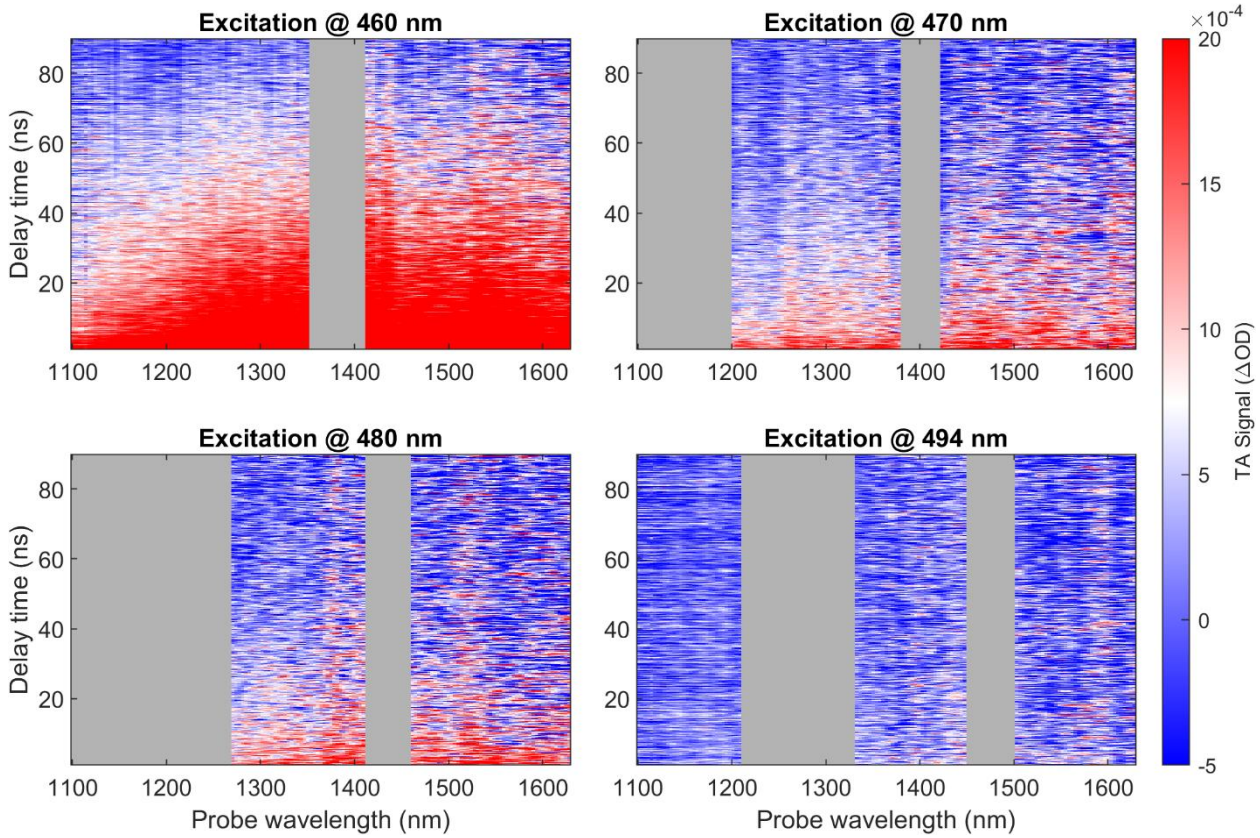


Figure S2.5. Nanosecond transient absorption dynamics in the NIR region following excitation at different wavelengths (specified in subfigure titles), each with 1 mJ energy per pulse. Excitation at 460 nm produces a strong absorptive signal characteristic of solvated electron generation. As the excitation wavelength is shifted to the red, the signal amplitude decreases, reflecting the reduced excitation energy available to drive electron ejection. At 494 nm, no detectable signal is observed, indicating that this was below the energetic threshold for solvated electron formation. The greyed-out regions in the spectra indicate spectral gaps where data could not be collected due to pump scatter. Although excitation was carried out at visible wavelengths (460–494 nm), higher-order diffraction from the detection grating results in apparent pump signal within the near-IR spectral range.

Revisions to the manuscript (substantially changed content in red, black text for context):

This NIR feature is consistent with solvated electrons in acetonitrile. By tuning the excitation wavelength, the generation of these NIR transients sharply diminishes as the pump wavelength becomes longer than ~460 nm, consistent with the calculated vertical detachment energy of Per•– (2.70 eV ≈ 459 nm photon, see SI Section 6 for details). Additionally, the yield of product correlates strongly with excitation wavelength, with shorter wavelength light resulting in higher yields (see Table S1 for the full data set).

13) Fig3D: The 'photocurrent' CV experiments are too superficial. Different scan rates and different substrate concentrations are needed to demonstrate this is a true trend and not due to experimental artefacts.

In order to fully characterize the impact of irradiation on the voltammograms of perylene both with and without substrate, we have added a systematic study of concentration, scan rate and light intensity. This more rigorous study provides much more comprehensive evidence that is fully consistent with the conclusions of the manuscript. Given the relevance to the questions asked about BET earlier, we have also added additional studies on a model ketone without a cyclopropane. This has a similar reduction potential to the cyclopropyl ketone but does not fragment upon SET reduction. Comparison of the two ketone substrates probes the impact of back electron transfer kinetics.

The data are reproduced below but they will be first described holistically for clarity. In Figure S1.6, we present baseline CV data for **Per** at varied scan rates and light intensities (including 0%, which are run in the dark). Of note, the crucial measurement is the ratio of the peak currents (shown in panel f of each figure) as this is a quantitative measurement of changes in reversibility. In the Figure S1.6 baseline measurements, we see that the differences observed by varying irradiation intensity do not impact reversibility of the feature. Next, Figure S1.8 illustrates that similarly minimal changes are observed under any of these conditions upon addition of styrene. In contrast, Figure S1.13 illustrates that irradiation of **Per** in the presence of a cyclopropyl ketone clearly causes a loss of reversibility. This effect is most pronounced at low scan rates, as expected for (photo)catalytic current. (Boucher and coworkers, https://chemrxiv.org/doi/full/10.26434/chemrxiv-2025-7h38h-v2).

As suggested, we examined the concentration effect for this phenomenon to validate that these are not spurious observations. Figure S1.6 shows that across a range of concentrations, styrene has no impact on reversibility, with or without irradiation. In contrast, upon irradiation, cyclopropyl ketone induces a clear concentration-dependent loss of reversibility as a function of concentration that saturates as expected. This concentration-dependent effect is lost in the dark, as expected. Figure S1.14 completes the CV study with a comparative analysis of a cyclopropyl ketone to an analogous aliphatic ketone that does not bear a cyclopropane and thus does not possess the same facile β-scission pathway (Figure S1.17). This final dataset validates that the cyclopropane is required to outcompete BET and induce the observed catalytic (photo)current.

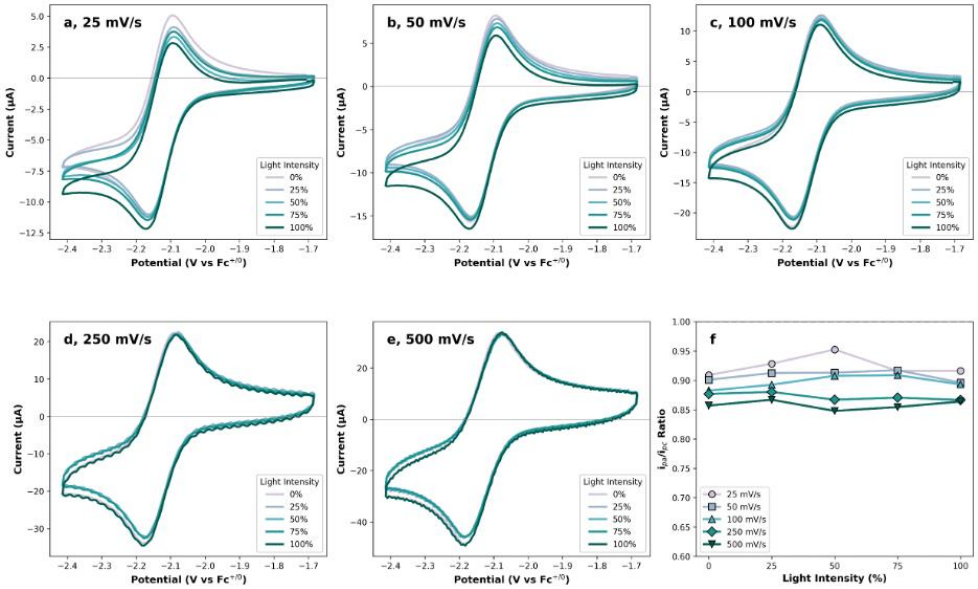


Figure S1.6. CV of **Per** (1 mM) in DMF containing 0.1 M $TEAPF_6$ at 25 mV/s (a), 50 mV/s (b), 100 mV/s (c), 250 mV/s (d) and 500 mV/s (e) at various light intensities with a 390 nm Kessil lamp. (f) impact of irradiation on the ratio of peak anodic to peak cathodic current for various scan rates. Lines are drawn to guide the eyes.

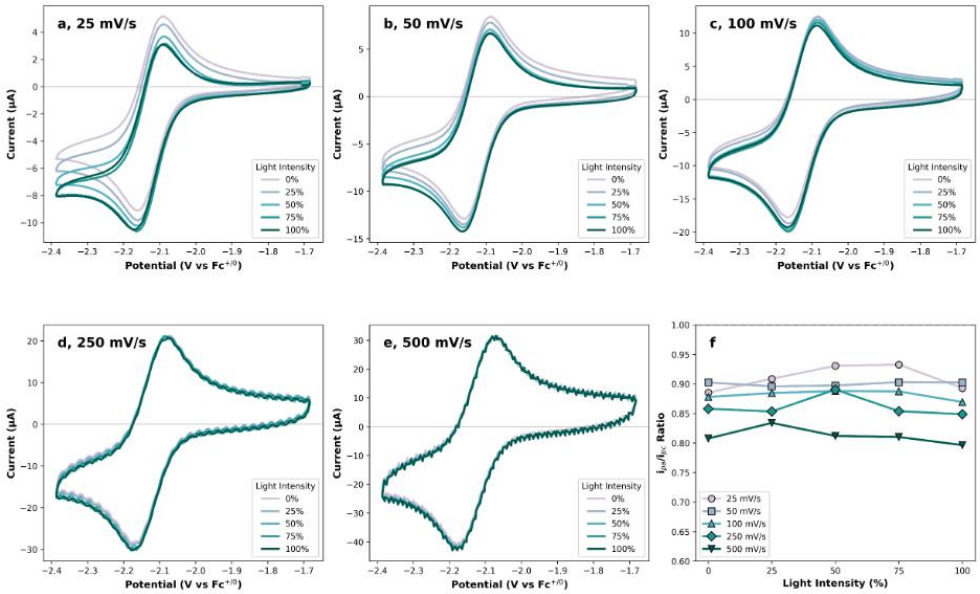


Figure S1.8. CV of **Per** (1 mM) in DMF containing 0.1 M styrene and 0.1 M $TEAPF_6$ at 25 mV/s (a), 50 mV/s (b), 100 mV/s (c), 250 mV/s (d) and 500 mV/s (e) at various light intensities with a 390 nm Kessil lamp. (f) impact of irradiation o the ratio of peak anodic to peak cathodic current for various scan rates. Lines are drawn to guide the eyes.

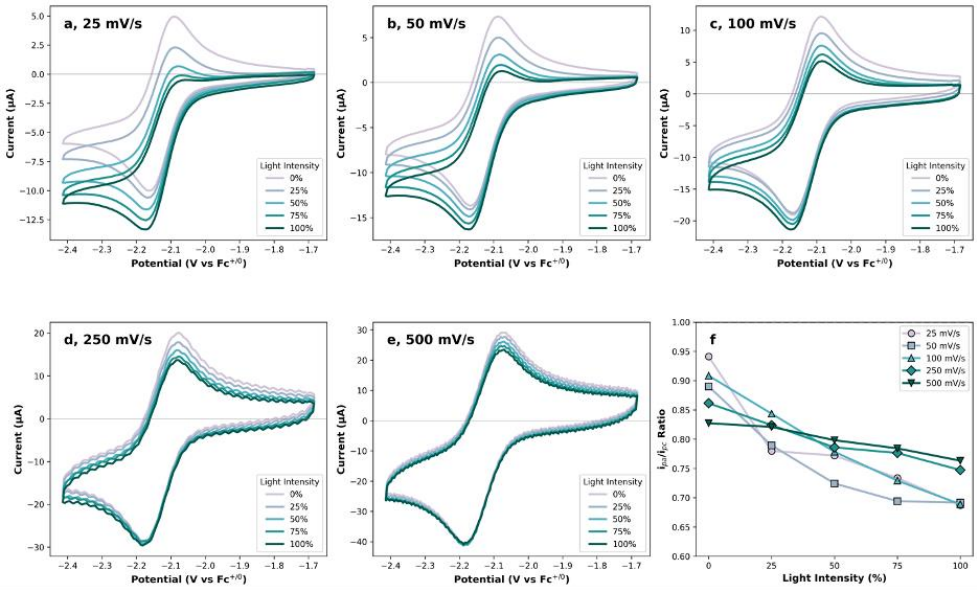


Figure S1.13. CV of **Per** (1 mM) in DMF containing 0.1 M **Ket-1** and 0.1 M $TEAPF_6$ at 25 mV/s (a), 50 mV/s (b), 100 mV/s (c), 250 mV/s (d) and 500 mV/s (e) at various light intensities with a 390 nm Kessil lamp. (f) impact of irradiation on the ratio of peak anodic to peak cathodic current for various scan rates. Lines are drawn to guide the eyes.

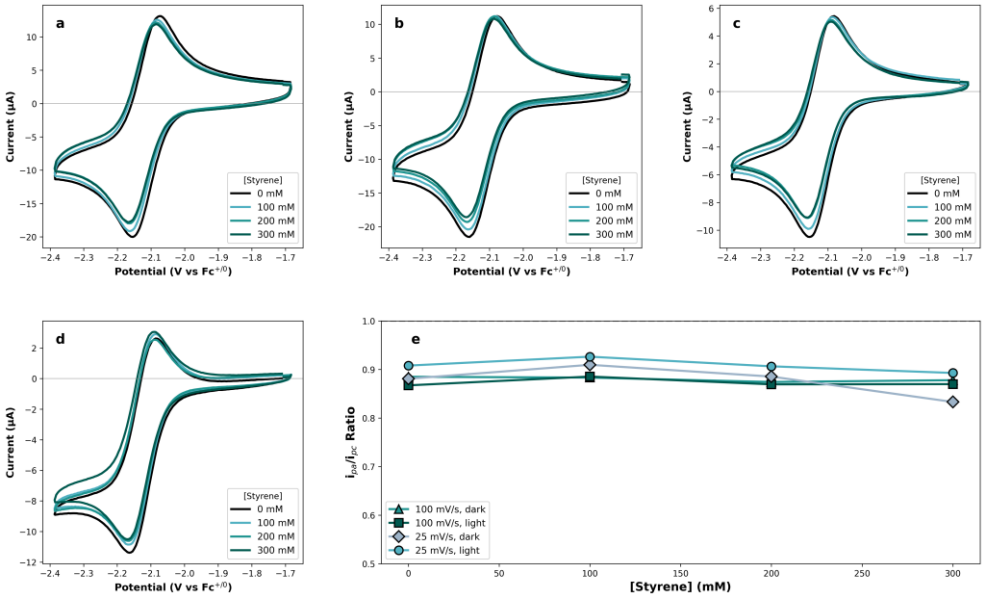


Figure S1.9. CV of **Per** (1 mM) in DMF containing various concentrations of styrene and 0.1 M $TEAPF_6$. (a) 100 mV/s, no irradiation; (b) 100 mV/s, 100% irradiation; (c) 25 mV/s, 0% irradiation; (d) 25 mV/s, 100% irradiation; (e) impact of styrene concentration on the ratio of peak anodic to peak cathodic current. Lines are drawn to guide the eyes.

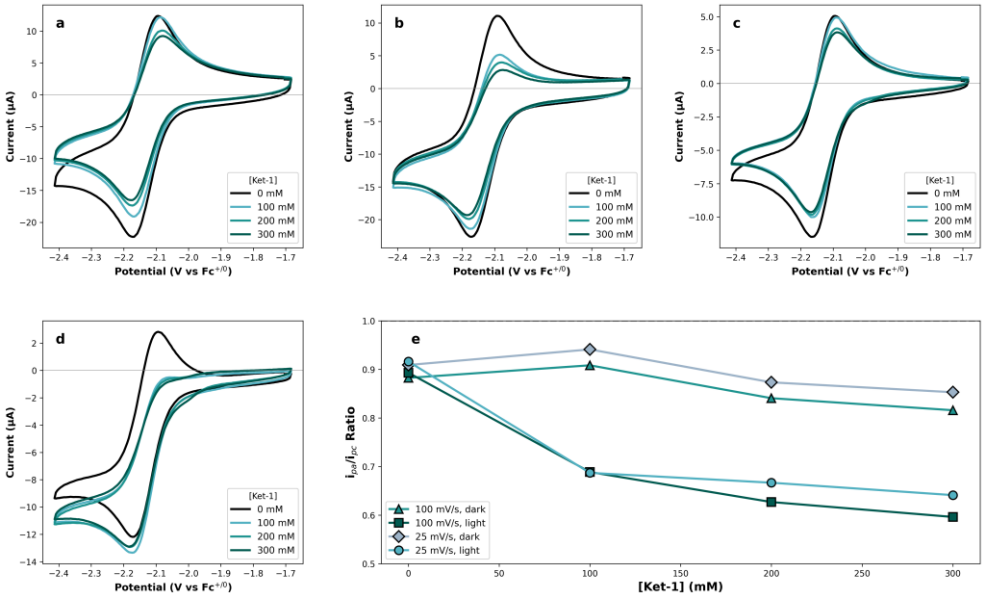


Figure S1.14. CV of **Per** (1 mM) in DMF containing various concentrations of Ket-1 and 0.1 M $TEAPF_6$. (a) 100 mV/s, no irradiation; (b) 100 mV/s, 100% irradiation; (c) 25 mV/s, 0% irradiation; (d) 25 mV/s, 100% irradiation; (e) impact of Ket-1 concentration on the ratio of peak anodic to peak cathodic current. Lines are drawn to guide the eyes.

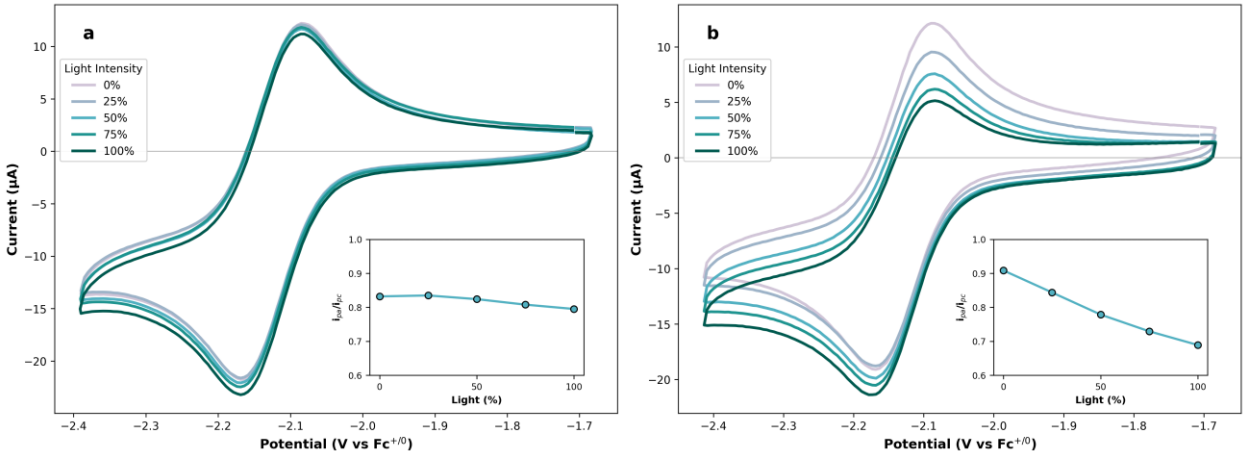


Figure S1.17. CV of **Per** (1 mM) in DMF containing 100 mM ketone substrate and 0.1 M $TEAPF_6$ at 100 mV/s with various light intensities (0%, 25%, 50%, 75%, 100%). (a) Cyclohexylmethyl ketone; (b) Ket-1. Insets show the impact of light intensity on the ratio of peak anodic to peak cathodic current (i_pa/i_pc). Lines are drawn to guide the eyes.

Integrated Response to Comments Regarding Novelty and Importance

1) The concept of capitalizing an irreversible bond cleavage post SET to compete with BET is not a new concept. The viability of such an approach was known since the 1970s (Kornblum, Kochi, Bunnett, among others): J. Am. Chem. Soc. 142, 5461 (2020), has been commonly applied with deprotonatable amines as reductive quenchers for decades and more recently to strain relief driven cleavages.

We certainly agree with the reviewer that the propensity of radical precursors to undergo fast chemical steps upon SET activation and escape unproductive BET is an established principle in photoredox chemistry. Indeed, BET is typically considered a "problem" that inhibits reactivity in photoredox catalysis and decades of research has exploited fast chemical steps to mitigate its impact.

The use of the relative ability of two substrates to outcompete BET to induce selectivity for a harder-to-reduce but faster-to-fragment substrate encounters major impediments as the mismatch in reduction potentials increases. Using conventional photoreductants, as the redox potential gap between substrates increases, the 'easier-to-reduce' reactant increasingly acts as a competitive inhibitor for the desired SET (e.g., to the harder-to-reduce reactant). As a result, the influence of relative BET rates erodes progressively as the potential gap widens. Thus, redox potentials continue to influence selectivity even with a modest potential mismatch and by ~250 mV BET competition becomes functionally irrelevant and redox potentials reassert dominance over selectivity.

The central contribution of our manuscript is that we demonstrate that potent photoreductants that operate in the diffusion-limited SET regime for at least one substrate remove this ceiling, enabling productive chemistry with mismatches exceeding 900 mV. This far exceeds the regime where relative rates of BET can overturn mismatched redox potentials using conventional approaches (Figure 2). This introduces a different way to approach designing selective photoredox reactions and offers distinct opportunities to established approaches using catalyst design.

Revisions to the manuscript:

We have revised the manuscript to more clearly contextualize our work against the prior work using irreversible steps to mitigate the deleterious impact of BET on *reactivity*. The most significant edits were made in our discussion of the broader theoretical assessment of the generality of our strategy, which accompanies figure 5 (as Fig 5c directly relates to these ideas). Additionally, we added citations in the introduction of seminal examples when we touch on the use of irreversible steps to outcompete BET to direct interested readers to the foundational

work using such strategies (Bunnett, Acc. Chem. Res. 1978, 11 (11), 413–420; Kornblum J. Org. Chem. 1987, 52 (14), 3102–3107; Kochi, J. Chem. Soc., Perkin Trans. 2 1992, No. 9, 1581.).

Revised discussion of Fig 5c (sentence in red was added to address the comments above, preceding sentences provided in black for context):

Here, selectivity is controlled simply by the ratio of the post-SET rate constants (k1/k2) until k1 is sufficiently fast to always outcompete BET. Thus, reaction design shifts entirely from redox potentials that control the initial SET to the rate constants that control the subsequent steps.[56–59] More broadly, our analysis indicates super-potent photoreductants can elicit selectivity from any pair of substrates as long as they react at different rates following reduction. This allows the strategies to outcompete BET that have been widely employed to drive reactivity (e.g., mesolytic cleavage)[18,60] to instead engender redox-potential-independent selectivity.

Refs 18 and 60 are newly added general reviews that highlight generally how irreversible steps have been used to outcompete BET in photoredox catalysis:

Melchiorre, P. J. Am. Chem. Soc. 2020, 142 (12), 5461–5476
Stephenson, C. R. J. Chem 2023, 9 (9), 2390–2415

2) It is questionable how this strategy can be general (if truly in operation?) and this is not sufficiently demonstrated in the current manuscript. If true- the strategy relies heavily on a delicate interplay of substrate engineering and interplay/co-incidence of multiple rate phenomena. The 'harder' substrate must have an in built irreversible bond cleavage that happens to be competitive in rate with ET from the 'easier' substrate back to catalyst. It is not intuitive nor clearly demonstrated how this strategy can be applied in a synthesis - practitioners would require to substantial resource and expertise to estimate such rates and could easily do so only computationally; direct quantification of back-ET requires non-routine transient spectroscopy.

The primary objective of this manuscript is to establish the principles underlying selectivity with potent photoreductants, based on the hypothesis that these principles will deviate from classical redox catalysts. *Establishing* these mechanistic principles required specialized techniques. However, we anticipate that *applying* them will be far more straightforward. That said, as we reread the manuscript, we recognized that we did not fully distill these simplifying lessons about reaction design.

If both SET and BET have rate constants that are at or near the diffusion-limit, selectivity becomes controlled by the relative rates of the elementary steps that occur after SET for each substrate (i.e. their ability to outcompete BET). To predict selectivity under this paradigm, practitioners need only ask: which substrate undergoes irreversible transformation faster upon reduction? As you noted in comment 1, this question has been answered for countless substrate classes over the past several decades in the context of inducing *reactivity* by outcompeting BET. The framework outlined in this manuscript now allows this broad body of knowledge to be translated into a general approach to *selectivity* by removing redox potentials from the equation. Overall, this assessment of relative fragmentation rates seems comparable in complexity to other routine qualitative assessments made regularly in reaction development efforts (e.g., estimating relative oxidative addition rates in cross-electrophile couplings).

This can be directly seen in the kinetic model we built in Figure 5c. The discussion provided below is in the SI of our revised manuscript:

For a reductant that is sufficiently potent to render the forward rates of electron transfer to both substrates diffusion limited, i.e. $k_{set,1} \approx k_{set,2} \approx k_{diff}$, the product selectivity from Eq S9 simplifies to

$$\frac{[Pdt_1]}{[Pdt_2]} = \frac{\boldsymbol{k_1}}{\boldsymbol{k_2}} \bullet \frac{k_{bet,2}[A] + \boldsymbol{k_2}}{k_{bet,1}[A] + \boldsymbol{k_1}}$$

This expression can be further simplified when BET is fast relative to $\boldsymbol{k_1}$ and $\boldsymbol{k_2}$

$$\frac{[Pdt_1]}{[Pdt_2]} = \frac{\boldsymbol{k_1}}{\boldsymbol{k_2}}$$

We have revised the discussion of generality that accompanies Figure 5c. To further facilitate adoption, we have added an extended discussion of selectivity origins oriented towards potential users of the method, including relevant citations providing rate data for reduction-induced fragmentations. Finally, the source code for Figures 5b and 5c is now included as supplementary software, enabling users to consider selectivity landscapes for new substrate combinations.

Discussion of Fig 5c (**sentence in red was added to address the comments above, preceding sentences provided in black for context):**

Here, selectivity is controlled simply by the ratio of the post-SET rate constants (k1/k2) until k1 is sufficiently fast to always outcompete BET. Thus, reaction design shifts entirely from redox potentials that control the initial SET to the rate constants that control the subsequent steps.[56–59] More broadly, our analysis indicates super-potent photoreductants can elicit selectivity from any pair of substrates as long as they react at different rates following reduction. This allows the strategies to outcompete BET that have been widely employed to drive reactivity (e.g., mesolytic cleavage)[18,60] to instead engender redox-potential-independent selectivity.

Refs 56–59 are newly added general reviews on tabulated fragmentation rates.

Costentin, C.; Robert, M.; Savéant, J.-M. J. Am. Chem. Soc. 2004, 126 (49), 16051–16057.
Maran, F. Chem. Soc. Rev. 2005, 34 (5), 418–428.
Newcomb, M. Radical Kinetics and Clocks. In Encyclopedia of Radicals in Chemistry, Biology and Materials; American Cancer Society, 2012.
Rusakov, A. I. Russ J Electrochem 2023, 59 (12), 999–1031.

As a strategic concept, I am yet to be convinced this is as elegant as more established concepts such as catalyst control / use of catalyst-substrate interactions. Pg2 asserts there are 'no general strategy to promote reactions that require SET to the harder-to-reduce of two reactants'. This claim of novelty feels overbloated. It is well known that metal co-ordination can modulate redox properties in situ (J. Am. Chem. Soc. 133, 1162 (2011), Ref21), allowing selective SET to the partner which is 'harder' when uncomplexed. Moreover, photocatalyst design has overtunred redox chemoselectivity in the literature, either between two redox labile substrates (e.g. Pospech & team: kinetic favored, selective oxidation of 'harder' stilbene in presence of 'easier' benzylamine (ΔE 0.25 V); ACS Catal. 11, 4862 (2021) or within one substrate containing two redox labile groups (e.g. König & team: selective reduction of 'harder' OPAr2 in presence of 'easier' ArBr; Angew. Chem., 60, 20817 (2021).

We completely agree that methods for catalyst control/substrate recognition are incredibly exciting and have been excited to follow rapid achievements in this area from Melchiorre, Barham, Koenig, Proctor, and many others. These established approaches cited are designed to limit where electron transfer occurs through substrates matched to the photocatalyst. In contrast, our strategy engenders selectivity through the *opposite approach*. We use promiscuous photoreduction to sample reduction of all possible substrates, regardless of their potentials, which selects for those that react fastest. While this unambiguously relies on substrate features (e.g., fragmentation rates), it also eliminates the influence of a previously dominant substrate feature: redox potentials. While catalyst-controlled approaches have been shown to be effective against modest redox-potential-biases (~250 mV), such examples remain rare and *no examples* exist that go meaningfully beyond that energetic mismatch. With our new strategy, we demonstrate effective couplings against biases of 900 mV in a reaction class that is mechanistically unambiguous because the desired product can only arise by engaging the ketone (see further discussion of the model reaction selection below).

Overall, whereas previously achieving selectivity against a 3–4 order of magnitude bias in Keq (e.g. 200–250 mV) was a notable achievement, our mechanism promotes selective reactions for substrate pairs with a Keq disfavored by 15 orders of magnitude (900 mV). We recognize that assessments of elegance are inherently subjective and we may not ultimately agree, but we hope our revised manuscript clarifies how the mechanism operating here is qualitatively distinct from prior strategies while also doing justice to this important prior work.

Edits to the text: We recognize that "general strategy" in the passage quoted leaves a fair amount open to interpretation and might unintentionally mislead readers. We have revised this passage to more clearly

contextualize our project relative to prior work and we have added citations to the representative examples of catalyst control cited by the reviewer.

Introduction (with added references on strategies based on inner-sphere SET)

Moreover, as described by Marcus theory, relative rates of SET are directly tied to relative redox potentials (Fig. 1a, bottom right).[15,16] As a result, selectivity remains tied to redox potentials across the full array of strategies to promote outer sphere SET (e.g., chemical reductants, photoredox catalysts, etc.). Pioneering efforts to mitigate the dominant influence of redox potentials on SET selectivity have focused on devising inner sphere mechanisms that exploit specific catalyst-substrate interactions.[17,18] Broadly, however, the very principles that have reliably delivered selectivity in SET reaction manifolds impose a fundamental barrier for the design of reactions that violate redox potential control.

3) Further to generality: The concept should be agnostic as to the types of 'easier/harder' substrates so long as radical anion of one has an irreversible cleavage, but authors particular model system herein is heavily biased due to cycloproyl ring strain relief. The current manuscript does not go far enough to demonstrate the concept over any other substrate class combination. Instead of a substrate scope involving mostly incremental changes to the same two partners, it would have been much more convincing if the concept would apply to other substrate class combinations/competitions. Solvated electrons can reduce fluoroarenes and alkyl chlorides (Fig.1A), reactions should be designed examining these as 'harder' substrates in presence of some 'easier' - e.g. can authors couple a fluoroarene to any radical trap in the presence of bromo- or chloroarene due to protective back-ET from the radical anion?

We completely agree that the framework we outline will be translatable to many other synthetic contexts. Our goal with this initial report is to establish the foundational design principles that underpin selectivity. In our view, the cycloaddition provides an ideal context to study these principles (for reasons outlined above and below), and we chose to dive deeply into mechanism using this reactivity as a model rather than surveying a broader range of reactions more superficially. We are, of course, excited about the prospect of translating these concepts to additional synthetic reactions and are currently developing several new methodologies unlocked by this paradigm. However, we view such efforts as out of the scope of this current manuscript since we focus sharply here on proof-of-concept mechanistic studies.

In regard to the reviewer's comments on incremental changes to the scope in figure 4, our primary goal with this scope study was to demonstrate how exacerbating differences in substrate reduction potentials does not have a deleterious impact on the observed selectivity. When viewed through this lens, the changes made are not incremental; we test olefins nearly a volt easier to reduce than the ketone. While we are also excited about the ability of this method to tolerate a variety of functional groups, including reductively sensitive pyridine derivatives, this is an ancillary point to the main goal of the figure. Since extensive prior work has already studied steric profiles in this reaction and the focus of our project was on chemoselectivity, we decided further changes along these other vectors were out of the scope of the project.

6) To comment on synthetic utility, reductive activation of these cyclopropylated ketones and their (3+2)-radial cycloadditions to olefins is well precedented in multiple papers, with much more simple, predictable chemoselectivity control factors (Sm/Ti/Mn as reductant and/or L.A.; H-bonding catalyst). In many cases with much broader scopes: Ref21 (includes non-aromatic ketones, including alkyne partners, more diversity on geminal position): J. Am. Chem. Soc. 146, 12799 (2024) (reductively labile functions ArX, C-F bond are tolerated); J. Am. Chem. Soc. 140, 3514 (2018) - see 14,23,24,27,29; almost identical scope stressing, the vinyl pyridine and acrylate are 'easier' than the ketone); Angew. Chemie 63, e202406845 (2024); Angew. Chemie 57, 5454 (2018). ChemSusChem 18, e202500521 (2025); ACS Catal. 13, 11277 (2023). In fact, the transformation is already reported using a radical anion photocatalyst (Qiao, Jiang & team: Angew. Chem. 63, e202406485 (2024), not cited), where pyrene was added as a energy transfer quencher. It was already investigated by TA by Ceroni & team (Ref28) and solvated electrons already found as the active reductant, so much of the mechanistic study herein is unsurprising. While the use of non-aromatic ketones is less represented in the above studies and is commended, this emphasizes the need to address point (3) and step outside the comfort zone of these cyclopropylated ketones.

Model reaction selection:

We have chosen to target the [3+2] cycloaddition, in part, because the mechanism is well understood. Since prior work has clearly established that each starting material affords a diagnostic product, this reaction offers a clean selectivity readout. Additionally, the fact that this reaction has been extensively studied, yet almost entirely

studied with aryl substituted ketones, makes it an authentic example of the constraints imposed by redox potentials.

Scope comparison to prior work:
As the reviewer notes, alkyl ketones are much less developed for this reaction. This is primarily because they introduce a fundamental redox incompatibility with many olefins. Synthetically, progress with aliphatic ketones has been stymied by the mechanistic requirement of Lewis-acid coordination to induce ring opening, which precludes the use of many of the olefins demonstrated in our scope that contain competitive Lewis bases.

We respectfully disagree with the characterization of the scope of Lin's work (*J. Am. Chem. Soc. 140, 3514 (2018)*) as "nearly identical" to ours. While they do show tolerance of acrylates and vinyl pyridines, they do so using aryl ketone substrates that are roughly a volt easier to reduce than the aliphatic ketones we employ. The sole unactivated ketone in the report uses styrene (entry 29), which does not possess these competitive Lewis bases. In a related inner sphere strategy, where SET generates a ketyl radical anion coordinated to a Lewis acid, beautiful recent work from Proctor in 2024 showed that SmI_2 selectively lowers the potential of aliphatic ketones, allowing aliphatic ketones to be more broadly engaged with alkynyl and vinyl arenes as coupling partners. However, this approach is still selectively changing the thermochemistry of ketone reduction through Lewis acid coordination, rather than obviating the control of redox potentials entirely. Accordingly, across these Lewis-acid-promoted strategies, *aliphatic ketones have never been productively coupled to olefinic partners bearing competitive Lewis bases (e.g., acrylates, vinylpyridines, etc.).*

In order to clarify these distinctions and what is and is not an advance of our work from a synthetic perspective, we have revised our discussion of the acrylate/pyridine examples in the main text.

Revised scope discussion:

We found that vinyl boronic esters (14, 15), acrylamides (16, 17), and acrylates (18) are selectively converted to the corresponding cyclic products albeit with low diastereoselectivity for those bearing α-substituents. Successful coupling with acrylates and acrylamides is particularly notable since their basicity would disrupt the inner sphere strategies that have successfully engaged aliphatic ketones by stabilizing the resultant ketyl radical.[25,26]

Mechanistic studies (specific quote from the reviewer reproduced for clarity):

In fact, the transformation is already reported using a radical anion photocatalyst (Qiao, Jiang & team: Angew. Chem. 63, e202406485 (2024), not cited), where pyrene was added as a energy transfer quencher. It was already investigated by TA by Ceroni & team (Ref28) and solvated electrons already found as the active reductant, so much of the mechanistic study herein is unsurprising.

The key mechanistic conclusions of our manuscript are fundamentally distinct from these precedents. Qiao and Jiang used radical anion photocatalysts, but all couplings involved ketones that were easier to reduce than the olefin. Pyrene was used in this study but as a mechanistic tool to evaluate energy transfer pathways. The Ceroni work implicates solvated electrons from excitation of 4DPAIPN•- as the active reductant in the Qiao/Jiang system. However, it does not touch on chemoselectivity nor does it study the photoactivity of reduced PAHs.

Below, we will elaborate on each of these prior reports and detail specific changes made to the manuscript:

The work from Qiao, Jiang, and coworkers (Angew. Chem. Int. Ed. 2024, 63, e202406845) actually *illustrates* the dominance of the redox-potential-grounded reaction design logic. The authors explicitly highlight at the outset that their aryl ketones are easier to reduce than their vinylpyridine coupling partners as they lay out the reaction. This shows how, even with super-reducing radical anion photocatalysts, the field has continued to apply traditional redox-potential-based logic for reaction design. To us, this underscores that our selectivity framework represents a genuine conceptual shift rather than an obvious extension of existing understanding, though we acknowledge that is a subjective assessment. This manuscript was originally uncited as we felt its primary advance was enantioselective catalysis of the 3+2 annulation, but we agree with the reviewer that there is a clear thematic connection due to the use of radical anion photocatalysis and have now cited it.

Prior mechanistic studies on radical anion photocatalysts, both in this annulation and more broadly, have largely focused on how these radical anions can be productive photocatalysts despite their short-lived doublet excited states. While these studies are unambiguously relevant, our manuscript is the first study to focus on how the combination of unselective substrate reduction and BET can induce redox-potential-independent chemoselectivity. To properly conduct our mechanistic studies, however, we had to first *identify* the active reductant in our *specific* system since no prior work studied photoactivity of reduced PAHs. Thus, solvated electrons, pre-association, or catalyst 'activation' were all viable possibilities based on prior literature reports. Overall, distinguishing between these possibilities was necessary, but we agree that it is not a meaningful source of mechanistic novelty. We have adjusted the language to more clearly delineate how our study of the active reductant draws on prior work.

Edits to the text:

These catalysts can (1) act as precursors to longer-lived (photo)chemical reductants, whether closed shell species[38,39] or solvated electrons;[40,41,29] or (2) pre-associate with substrates prior to excitation, circumventing the requirement for diffusive bimolecular reactivity.[42–45] While these possibilities are the outcome of extensive mechanistic scrutiny, the origin of photoactivity for the catalysts we employ herein remains unclear and must be established prior to kinetic investigation into the origin of selectivity. We first examined whether the first doublet state (D1) of Per•–* could be oxidatively quenched by either substrate.

7) It is claimed products could be made 'with a range of steric profiles', this is not true of gem substituents on the cyclopropane, only Me and pyran. Different gem substitutions should be included.

While we are excited that various substitution patterns can be employed in the reaction, upon review we recognize that our initial claim of accessing diverse steric profiles could be interpreted as overstated. Since our primary goal of the scope is to demonstrate how the redox potential of the coupling partner can be modulated without impeding coupling, in our view further exploring changes to the gem substituents of the cyclopropane would distract from central conclusion of the manuscript. Therefore, we have edited the main text to remove the language regarding steric variations to keep the discussion focused on the central point of mismatched reduction potentials.

14) Many compounds in the scope are not isolated, about half in Fig.4 are 1H NMR yields. This is insufficient for Nature. For this method to be a synthetically meaningful access to cycloadducts from non-aromatic cyclopropyl ketones which is a pillar of its novelty, authors need to demonstrate proper isolation.

Unfortunately, premature reduction of the benzylic radical results in linear (uncyclized) impurities that have very similar physical properties to the desired annulation products. While we show that these impurities can be purged using careful iterative chromatography, we determined that following this laborious procedure for each individual entry was not necessary because we view the mechanistic principles, not the preparative use of the reaction, as the primary source of novelty for this work. However, we recognize that sufficient isolation of each compound to unambiguously characterize the products is necessary and instead performed more rapid purifications with this goal in mind, sacrificing isolated yield for purity. As a result, we consider the NMR yields more representative of the reaction performance.

Manuscript:
Fig1B seems misleading, suggesting visually the quenching rate of solvated electrons by both substrates is at the diffusion limit. In fact the ketone (4 x 10^9) lies ~6x below the diffusion limit (2.5 x 10^10).

We cite Figure 1B while explicitly talking about prior work with super potent reductants, as diffusion-limited SET is a well-established concept for such systems. However, we can certainly see how this could be interpreted as claiming what we will do in our work from the figure on its own. To clarify this, we have adjusted the language provided under the curve from "both substrates reduced at kD" to "both substrates reduced *near* kD." In addition to avoiding misunderstanding of what we later show in the manuscript, this also highlights that the influence of redox potentials on SET selectivity is reduced due to *contributions* from diffusion before the absolute diffusion limit has been reached (which is relevant to the present study).

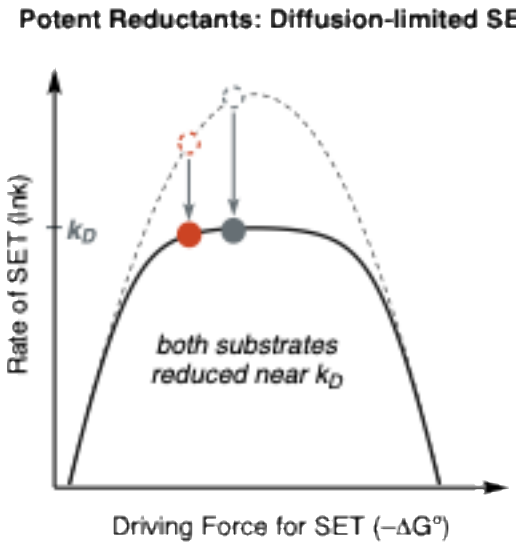


Figure 5A shows a barrier of ~10 kcal mol-1 for the BET from styrene radical anion. However, the barrier is ~8 kcal mol-1 for BET from ketyl radical, so the red arrow 'BET' should be added here also.

Our intention with the arrows is to communicate which reaction steps kinetically dominate but we definitely agree that BET is energetically accessible for both substrates and omission of that arrow entirely was confusing. In the revision, we labeled both BET from the ketyl and protonation of styrene radical anion with dashed grey arrows to explain what the steps are while still differentiating them from the faster competitive steps.

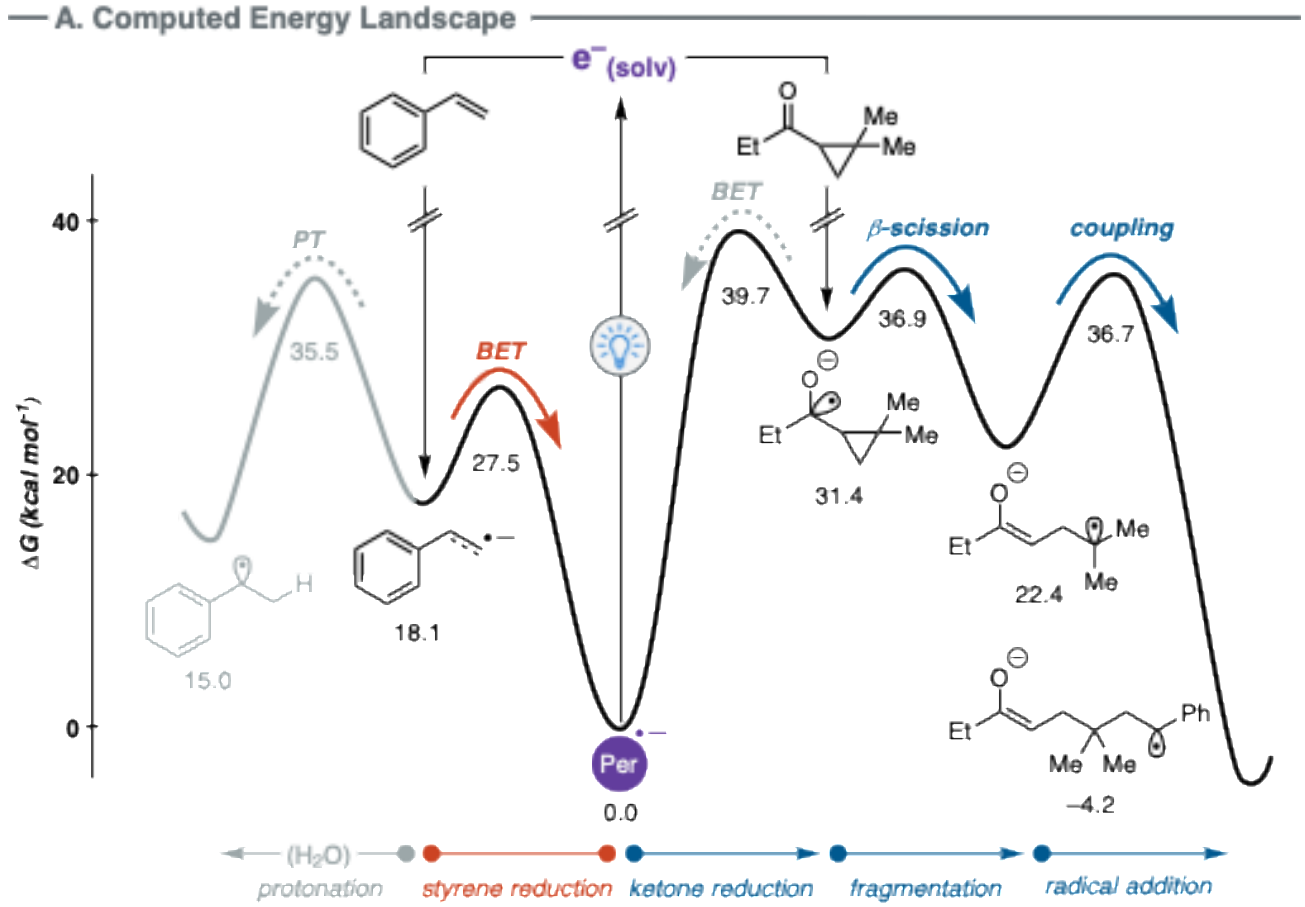


Fig.4 reaction scheme: Pery? ; Fig.4 title: 'c' 1.5 equiv w.r.t. ???

We have added clarification that under these conditions we employ limiting olefin and corrected the catalyst abbreviation.

Reference 30: Should be expanded to earlier reports important contributions including authors' own: Ref27; ACS Catal. 14, 2252 (2024); Reference 33: Should be expanded to earlier reports important contributions: König & team (2021); ACS Catal. 12, 6047 (2022)

We have added these references to the manuscript. Additionally, while not a radical anion, we also added a citation to a detailed study from Barham examining the role of pre-association in radical cation photocatalysis, which has the same lifetime problems as radical anion chemistry.

Pg5: 'marginally' is not the correct word for an order of magnitude difference.

We have revised the text to remove this ambiguous qualitative wording.

Role of TEABr and a speculated proton source for forming hydrogenated product 'A' should be mentioned somewhere.

TEABr is added to the anodic chamber of the divided cell to prevent passivation of the zinc anode by promoting the formation of $ZnBr_2$ (Li, Chemical Engineering Science 310 (2025) 121527). This point and the accompanying reference have been added to the supporting information.

SI file:
Although SI file is data rich, the authors have not taken good care checking the SI file for type-o and formatting. Some of these issues were somewhat surprising for a manuscript submitted to Nature: The word 'sorry' appears in the SI file (S21). 5 mutes should be 5 minutes (S21). Lazy formatting (S23, most of section 9, format of S3-S7 differs in font size). Beta Greek symbol missing (S29, S81). Missing word in a sentence (S26). Invalid compound/procedure number 'XX' (S89,93).
Table S5, put equivs of reductants, it implies stoichiometric. e.g. entry 3, terminal reductant is DIPEA not Fukuzumi acridinium.
Table S6-S10 titles: 'Stern-Volmer plot' is incorrect, refers exclusively to emission. Solvated electrons being quenched are ground state species.

We appreciate your careful proofreading and the revised SI has now been carefully edited.

Referee #3 (Remarks to the Author):

This work aims to establish a previously unrecognized paradigm in which highly potent reductants, specifically solvated electrons, evade the conventional thermodynamic selectivity criteria for substrate single-electron transfer (SET) based on redox potential differences. Instead, the authors propose that selectivity is determined after SET, governed by the competition between back electron transfer (BET) and annulation pathways. To validate this hypothesis, the authors employ a combination of femtosecond-TA (fsTA) and nanosecond-TA (nsTA) spectroscopy, cyclic voltammetry, Stern-Volmer analysis, and steady-state UV/Vis absorption studies coupled with computational chemistry within an electro-photochemical framework. Overall, this paper is novel while inspired by recent works on the generation of solvated electrons and closed shell Meisenheimer species and it has the potential to provide insight into photocatalyst excited state dynamics and how they influence reactions. This manuscript should be published after major outlined suggested below.

We appreciate the positive assessment of our work as well as the time taken to suggest specific revisions. The revised manuscript presents a substantially strengthened mechanistic discussion. Please find our responses point-by-point below.

A hypothesis of the work is that electrochemically generated Per•−, when excited at 570 nm, is incapable of substrate activation due to its reported picosecond-scale excited-state lifetime observed by fsTA. While the short lifetime is clearly demonstrated, the conclusion that substrate activation is precluded is not directly validated on lines 126-127, as quenching experiments with relevant substrates were not performed under these conditions. As such, it remains unclear whether ultrafast SET events could still occur with the pico-seconds lifetime or if pre-association might facilitate that. Authors should evaluate for the possibility of pre-association.

We agree we pre-maturely excluded the possibility of photoactive doublet states in the original submission. In our revised manuscript, we have directly evaluated whether the doublet excited states could promote ketone reduction themselves. Transient absorption spectroscopy on the ps timescale found no detectable quenching of perylene radical anion doublet features upon addition of ket-1. Moreover, we observe near-complete recovery of the radical anion ground-state bleach, an outcome inconsistent with efficient SET arising from pre-complexation of perylene radical anion with the ketone. To supplement this experimental analysis, we probed the formation of complexes between the radical anion photocatalyst and both substrates computationally. This analysis indicates that EDA complex formation is endergonic for both styrene (ΔG = +4.1 kcal/mol, $K_{eq} = 10^{-3}$) and the ketone (ΔG = +4.2 kcal/mol, $K_{eq} = 10^{-3}$). In a case where pre-association has been directly quantified for doublet radical anion reactivity, Ka was 185 M^{-1} (Wenger, Nat. Commun. 2024), orders of magnitude larger than the computed Keq for our system (10^{-3}). While EDA formation remains a plausible rationale for the photoactivity of other radical anions, these additional experiments indicate it is not responsible for the selectivity observed in our system. A section containing these data and discussion have been added to the supporting information.

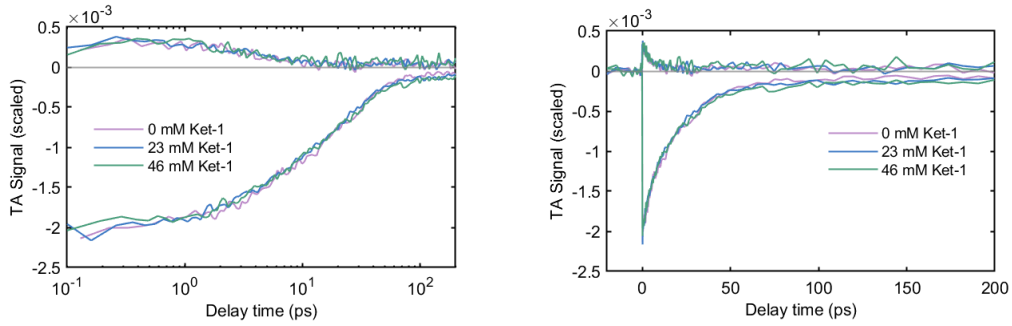


Figure S2.35. Excited state absorption decay and ground-state bleach recovery of Per•– monitored at 505 and 575 nm, respectively, following 520 nm excitation (500 nJ pulse energy). Addition of Ket-1 leads to small changes in the Per•– concentration; transient traces were therefore normalized by the peak Per•– absorption to enable direct comparison of the amplitudes of the decay traces. Data are plotted on a log scale (left) and linear scale (right)

Specific revisions: While these short lifetimes preclude simple bimolecular SET, we performed quenching experiments with **Ket-1** to exclude pre-association mechanisms that could nonetheless remain operative. These experiments revealed no evidence for direct doublet quenching.

Another central hypothesis is that diffusion-limited BET enables selective substrate reduction. The introduction ignores decades of photocatalysis research in which charge recombination is often faster than diffusion and occurs before the electron donor and acceptor escape the solvent shell. It is important that BET is slower with a solvated electron than with an excited state reductant.

Consistent with your point, we initially suspected that photogenerated solvated electrons were uniquely effective for these reactions since BET from the ketyl radical anion to neutral catalyst is a bimolecular process that cannot proceed faster than diffusion. However, when we removed the diffusion cap on BET from our modeling we observed only minimal changes in the predicted selectivity.

Your comment prompted us to recognize, however, that this is likely a consequence of the *specific reaction we selected as a model*. This insensitivity to faster-than-diffusion BET is presumably a consequence of the large differential in rates between styrene radical anion protonation and ketyl β-scission in the present reaction. When we re-evaluate our kinetic model using a slower rate constant for fragmentation, the impact of capping the rate of BET at diffusion becomes far more significant. We have added a discussion of these broader implications of our catalyst system, alongside contextualization with established faster-than-diffusion BET in photoredox catalysis, to the discussion of catalyst features. Additionally, we adjusted the language in the introduction to avoid confusion on this topic.

Specific revisions: Black text for context, red text for relevant change

The electrophotocatalytic conditions we have used exemplify this phenomenon: solvated electrons are photogenerated concomitantly with perylene, providing a mechanism for both SET and BET to proceed at the

diffusion limit. Indeed, this system is ideally suited to exploit diffusion-limited electron transfer processes because conventional excited state reductants often undergo in-cage BET,[54,55] which can occur faster than diffusion and imposes an additional bias against productive ketone reduction. While high BET rate constants are unambiguously required, our kinetic model indicates that capping BET at the diffusion limit is not a strict requirement for this reaction due to the rapid β-scission pathway but will likely facilitate implementation in processes involving slower downstream steps (for detailed discussion of BET rates, see SI Section 7).

SI section 7:

Impact of Diffusive BET

We questioned whether the photogeneration of solvated electrons is uniquely well suited to promote radical formation since BET is a bimolecular process that cannot proceed faster than the diffusion limit. In contrast, substrate reduction from an excited state can undergo BET via in-cage charge recombination that will not be limited by diffusion. To probe this hypothesis, we modified our kinetic model in figure 5b to mimic the effects of in-cage charge recombination by removing the diffusion limit on BET (Figure S2.27). However, this change only leads to minor differences in the photocatalyst driving forces needed to elicit the desired selectivity profile, indicating that the diffusive nature of BET is likely not a major origin of selectivity for the model annulation reaction. We suspect that this insensitivity to faster-than-diffusion BET is a consequence of the large differential in rates between styrene radical anion protonation and ketyl β-scission in the present reaction. When we re-evaluate our kinetic model using a slower rate constant for fragmentation, the impact of capping the rate of BET at diffusion becomes far more significant (Figure S2.28 and S2.29).

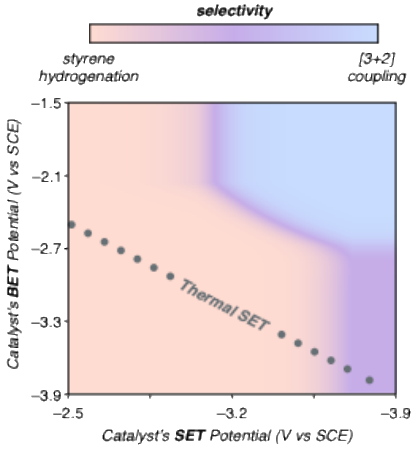


Figure 5c: Kinetic Selectivity model as a function of driving force for SET and BET.

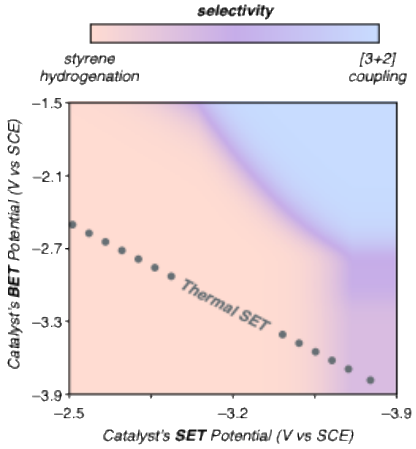


Figure S2.27: Reproduced from Figure 5c but with no diffusion cap on the rate of BET to mimic the impact of in-cage charge recombination

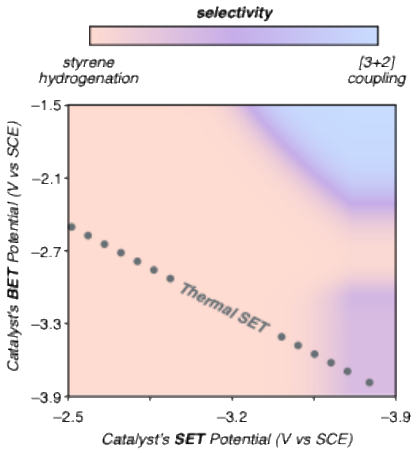


Figure S2.28: Reproduced from Figure 5c but with no diffusion cap on the rate of BET to mimic the impact of in-cage charge recombination and the rate of the radical formation is 100 times slower

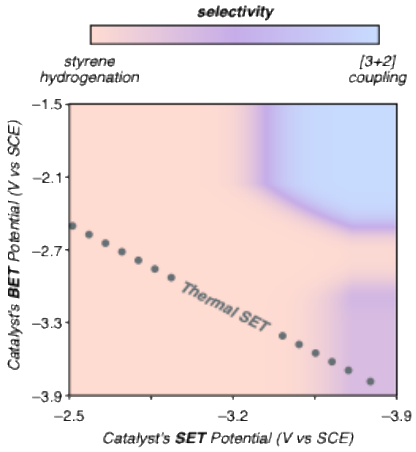


Figure S2.29: Reproduced from Figure 5c but the rate of the radical formation is 100 times slower

Upon shorter-wavelength excitation (390-460 nm), the formation of neutral Per is observed, which the authors attribute to photoionization and the generation of solvated electrons. This assignment is supported by NIR transient absorption measurements (1100-1600 nm) showing a characteristic absorption band centered near 1450 nm, consistent with solvated electrons in MeCN. Stern-Volmer analysis using two substrates further reveals nearly identical quenching rates approaching solvent diffusion limits, supporting the assertion that electron transfer occurs independently of substrate redox potentials. The authors further support their post-SET selectivity argument through nsTA studies using pyrene as a substrate, proposing that pyrene rapidly traps solvated electrons to form Pyr•−, followed by fast BET to regenerate Per•−. While transient features assigned to Pyr•− and Per-derived species are presented, the evidence for BET remains largely qualitative. A more direct and compelling validation would involve correlating the decay of Pyr•− with the simultaneous decay of Per based transients on identical timescales, thereby establishing kinetic coupling consistent with BET. Showing decay of the neutral Per would provide additional evidence of BET between Pyr•− and Per.

We agree that direct kinetic correlation between pyrene radical anion (**Pyr$^{\bullet-}$**) and neutral perylene (**Per**) decay transients would provide the most compelling evidence for back-electron transfer (BET). However, due to weaker probe intensity in this spectral window combined with strong overlapping absorption from perylene, these signals are noisier than the rest of the spectral window.

Despite these limitations, the data reveal that, alongside **Pyr$^{\bullet-}$** absorption, features attributable to neutral **Per** are also present and decay on comparable timescales. Moreover, global analysis of the full transient dataset using a two-exponential kinetic model provides additional support for kinetic coupling. The faster component ($\tau \approx 9$ ns) is dominated by the formation of **Pyr$^{\bullet-}$**, while the slower component ($\tau \approx 179$ ns) corresponds to the

concurrent decay of the **Pyr**$^{\bullet-}$ and **Per** absorption, accompanied by regeneration of **Per**$^{\bullet-}$. This correlated behavior is fully consistent with a BET process between **Pyr**$^{\bullet-}$ and **Per**.

We have added a discussion of these considerations to the supporting information and reproduced the relevant figures below:

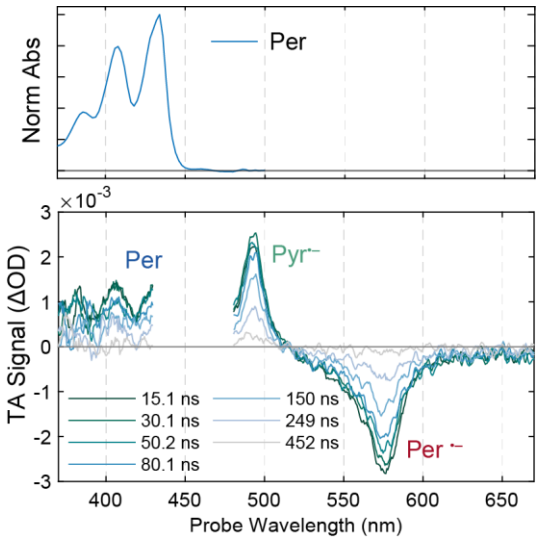


Figure S2.24 A: Spectral slices at selected delay times from the nanosecond transient absorption map in the visible region, obtained by exciting a solution of **Per**$^{\bullet-}$ in the presence of pyrene at 460 nm (1 µJ per pulse). (An absorption spectrum of neutral perylene is shown for comparison.)

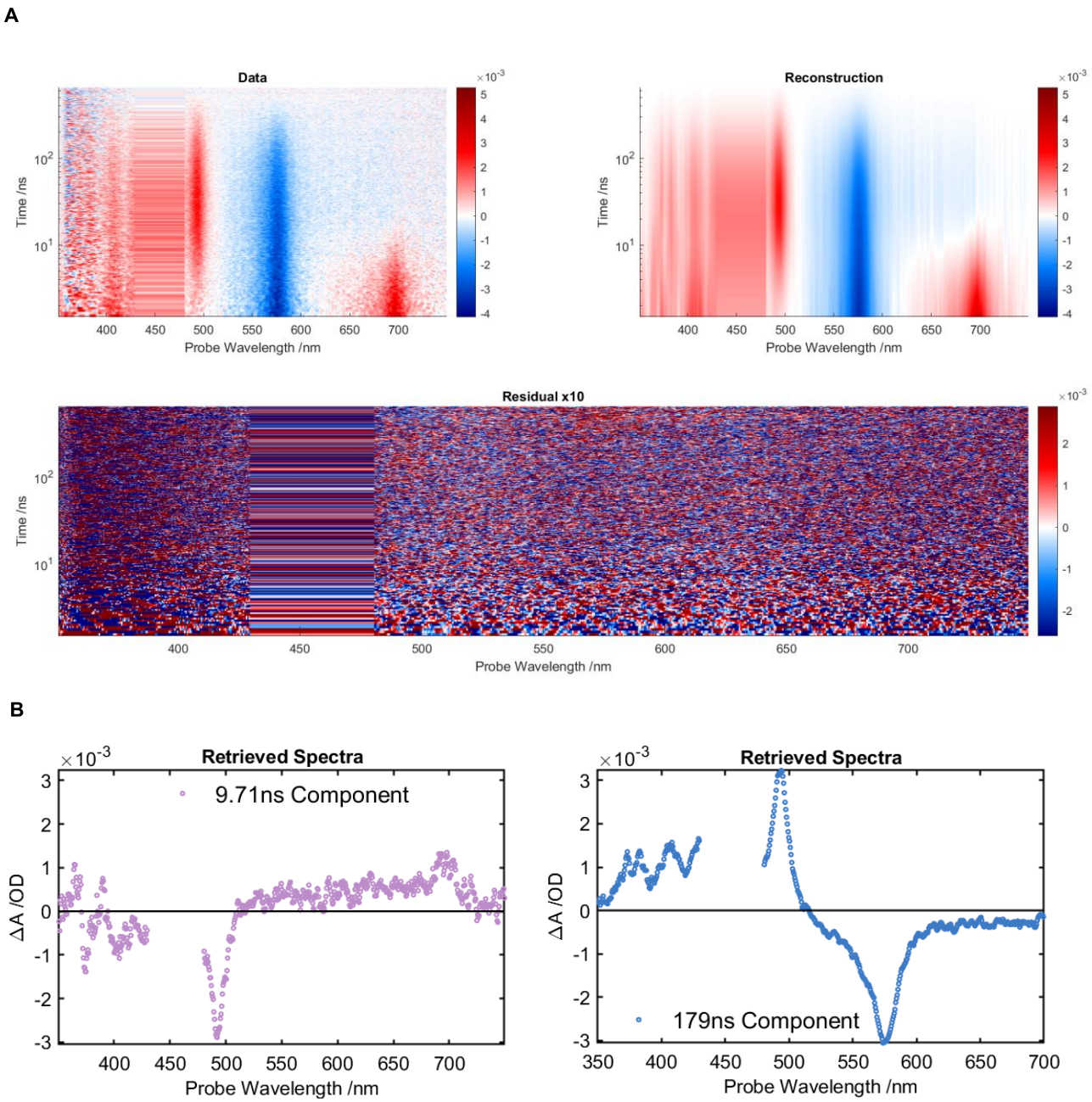


Figure S2.25. (A) The complete set of raw transient absorption data (slices out of this set are shown in the figure above) collected for Per•– in room temperature MeCN (left) after excitation with 460 nm (pulse energy of 1 µJ) along with a reconstructed global analysis model (right) comprised of a biexponential decay process. The residuals are shown in the bottom panel. (B) The decay associated spectra retrieved from global analysis mentioned above.

A paper that was cited in the article titled, 'P. Organic Super-Reducing Photocatalysts Generate Solvated Electrons via Two Consecutive Photon Induced Processes' by Paola Ceroni stated that recombination of the solvated electrons with the parent molecule is forbidden in the computation they carried out. To show that there is recombination of the solvated electron with the parent molecule, Per, juxtaposing the kinetic of the solvated electrons against the decay of the neutral Per and having similar lifetimes would go a long way to make the argument on the recombination compelling.

We agree with the reviewer that directly correlating the decay of solvated electrons with the recovery of neutral perylene provides a compelling test for recombination with the parent molecule. To make this relationship explicit, we have overlaid representative kinetic traces at 408 nm (neutral perylene) and 1457 nm (solvated electron). The close correspondence between these decay profiles demonstrates that the loss of solvated

electrons occurs on the same timescale as decay of neutral perylene, providing direct experimental evidence for recombination of the solvated electron with its parent chromophore.

We have added a discussion of these considerations to the supporting information and reproduced the relevant figure below:

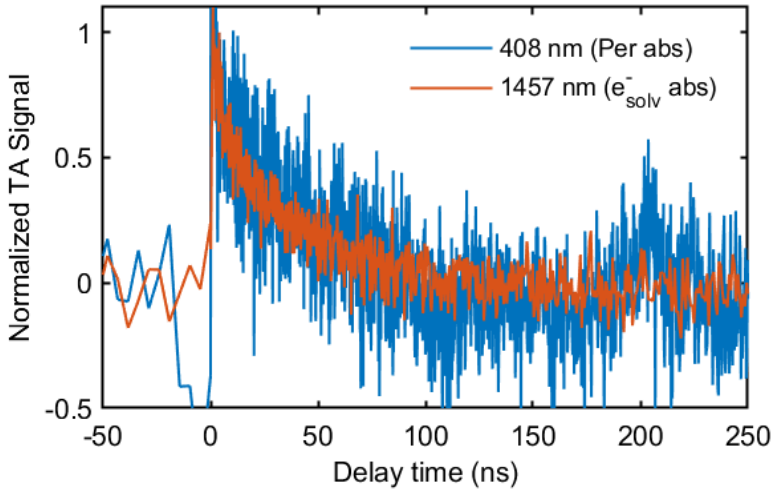


Figure S2.7b Normalized decay traces at selected wavelengths illustrating the concurrent decay of neutral perylene and the solvated electron following excitation at 460 nm (1 µJ pulse energy).

I realized the authors were unable to achieve a pure Per•− and some amount of neutral Per was present in the experiments at all times. When doing quenching studies, the authors subtracted the quenching rate by the neutral Per from the quenching by the reactants, which is a convoluted approach to obtain an electron transfer rate constant. Is it not possible to generate a pure Per•− instead of the mixture?

While it is feasible to generate samples containing predominantly $Per^{\bullet-}$ with minimal neutral perylene, we found that such conditions are not experimentally viable under pulsed laser irradiation. In our initial attempts to work with highly enriched $Per^{\bullet-}$ samples, photoionization produced solvated electrons that were rapidly scavenged by trace impurity species, leading to irreversible loss of the perylene radical anion and poor sample stability.

Maintaining a controlled background concentration of neutral perylene renders the system reversible and experimentally stable, allowing reproducible transient absorption measurements to be performed. Under these conditions, recombination of the solvated electron with neutral perylene serves as a stabilizing pathway that preserves the overall redox balance of the system during repeated laser excitation.

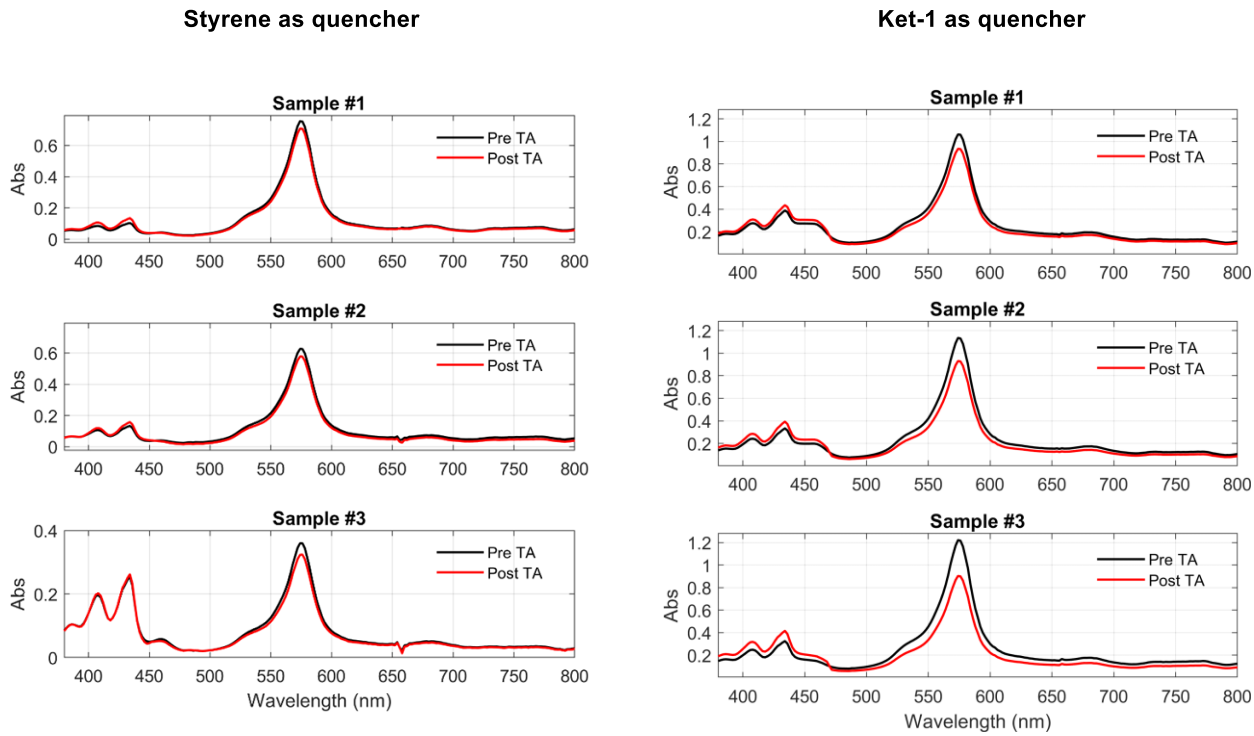
Importantly, the presence of neutral perylene does not preclude quantitative analysis of electron-transfer kinetics. Because the rate constant for electron transfer to neutral perylene is independently determined, its contribution to the overall quenching of the solvated electron can be explicitly accounted for and subtracted. This treatment enables reliable extraction of electron-transfer rate constants to the reactants and avoids ambiguities that would otherwise arise from sample degradation in nominally “pure” $Per^{\bullet-}$ systems.

Thus, the mixed Per/$Per^{\bullet-}$ system represents a deliberate experimental design choice that ensures sample stability while still permitting rigorous and quantitative kinetic analysis.

The UV/Vis for the sample after the TA was not re-taken to confirm that degradation is not happening. The concentration of neutral Per is high at the onset of the TA experiment and changes as a function of time with ketone reduction. A UV-vis spectrum before and after TA is important to show that the electron transfer is cyclical and the relative concentrations of reduced and neutral Per does not change during the TA experiment.

We have recorded UV–visible absorption spectra before and after the transient absorption experiments. Representative spectra collected in the presence of styrene and cyclopropyl ketone (Ket-1) are shown below. In both cases, only small changes in the perylene absorption profile are observed, indicating that significant catalyst degradation does not occur during the TA measurements. The larger change observed with Ket-1 is expected, as electron transfer to the cyclopropyl ketone leads to substrate fragmentation and therefore does not constitute a fully cyclical process.

These data validate that the TA measurements probe chemically relevant electron-transfer dynamics rather than catalyst decomposition. These studies have been added to the SI.



UV–visible absorption spectra recorded before and after nsTA experiments, confirming catalyst stability during measurements used to quantify electron-transfer rates to substrates. These data have been added to the SI.

It needs to be clearly stated that recombination is not necessarily between the solvated electron and neutral Per from recently oxidized Per•− because the starting [Per] is high. Further, how does high [Per] affect the BET rate and competition with annulation?

It is true that in our proposed mechanism the solvated electron undergoes cage escape, making it likely that recapture can occur with a different neutral perylene molecule. We have edited the main text to clarify this observation.

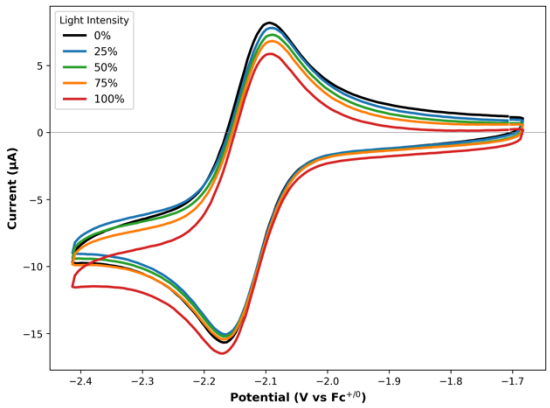
Our transient absorption data indicate that recapture of the solvated electrons by neutral perylene is a minor pathway under catalytically relevant conditions. Recombination with neutral perylene occurs at a rate of 8×10^{10} M^{-1} s^{-1}, whereas reduction of styrene and the ketone occur at rates of 3×10^{10} M^{-1} s^{-1} and 4×10^{9} M^{-1} s^{-1}, respectively. After adjusting for concentration differences under catalytically relevant conditions (80 mM for the substrates vs at most 6 mM perylene), substrate reduction becomes the kinetically dominant fate of solvated electrons ($k_{rel,}$ (styrene) = 50; $k_{rel,}$ (Ket-1) = 7). Considering the multistep BET sequence that reoxidizes ketyl radical and inhibits annulation, the low concentration of neutral Per again is relevant. Since styrene is present in much higher concentration than perylene, our calculations indicate styrene mediates BET from the ketyl to Per. Of note, each of these calculations assume all of the catalyst is in its neutral form, while in reality some fraction of perylene is present as the radical anion.

We added a more detailed discussion of BET pathways, which mirrors what was stated above, to the supporting information Section 6.

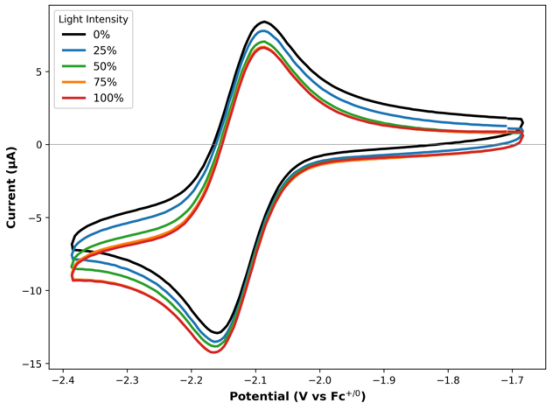
Cyclic voltammetry was used to argue that BET dominates in the presence of styrene, as evidenced by reversible voltammograms upon substrate addition, whereas the authors state that ketone substrates induce increased cathodic currents and diminished anodic return, consistent with catalytic turnover. However, the ia/ic ratios are nearly identical in dark and light with ketone. This is not catalytic current (see Nicholson and Shain Analytical Chemistry, 1964, 36, 707-723). The lack of catalytic current may result from low excited state concentration at the electrode surface.

Thank you for catching this, we agree that our initial CV study was not sufficiently detailed to conclusively support our interpretation. Previously, our experimentation was limited by technical impediments to conducting quantitatively accurate CVs upon irradiation. However, we drew inspiration from a recent report uploaded to ChemRxiv (https://chemrxiv.org/doi/full/10.26434/chemrxiv-2025-7h38h-v2) that mitigated these challenges and allowed a far more complete CV analysis, including quantitative analysis of ia/ic ratios under varied conditions.

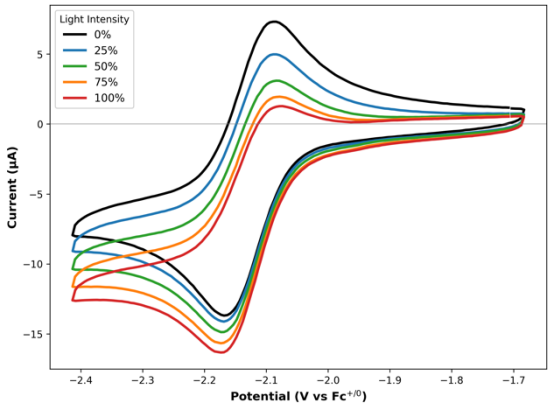
We have now observed unambiguous changes to the peak current ratios as a response to increasing the cyclopropyl ketone concentrations and systematically varying the light intensities. These revised data show that, upon irradiation, the ratio of anodic to cathodic current does decrease upon addition of the ketone while remaining constant upon the addition of styrene. We have added these data to the SI and reproduced the relevant section here for convenience. The full data set has also been included in our response to reviewer 2's related request for a more extensive CV analysis, which shows similar trends at various scan rates. Moreover, an acyclic aliphatic ketone lacking the cyclopropane (1-cyclopentylethan-1-one) shows no change in i_a/i_c upon irradiation despite identical driving force for BET. This confirms that the catalytic current observed with the cyclopropyl ketone arises from irreversible fragmentation, not from differences in BET kinetics (see response to Reviewer 2, Point 4 and Point 13 for full analysis).



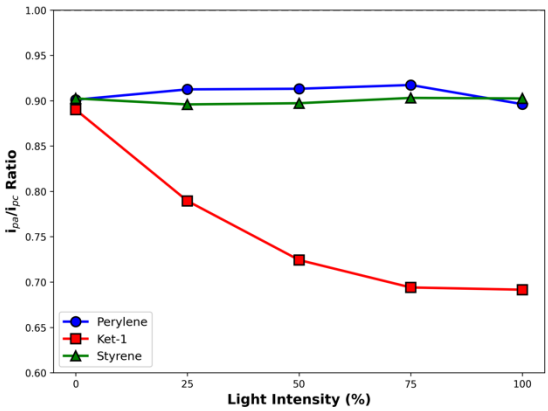
CV of **Per** (1 mM) in DMF containing 0.1 M $TEAPF_6$ at 50 mV s^{-1} at various light intensities with a 390 nm Kessil lamp.



CV of **Per** (1 mM) in DMF containing 0.1 M $TEAPF_6$ and 0.1 M styrene at 50 mV s^{-1} at various light intensities with a 390 nm Kessil lamp



CV of **Per** (1 mM) in DMF containing 0.1 M $TEAPF_6$ and 0.1 M **Ket-1** at 50 mV s^{-1} at various light intensities with a 390 nm Kessil lamp



Impact of light intensity with a 390 Kessil lamp on the ratio of peak anodic to peak cathodic current for a solution of 1 mM perylene (blue dots), 1mM perylene with 0.1 M Ket-1 (red squares) and 1mM perylene with 0.1 M styrene (green triangles) at 50 mV/s. Lines are drawn to guide the eyes.

The kinetics for ketone bond cleavage and protonation of the reduced alkene are important for the selectivity argument regarding kinetic competition with BET. Although the manuscript acknowledges the importance of evaluating these kinetic parameters with a section titled "Kinetic Model for Emergent Selectivity," only thermodynamic properties are discussed in that section. Can the calculations provide an approximation of the relevant rate constants, particularly scission and protonation?

In order to derive our kinetic model shown in Figure 5b, we used the computed rates of ketone bond cleavage ($\Delta G^{\ddagger}$ = 5.5 kcal/mol) as well as protonation of styrene radical anion ($\Delta G^{\ddagger}$ = 9.4 kcal/mol). We have now explicitly stated that these calculations were used to derive the rate constants used in the model.

The thermal control reaction using Na⁰ results in extensive ketone reduction but no formation of product B. While this observation is consistent with the authors' assertion that SET alone is insufficient for productive chemistry, the manuscript does not adequately address why thermally generated ketone radical anions fail to access the annulation pathway observed under electro-photocatalytic conditions. A more explicit discussion of this discrepancy would strengthen the mechanistic framework and clarify the role of post-SET dynamics in influencing selectivity.

By using a potent thermal reductant such as sodium metal, SET can be rendered indiscriminate and therefore unlock activation of the ketone. However, this alone is insufficient to promote the desired [3+2] reaction for several reasons. Unfortunately, we were not able to identify specific byproducts under these conditions. The ketyl radical likely does form and fragment under these conditions, but productive annulation is precluded by several downstream problems:

1. There is no mechanism to protect styrene from decomposition. Under a regime where both substrates are reduced, SET to styrene will result in decomposition unless there is a mechanism to reoxidize styrene radical anion. By leveraging a photoreductant, BET is rendered fast and favorable. However, with a thermal reductant BET is highly endergonic and thus no recovery of styrene is expected.
2. The accumulation of styrene radical anion can lead to additional side reactions. Styrene radical anion is both basic and nucleophilic, which likely contributes to side reactions with the ketone in the absence of proton source. We anticipate this side reactivity contributes to the poor mass balance of the reaction.
3. Sodium can drive the pernicious overreduction of carbon radicals. For example, we observe up to 10% of the linear ketone byproduct derived from ketone reduction followed by premature reduction of the nascent radical. Thus, even when the ketone is reduced, we anticipate intermediates on-path to product can be intercepted.

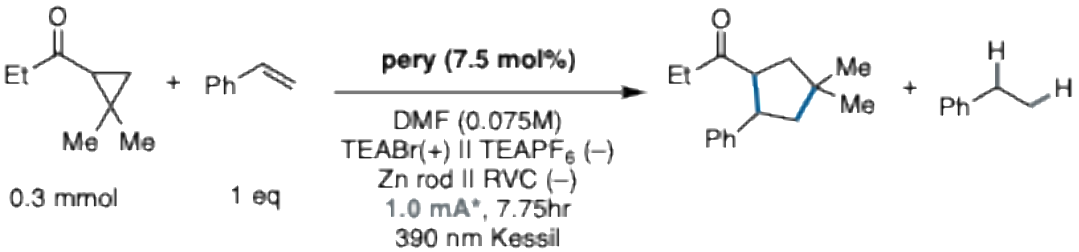
We have added a discussion mirroring the above points to the supporting information.

A constant current of 1mA was applied during electro-photocatalytic reactions. Please provide evidence that the voltage is not shifting to more negative values, thereby resulting in competing direct electrolysis of the substrates.

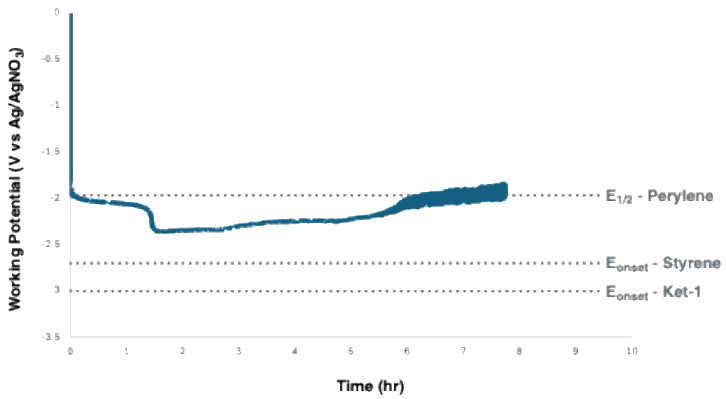
While we typically employ constant current for electrosynthetic methodology because it facilitates reaction screening, it certainly does allow the working potential to drift to more reducing values and creates precisely the mechanistic ambiguity identified by the reviewer. Monitoring the working potential under our optimal constant current electrolysis illustrates that the working potential does shift to more reducing potentials during the course of electrolysis.

Accordingly, we next evaluated potential contributions from direct electrolysis. Since direct electrolysis of either substrate requires more negative potentials than those accessed during electrophotocatalysis, the observed [3+2] annulation is unlikely to arise from direct electrolysis as it would require significantly uphill cathodic SET. Moreover, the onset for cathodic styrene reduction occurs ~300 mV positive of ketone reduction, suggesting that any direct electrolysis contribution would selectively reduce the olefin rather than drive product formation via ketone reduction. Consistent with this supposition, performing the reaction under constant current in the absence of perylene or irradiation results in exclusive styrene hydrogenation with minimal ketone conversion (93% RSM), confirming this prediction. These data indicate that contributions from direct electrolysis cannot account for the observed [3+2] annulation reactivity under electrophotocatalytic conditions. Of note, these data do suggest other catalyst redox states could also promote the observed reactivity (e.g., perylene dianion). While such possibilities can never be fully excluded, we performed the reaction under constant working potential at the half-wave potential of perylene to verify that the catalytic system that was the subject of our mechanistic studies is appropriate. Under these conditions, perylene effectively promotes the desired reaction (49% yield) with minimal styrene hydrogenation (2%). These data unambiguously illustrate that perylene anion is competent to unlock the selective [3+2] chemistry and confirm that it is an appropriate subject for our detailed mechanistic study, even if the optimal constant current conditions result in a more complex scenario.

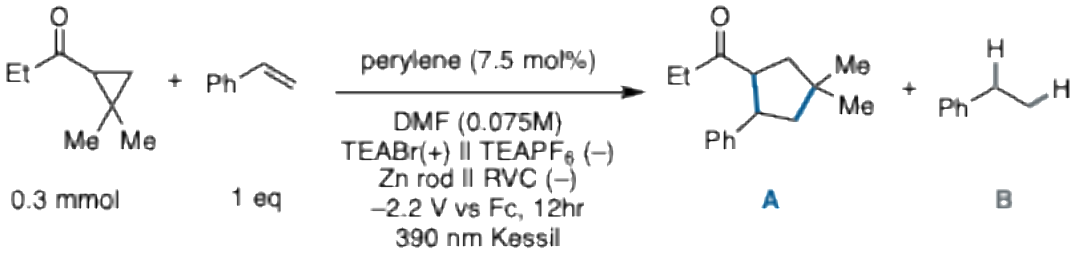
We have added a discussion of these considerations to the supporting information and reproduced the relevant figures below:



**reaction performed on a potentiostat to monitor the working potential*



Electrolysis Trace 1: working potential of the cathode measured during the course of constant current electrolysis. Superimposed lines represent the half-wave potential for perylene and onset potentials for styrene and Ket-1 measured by cyclic voltammetry.



Entry	Variation	ketone RSM	Styrene RSM	A	B
1	none	10	28	49	2
2	dark	92	93	0	0
3	no styrene	37	-	-	-
4	no styrene, dark	96	-	-	-
5	no ketone	-	76	-	16
6	no ketone, dark	-	95	-	4

Minor typo noted: "Rapid Substrate Reduciton" on line 169.
Rate constants for annulation

We thank the reviewer for their thorough read and have checked all submitted documents for typos and errors.

Summary

Overall, we sincerely appreciate the constructive feedback from the initial submission from all three reviewers. We believe that these comments have helped us substantially improve the manuscript, both in terms of the presentation, and the supporting data. Through this revision, we have directly addressed each of the reviewers' concerns. We hope the referees are as excited about our revised manuscript as we are.

Prof. Zachary K. Wickens
Associate Professor, Department of Chemistry
1101 University Ave, Madison, WI 53706
608-262-4906 & E-mail: wickens@wisc.edu

May 11, 2026

[redacted]

We believe this revised article addresses the reviewers' concerns and that it is appropriate for publication in *Nature*. In the point-by-point response, reviewer comments are denoted with blue text, our responses are denoted with black text, and specific changes made to the manuscript or supporting information are denoted with red text.

Response to referee #2

We are glad to hear that you agreed with us that the changes we to main text and supporting information have resulted in a substantially improved manuscript. And we understand how the aspect of your initial review that we deemed out of the scope of our manuscript (additional reaction types) remains a concern for you. However, similarly, we maintain our position that these are beyond the scope of our study and that the sharp mechanistic focus is appropriate for this venue. Rather than reiterate our perspective, we will focus our response on the mechanistic concerns raised in this second round of review. Your mechanistic questions to our revision raised concerns that are unambiguously within the scope of our study. While we may ultimately disagree about the precise venue to report these findings, we hope you will agree that our additional experiments strengthen the mechanistic conclusions of our report and exclude the concerns you raised.

Specific responses:
1) In responding to the possibility of a chain mechanism, the authors have computed Marcus barriers for SET (Figure S2.30) between various combinations to substantiate that even in the operation of a chain the general concept holds at the point of re-initiation. Authors need to confirm if these calculations were done using proper DFT or through approximations (DFAs). Specifically, whether any interaction exists between the ketyl radical and the C=O pi star that could direct selectivity but may habe been missed.

The possibility that stabilizing interactions promote chain propagation is an intriguing new idea. In our revised manuscript, we present additional computational experiments that directly probe this hypothesis. We computationally investigated potential ketyl radical anion → C=O π* interactions between the product•– and Ket-1. We found that these donor–acceptor complexes are thermodynamically disfavored by 7.8 kcal/mol, and orbital overlap is destabilizing. These results are inconsistent with a radical chain BET pathway driven by donor-acceptor orbital interactions. We have added a discussion of these points to the supporting information in our discussion of chain mechanisms and reproduced the relevant section below.

More broadly, all calculations were performed using Kohn–Sham density functional theory (DFT) using the M06-2X and ωB97X-D functionals, as described in the Computational Details section of the supporting information. We note that, by construction, all practical implementations of DFT necessarily rely on density functional approximations (DFAs) for the exchange–correlation functional as there is no exact functional available for practical use (Parr, R. G.; Yang, W. Density-Functional Theory of Atoms and Molecules; Oxford University Press: New York, 1989; Koch, W.; Holthausen, M. C. A Chemist's Guide to Density Functional Theory, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2001.) Accordingly, the calculations reported here correspond to a standard and universally accepted DFT implementation protocol, and no lower-level or semiempirical approximations were employed. The chosen DFAs were selected based on established benchmarks for thermodynamics and activation barriers for radical processes, and the key results are consistent across commonly used and well-validated functionals.

Additions to the supporting information:

Complexation of product radical anion with cyclopropyl ketone

To further explore an alternative radical chain mechanism involving SET from $\mathbf{E}_{\mathbf{ket}}$ to the reactant ketone $\mathbf{A}_{\mathbf{ket}}$, we investigated the possibility of donor–acceptor complex formation between these species (**Figure S3.13**)

Specifically, we probed whether the HOMO or SOMO of the donor ketyl radical anion could interact with the C=O π* orbital of the acceptor ketone, thereby facilitating SET. Three distinct modes of donor–acceptor complexation were considered:

Type 1: interaction between the oxygen lone pair of the ketyl radical anion and the acceptor C=O π* orbital;

Type 2: interaction between the carbon-centered SOMO of the ketyl radical with the acceptor C=O π* orbital;

Type 3: complexes lacking specific orbital interactions, stabilized instead by dispersive interactions.

Association of the donor $\mathbf{E}_{\mathbf{ket}}$ with the acceptor $\mathbf{A}_{\mathbf{ket}}$ is strongly disfavoured, with complex formation being endergonic by 7.8 kcal mol^{-1}.Type 1 complexes were found to be unstable, with optimization leading away from the intended orbital overlap toward Type 3 geometries, likely to relieve steric strain. While Type 2 complexes, which exhibit SOMO–π* interaction, could be optimized, they are less stable than the corresponding Type 3 complexes (by 6.3 kcal mol^{-1}). Type 3 complexes, stabilized by dispersive interactions, are the most stable mode of association, as they avoid the destabilizing steric interactions associated with orbital overlap.

Overall, we see that donor–acceptor complexation between $\mathbf{E}_{\mathbf{ket}}$ and $\mathbf{A}_{\mathbf{ket}}$ is not only thermodynamically unfavorable, but that the very orbital interactions that could facilitate SET are intrinsically destabilizing. These results are inconsistent a radical chain SET pathway driven by donor-acceptor orbital interactions.

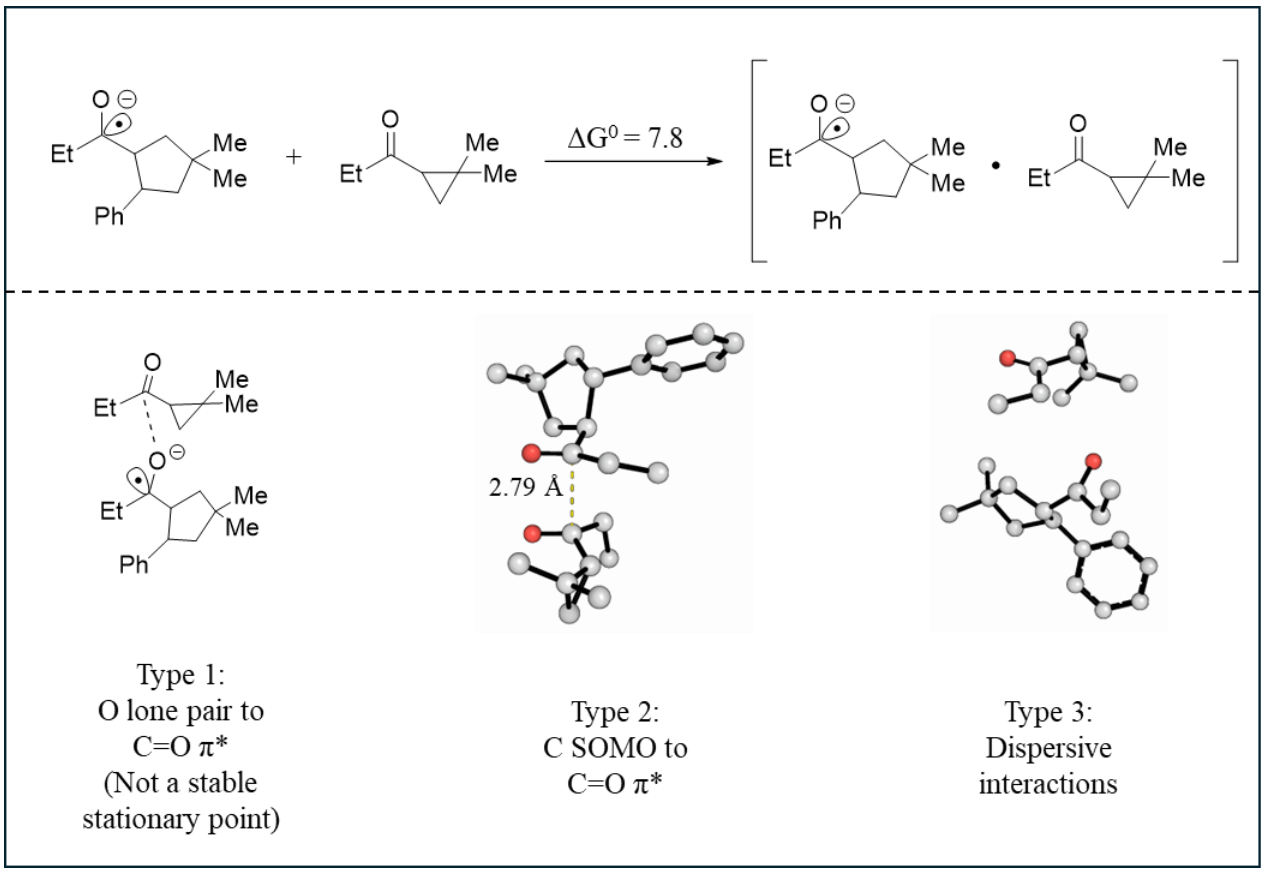


Figure S3.13: (Top) Donor-acceptor complex formation between $\mathbf{A_{ket}}$ and $\mathbf{E_{ket}}$ and the free energy of association (in kcal/mol). (Bottom) Different modes of complexation examined.

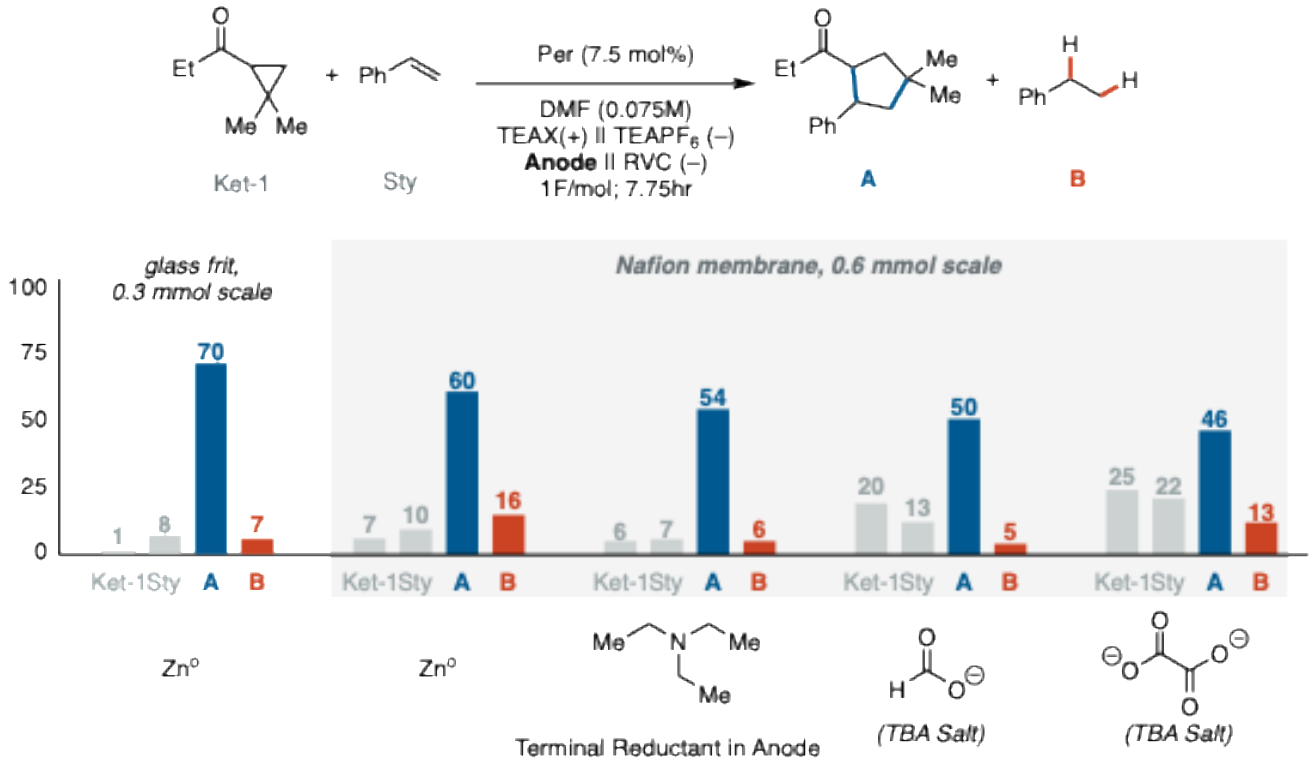
2) Authors raised the generation of ZnBr2, which can be seen visually in copious amounts in the electrochemical cell on Figure 1.3 of SI, even particles in the cathodic chamber can be seen between the stirrer and carbon cathode (which seem not to be gas bubbles from HER as it is coming up from the stirrer even not just around the cathode). It should be noted that these cells are not truly divided, the porosity reflects a pore size diameter of hundreds of microns allowing ZnBr2 to pass through to the cathodic chamber. The Lewis acidity of M(II) salts to activate carbonyl groups including aliphatic carbonyls to reduction is well known (Science 362, 225 (2018); J. Am. Chem. Soc. 43, 651 (1921); reaction rate accelerated adding zinc chloride). It is known to accelerate migratory insertion of Ni complex carbon moiteies to aliphatic carbonyls: e.g. J. Am. Chem. Soc. 141, 1823 (2019) (Scheme 4 therein and the proposed mechanism). There seems to be a severe risk that all the unconventional selectivity behaviours may not be down to the proposed promiscuous reduction and selective BET and be simply down to in-situ generation of a M(II) Lewis acid, that migrates over to the cathodic chamber, lower redox potential of the carbonyl into a normal redox potential regime, probably in a controlled chain mechanism? There could be other reasons why a chain would continue to engage the ketone vs the styrene upon re-initiation, e.g. if metal(II) salts are around. E.g. well known Pinacol coupling involves such an interaction and similar interaction modes could direct ET to the ketone. This concern over presence of M(II) salts in cathodic chamber is a critical concern to address. Authors should examine the contents of the 'cathodic chamber' by ICP-OES for presence of Zn before and then after the reaction to see if a substantial increase. Authors should run the reaction with a proper membrane separator eg Nafion or Celgard, to completely preventing Zn from migrating. What is by CV the redox potential of the ketone in presence of ZnBr2? In the case of the consecutive photoinduced ET reactions the radical cation of the amine or a protonated amine byproduct can act as an acid activator of the carbonyl: J. Org. Chem. 81, 6959 (2016). Although authors show conPET did not work.

We appreciate this careful observation and agree that glass frits, given their pore sizes, allow for some amount of mixing of the anodic and cathodic chambers. Therefore, the possibility that zinc(II) salts act as in situ Lewis acid activators of the carbonyl, lowering its effective reduction potential, is a reasonable possibility and excluding it is clearly within scope of this manuscript.

The reviewer's suggestion of conducting the reaction with a selective membrane seems like the most unambiguous approach to exclude Zn salts from the reaction system. Accordingly, we replaced the glass frit with a Nafion membrane (proton selective) and re-evaluated the reaction. Without any re-optimization for these modified conditions (e.g., changes to resistance, electrode distance, scale, etc.), this change in reaction setup had only a minimal impact on reaction efficiency, selectively promoting the model annulation with comparable performance. While Nafion should preclude Zn migration, we also replaced the zinc anode with a reticulated vitreous carbon (RVC) anode paired with various sacrificial reductants in the anodic chamber. Using triethylamine, tetrabutylammonium formate, or tetrabutylammonium oxalate as the terminal reductant each afforded the desired [3+2] annulation product selectively over hydrogenated styrene. Taken together, these results confirm that a zinc anode is not required to observe selective ketone activation. The formate and oxalate entries are particularly informative in this regard, as the anodic oxidation of these substrates produces carbon dioxide as the terminal oxidant byproduct, entirely precludes the in situ generation of any sort of Lewis acidic species that could migrate to the cathodic chamber and influence reaction selectivity. Since these experiments were all diagnostic in nature, we did not reoptimize the experimental conditions to render them more efficient as we deemed this out of scope. Overall, these data conclusively exclude Lewis acids inducing the observed selectivity and we determined further investigation to be out of scope since Zn was clearly not essential to selectivity.

Of note, these data are consistent with the conclusions drawn in the scope discussion that suggest Lewis acids are likely not responsible for selective ketone activation. Several of the olefin coupling partners incorporated in the scope have carbonyls that would act as Lewis bases and preclude selective activation of the ketone (e.g., acrylamide and acrylate substrates). Nonetheless, these olefins can be successfully employed as coupling partners.

The data from these experiments are reproduced below:



Changes to the supporting information: A discussion of the data ruling out contributions from zinc salts on selectivity, which mirrors what is described above, has been added to the SI to accompany the figure displayed above.

3) In authors response re-simulating the selectivity with the calculated Marcus barriers, then vs arbitrarily assuming same barrier, for both they claim no difference but there is a difference in S2.32 vs S2.31. The selectivity starts to blurr in bottom right quadrant. It is possible that all it takes is some adventitions Zn(II) salts to bring the barrier below that of the styrene reduction and disrupt completely the selectivity profile, meaning

point (2) is of utmost importance. This is another reason why the concept should be demonstrated for another hard-to-reduce vs easy-to-reduce couple, where the risk of traditional activations modes of carbonyls is completely eliminated (eg. ArF vs ArBr/Cl)

We agree that the lower right quadrant (which corresponds to strong chemical reductants) shifts from being slightly selective for styrene hydrogenation when using to computed rates for propagation to unselective when the propagation rate is intentionally overestimated. We have modified the discussion of these changes in the supporting information and have included these changes below. As discussed above in our point 2 response, we have experimentally excluded Zn as the origin of the observed selectivity.

Changes to the supporting information *(changed text in red, black for context):*

Stress-testing the model. Even if the propagation step were significantly faster than the calculations suggest, persistent reinitiation would still be required to promote coupling. To evaluate this, the barrier for SET from product•– to cyclopropyl ketone was arbitrarily set equal to that of SET to styrene — a 9.7 kcal/mol decrease relative to the calculated value, representing a vast overestimate of the likely propagation rate (Figure S2.32). When that change is made, without modifying the influence of substrate redox potential on any other step, the predicted kinetic selectivity profile remains similar. However, the lower right quadrant – which is the domain of a strong chemical reductant with little to no driving force for BET – becomes entirely unselective. Here there is no kinetic preference for propagation leading to product, versus termination leading to hydrogenation.

4) The use of Melchiorre thiolate catalyst is intriguing, but the conditions are biased as there is no proton source(?) so the formation of the hydrogenated styrene is inherently chemically not possible. This is a corollary to the main electrophotocatalytical experiments that need to be confirmed not to be due to M(II) carbonyl activation as in point (2).

Our intention for including the Melchiorre thiolate conditions is mechanistic in nature. While our study predominantly focuses on polycyclic aromatic hydrocarbon electrophotocatalysts, an important feature of our mechanistic model is that this new selectivity mode could, in principle, emerge from any photoreductant sufficiently potent to indiscriminately reduce both substrates while retaining fast and favorable back electron transfer. The ability of the thiolate photocatalyst to promote the model annulation reaction is included to show that overturing redox potential control is *feasible* with other potent photoreductants. The goal of this experiment is not to compare the performance of various photoreductants, and therefore we view extensive optimization of these conditions as out-of-scope. Rather, we view the performance of the previously reported conditions as the most appropriate data to include precisely because those conditions had been optimized for a different reaction and yet nonetheless translate to the model annulation that is the subject of our study.

Additionally, we note that lack of a direct proton source does not preclude styrene hydrogenation nor does precluding hydrogenation guarantee productive annulation. First, these reactions still possess numerous proton sources (e.g., solvent, the ketone) or hydrogen atom donors (e.g., formate). Of note, the thiyl radical is also turned over by formate, presumably via HAT that produces a thiol that could act as either a H-atom or proton donor as well. Next, even if hydrogenation could be fully prevented, styrene would become an extremely potent inhibitor for the desired annulation if it's rate of reduction were not diffusion-limited reduction. If styrene is selectively reduced over the ketone by the magnitude predicted by redox potentials, then even if styrene radical anion is fully protected by back electron transfer due to low rates of hydrogenation, the ketyl radical is still never formed and thus annulation product is not obtained.

We have revised the text contextualizing the studies of varied reaction conditions, which clarifies that none of these experiments were intended as "comparisons" and also included a brief discussion of how intentionally excluding explicit proton sources is insufficient to promote the desired reaction on its own. Given that revised framing, we hope that how the thiolate catalyst fits into our study is now clearer.

Changes to the main text *(changed text in red, black for context):*

As a specific model reaction, we targeted the annulation of styrene and aliphatic ketone Ket-1, a pair of substrates that are mismatched for the desired reaction by ~600 mV (K_{eq} = 10^{10} favoring undesired styrene reduction at 25 °C). First, we performed a series of experiments to validate that, despite fast and favorable cyclopropane ring openings, the difference in redox potentials translates into a kinetic bias against the annulation. Calculated Marcus barriers with an array of representative thermal reductants predict that SET to styrene is many orders of magnitude faster than ketone reduction (see Fig. S3.7 and accompanying text for details). Both direct and mediated electrolysis – representative of outer sphere SET reductants – were found to

exclusively promote styrene hydrogenation without any productive annulation (Fig. 2, left; see Table S1.4 for full dataset). These data illustrate that, even under conditions that suppress the rate of styrene hydrogenation (e.g., by limiting access to proton equivalents), this model reaction cannot be simply driven by fast cyclopropane ring opening via a Curtin–Hammett kinetic scenario.[28,29] Finally, we probed whether indiscriminate substrate reduction alone, which would provide access to the ketyl radical, could be sufficient to drive selective annulation via a chain mechanism (for detailed discussion of the potential role of chain mechanisms, see SI Section 8).[30] We found that potent thermal reductants convert both coupling partners but fail to deliver cyclized product (See Table S1.5 and accompanying text for details).[31]

Having established that the annulation of Ket-1 and styrene represents a case where conventional reductants conform to redox potential control, we then evaluated whether super-potent photoreductants could overturn the profound thermodynamic bias presented by this model reaction. We recently found that polycyclic aromatic hydrocarbons (PAHs) are remarkably potent photocatalytic reductants following electrochemical activation and even provided unexplained changes in selectivity upon irradiation.[32] However, this prior context was mechanistically ambiguous, as reduction of either starting material could lead to product formation.[33,34] To evaluate whether these photoreductants were sufficiently potent to obviate redox potentials, we systematically evaluated a range of PAHs for activity in the model cycloaddition. These investigations revealed that, under electrophotocatalytic conditions, diverse PAHs promote the desired reaction with dramatically suppressed hydrogenation (see Table S1.1 for full optimization data). We also tested several of the recently reported potent photoreductant systems (see Table S1.5 for details). These studies revealed that Melchiorre's thiolate photocatalyst,[35] a super-potent single-photon reductant ($^*E_{1/2}$ = –3.4 V), promotes the [3+2] annulation, albeit in diminished yield. Intriguingly, established potent consecutive photoinduced electron transfer (conPET) systems were found to be ineffective despite, in principle, offering comparably potent reduction potentials.[36] Rather than illustrating specific catalyst limitations, however, we suspect this observation reflects the problematic byproducts derived from the amines used as reductants (see SI Section 1 for details).[37] Overall, these data are consistent with our proposal that redox-potential-independent selectivity can emerge from diverse super-potent photoreductants.

Referee #3 (Remarks to the Author):

The authors responded to questions thoughtfully and with appropriate data. The revised manuscript provides a more clear mechanistic description. A few minor concerns/suggestions remain and are listed below.

We thank the reviewer for their detailed mechanistic comments, which helped us significantly improve the manuscript in the first round of review. We have addressed each of the additional comments from this next revision round below.

The cyclic voltammetry data now show irreversible current in the presence of Ket-1 with light, consistent with reduction of the ketone. In agreement with this, the UV-vis before and after transient absorption with Ket-1 are not identical, pointing to an incomplete cycle. It would strengthen the argument to add a TA spectrum to the SI showing incomplete recovery of the ground state bleach with Ket-1.

We have added these data to the supporting information to supplement the CV data. Consistent with our model, these data show incomplete recovery of the ground state bleach, indicative of irreversible ketone reduction. The data are reproduced below.

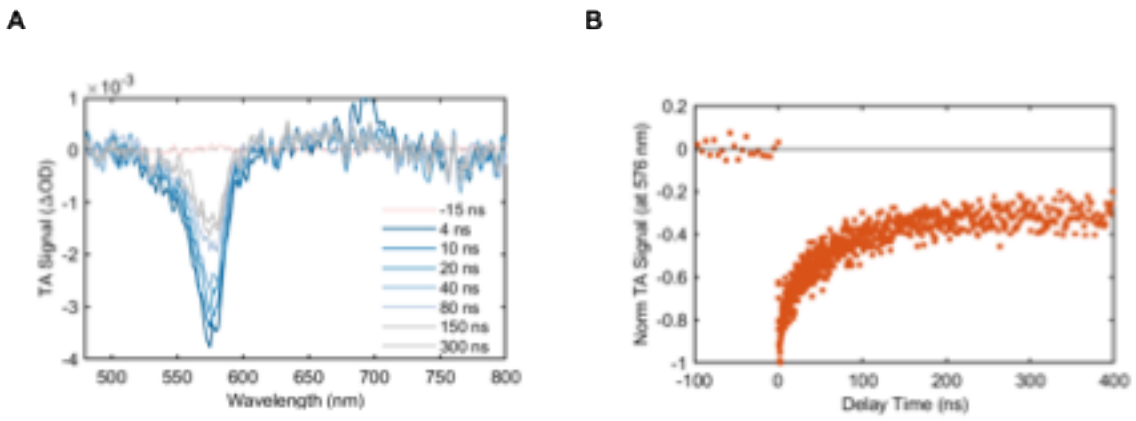


Figure S1.17 (A) Transient absorption spectra at representative delay times as indicated in the legend. Data were acquired following 460 nm excitation of perylene radical anion in the presence of 0.9 mM Ket-1. (B) Normalized transient absorption trace of the ground-state bleach (GSB) of the perylene radical anion at 576 nm. Incomplete recovery of the GSB, reflected by a persistent offset, is consistent with irreversible electron transfer.

In agreement with Reviewer 2 regarding figure 2, it does not seem fair to compare constant current to constant potential and the reducing environment should be sufficient to reduce both ketone and styrene substrates. In the case of mediated electrolysis, the -2.5 V vs Ag/AgNO3 applied potential is sufficient to reduce styrene but not the ketone. For the conventional photoredox system, the redox potential of excited PTH has been shown to have a potential of just over -2 V vs SCE, which is inadequate for reduction of either substrate. It would be helpful to compare selectivity with reducing systems that are capable of reducing either substrate. The diffusion limitation argument should be distinct from the potency of a reductant. Solvated electrons are shown to have high diffusivity usually limited by the solvent diffusivity coefficient. To make synthetic comparisons with other photocatalysts, they should be potent enough to reduce either substrate (thermodynamically possible) but have kinetics that are much less than the solvent limit to demonstrate this. It is distracting to compare systems that are thermodynamically impossible to thermodynamically possible systems.

We recognize that, based on this comment and the prior comment from reviewer 2, our discussion of these data was unclear. In this response we will first clarify the goal of these experiments and then outline specific changes made to the main text to clarify these points.

The goal of Figure 2 is to experimentally validate that the [3+2] annulation reaction is an appropriate model reaction, which means confirming it obeys the expected redox potential control despite the fast cyclopropane fragmentation. As the reviewer points out, several of the conditions tested are not expected to afford product and are not meant to be interpreted as "comparisons" to the electrophotocatalytic conditions. Rather, they are designed to validate that the difference in substrate redox potentials is sufficiently large enough that the reaction cannot simply be promoted by fast fragmentation of the cyclopropane ring. These data are crucial because they exclude the possibility that uphill SET to the ketone can be selectively driven by the fast cyclopropane ring opening, which is a widely established phenomenon in electrocatalysis (for details, see: Chem. Soc. Rev., 2014, 43, 2492—2521). This is an issue since the net [3+2] reaction is thermodynamically favorable without even factoring in reductant quenching because strain release subsequent C–C bond formation are the thermodynamic driving forces for the process. The expected problem for the weaker reductants is thus *kinetic in nature* (the necessary ketyl radical is not even transiently accessed) not *thermodynamic impossibility*.

The thesis of our work is that any reductant that is both (1) super potent and (2) photochemically-driven should exhibit the unique selectivity behavior. Accordingly, the experiments with other reductants are not "synthetic comparisons" but rather validations that the model reaction requires both of these properties. To that end, we tested all permutations (reductants that are: weaker / thermal (classic PAH mediation in the dark); super potent / thermal (Na0); weaker / photochemical (PTH); super potent / photochemical (both PAH and thiolate, to validate the performance is not tied to our specific catalyst system).

Below we provide more detail about the precise mechanistic scenarios that are being probed by each of these entries. A discussion of these points, which mirrors the text below, has also been added to the supporting information to summarize the data presented in Section S1.

Mediated Electrolysis: It has been shown that moderately endergonic SET from an electrochemical mediator can be leveraged for substrate activation if the substrate undergoes a sufficiently fast second step (For a review of such reactions see Franke and Little, Chem. Soc. Rev., 2014, 43, 2492—2521). An electrochemical mediator can be used to reduce the ketone, and in fact this has been previously shown in a mechanistic context to measure the redox potentials of cyclopropyl ketones (Tanko, JACS 2002, 124, 16, 4271–4281). If styrene had a similar reduction potential to the ketone, then a mediator that is sufficiently reducing to activate both substrates via endergonic SET could, in principle, drive productive annulation since SET to the ketone would be followed by rapid β-scission. However, we find that even a comparatively mild reductant (pyrene radical anion) efficiently catalyzes styrene hydrogenation before SET to the ketone is even thermodynamically accessible (the barrier to SET from pyrene radical anion to Ket-1 was calculated to be 34 kcal/mol). This outcome confirms that the difference in substrate reduction potentials is large enough to preclude access to the requisite ketyl radical in the presence of styrene under a mediated electrolysis manifold. Therefore, these data are informative not simply

because pyrene cannot mediate reduction of the ketone, but rather that styrene hydrogenation is nonetheless promoted by the same mediator.

Direct Electrolysis: If reversible SET between two substrates is thermodynamically accessible, selective activation of the harder to reduce substrate can be achieved via a Curtin-Hammett scenario (For an example see Moeller, Org. Lett. 2011, 13, 7, 1678–1681). By cyclic voltammetry styrene is observed to be reduced approximately 300mV more positive than Ket-1, indicating that styrene radical anion will be preferentially generated under direct electrolysis. Therefore, these conditions test whether styrene radical anion itself is a competent SET reductant to promote the model reaction via a Curtin-Hammett scenario. Notably, the barrier for SET from styrene radical anion to the ketone was computed to be 27.5 kcal/mol, suggesting this pathway may be accessible under the reaction conditions, which are heated to 40 °C. However, we observe that this pathway is insufficiently fast to outcompete styrene hydrogenation, which is the only observed product under direct electrolysis.

As requested, we also performed an additional constant working potential direct electrolysis experiment in which the potential was held at –3.3 V vs Fc, which is ~200 mV cathodic of the onset of Ket-1 reduction. This results in low but approximately equal conversion of both Ket-1 (10% conversion) and styrene (14% conversion) alongside 9% styrene hydrogenation and no detectable [3+2] product. While the result is a bit convoluted by the fact it stalled a low conversion (presumably due to fouling) this outcome is consistent with indiscriminate SET from potent thermal reductants that can unlock the reduction of both substrates but fails to promote radical coupling. These data have been added to the supporting information.

Sodium Metal: While thermal reductants like sodium metal are sufficiently potent to reduce both substrates, they nonetheless are ineffective at promoting the desired annulation reaction. This is because SET from potent thermal reductants is intrinsically irreversible, preventing recovery of styrene radical anion. We further suspect that the accumulation of styrene radical anion can lead to addition side reactions, contributing to the poor mass balance of this reaction (See SI Table S1.5 and accompanying discussion for details).

Conventional Photoredox: Since photoinduced SET is followed by fast and favorable BET, photoreductants broadly can be selective for the activation of substrates that fragment upon SET reduction. Our intention with this entry was to show that, despite the rapid downstream fragmentation step, classic photoreductants cannot promote the annulation because they are insufficiently reducing to access the ketyl radical. However, we certainly see how this could be confusing and also that the mediated electrochemical studies already exclude the most plausible scenario where a modest reductant could induce selectivity for annulation. To avoid confusion, we have moved this entry exclusively to the supporting information.

Super-potent Photoredox: Our mechanistic proposal is that the observed selectivity for annulation over styrene hydrogenation should not be tied specifically to polycyclic aromatic hydrocarbon electrophotocatalysts. Rather, any photoreductant sufficiently potent to indiscriminately reduce both substrates while retaining fast and favorable back electron transfer could, in principle, circumvent redox potential control. The Melchiorre thiolate system supports this hypothesis and shows that radical coupling is feasible, even without extensive optimization. This result is particularly notable given the difference in active reductant between our system (solvated electrons) and Melchiorre's (the thiolate excited state), which indicates these design principles will be conserved across various potent photoreductant systems.

Changes to the main text *(changed text in red, black for context):*

As a specific model reaction, we targeted the annulation of styrene and aliphatic ketone Ket-1, a pair of substrates that are mismatched for the desired reaction by ~600 mV (K_{eq} = 10^{10} favoring undesired styrene reduction at 25 °C). First, we performed a series of experiments to validate that, despite fast and favorable cyclopropane ring openings, the difference in redox potentials translates into a kinetic bias against the annulation. Calculated Marcus barriers with an array of representative thermal reductants predict that SET to styrene is many orders of magnitude faster than ketone reduction (see Fig. S3.7 and accompanying text for details). Both direct and mediated electrolysis – representative of outer sphere SET reductants – were found to exclusively promote styrene hydrogenation without any productive annulation (Fig. 2, left; see Table S1.4 for full dataset). These data illustrate that, even under conditions that suppress the rate of styrene hydrogenation (e.g., by limiting access to proton equivalents), this model reaction cannot be simply driven by fast cyclopropane ring opening via a Curtin–Hammett kinetic scenario.[28,29] Finally, we probed whether indiscriminate substrate reduction alone, which would provide access to the ketyl radical, could be sufficient to drive selective annulation via a chain mechanism (for detailed discussion of the potential role of chain mechanisms, see SI Section 8).[30]

We found that potent thermal reductants convert both coupling partners but fail to deliver cyclized product (See Table S1.5 and accompanying text for details).[31]

Having established that the annulation of Ket-1 and styrene represents a case where conventional reductants conform to redox potential control, we then evaluated whether super-potent photoreductants could overturn the profound thermodynamic bias presented by this model reaction. We recently found that polycyclic aromatic hydrocarbons (PAHs) are remarkably potent photocatalytic reductants following electrochemical activation and even provided unexplained changes in selectivity upon irradiation.[32] However, this prior context was mechanistically ambiguous, as reduction of either starting material could lead to product formation.[33,34] To evaluate whether these photoreductants were sufficiently potent to obviate redox potentials, we systematically evaluated a range of PAHs for activity in the model cycloaddition. These investigations revealed that, under electrophotocatalytic conditions, diverse PAHs promote the desired reaction with dramatically suppressed hydrogenation (see Table S1.1 for full optimization data). We also tested several of the recently reported potent photoreductant systems (see Table S1.5 for details). These studies revealed that Melchiorre's thiolate photocatalyst,[35] a super-potent single-photon reductant ($^*E_{1/2}$ = –3.4 V), promotes the [3+2] annulation, albeit in diminished yield. Intriguingly, established potent consecutive photoinduced electron transfer (conPET) systems were found to be ineffective despite, in principle, offering comparably potent reduction potentials.[36] Rather than illustrating specific catalyst limitations, however, we suspect this observation reflects the problematic byproducts derived from the amines used as reductants (see SI Section 1 for details).[37] Overall, these data are consistent with our proposal that redox-potential-independent selectivity can emerge from diverse super-potent photoreductants.

Note: the PTH discussion is omitted in the revised text above (we have left these data in the supporting information for interested readers).

Summary

Overall, we sincerely appreciate the constructive feedback on our revised manuscript from both reviewers. Through this revision, we have directly addressed each of the reviewers' remaining concerns. We believe that these comments have helped us further improve the manuscript. We hope the referees are as excited about our revised manuscript as we are.

Prof. Zachary K. Wickens
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608-262-4906 & E-mail: wickens@wisc.edu

June 28, 2026

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Response to referee #2

The revise manuscript of Paton, Damrauer, Wickens & team thoroughly addressed concerns raised in the previous round of review.

In particular:

1) The authors have clarified ambiguities around the calculations done and have probed for specific C=O pi star interaction, which was found to be marginally uphill (8 kcal/mol) and can be excluded.

2) The successful reaction with a Nafion membrane is sufficient to completely preventing any sacrifised Zn from migrating. This excludes a critical concern about some ZnX2 salt being a Lewis acid activator of the substrates carbonyl groups.

3) The authors have clarified their motivation and purpose of testing the Melchiorre thiolate catalyst and this rationale is now available to readers.

While I continue to regret the non-extension to other substrate combinations that would have convinced of the generality of interest for Nature, the efforts made by the authors to exclude prior concerns have convinced me that the manuscript is now ready for publication from the scientific side. Congratulations on the authors for this curious discovery.

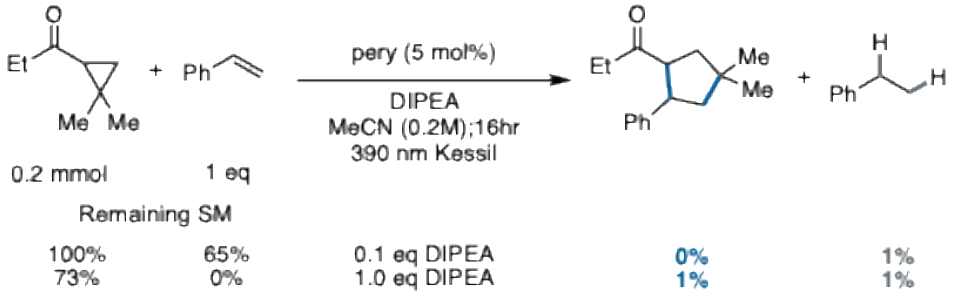
We appreciate the reviewer's detailed comments throughout the review process as the revisions have resulted in a substantially improved manuscript. We look forward to sharing results expanding the concepts that we have validated in this manuscript to new substrate classes in due course.

Response to referee #3

In the most recent revision, the authors clarified control reactions to investigate the Curtin-Hammett scenario. It is still not clear why a different photocatalyst was selected for the classic conPET while assuming that the amine used was the reason for the lack of yield when they could have used the same perylene they used in the electron primed system for the classic conPET instead of mesityl acridine. This would have made the sacrificial electron donors only variable, which would move the speculative argument of the role of sacrificial electron donors influencing reaction to a more factual statement.

We have included the requested experiment using perylene under ConPET conditions in the supporting information and have reproduced the relevant data below. This control demonstrates that perylene alone does not promote the desired [3+2] annulation in a purely photochemical manifold. We selected the acridinium catalyst to examine conPET because it has been shown to promote couplings between ketones and olefins and recent work has suggested that it can also generate solvated electrons through photoreduction. The thiolate catalyst we identified as effective (using formate as a terminal reductant) was identified by evaluating a range of previously reported strongly reducing photocatalysts.

Data from the supporting information



Additionally, spectroscopic evidence for the perylene radical formation is preferred over a statement of visible color change.

We have added an additional comment in the supporting information highlighting that the formation of perylene radical anion is also confirmed spectroscopically.