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Communication

Unveiling Potent Photooxidation Behavior of Catalytic Photoreductants

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ABSTRACT: We describe a photocatalytic system that reveals latent photooxidant behavior from one of the most reducing conventional photoredox catalysts, *N*-phenylphenothiazine (**PTH**). This aerobic photochemical reaction engages difficult to oxidize feedstocks, such as benzene, in $C(sp^2)-N$ coupling reactions through direct oxidation. Mechanistic studies are consistent with activation of **PTH** via photooxidation and with Lewis acid cocatalysts scavenging inhibitors inextricably formed in this process.

Reactions driven by single electron transfer (SET) are pervasive in organic chemistry. Consequently, new strategies to induce redox events are poised to profoundly impact synthetic chemistry.[1−4] Photoredox catalysis has unlocked a broad range of attractive new transformations through conversion of energy from readily accessible LEDs into chemical redox potential.[5−8] However, only a portion of this energy[9] can be harnessed due to inevitable energy losses from vibrational relaxation, internal conversion, and intersystem crossing.[10] Despite tremendous effort in photoredox catalyst design,[10−17] excited state potentials beyond roughly −2 and +2 V vs SCE remain difficult to achieve using conventional photocatalyst design principles wherein a single photon from commercial LEDs is used as the primary energy source (Figure 1A).[18−22] Unfortunately, this redox window excludes numerous abundant hydrocarbon feedstocks from facile photoinduced electron transfer.[23]

To overcome the energetic limitations intrinsic to conventional photoredox catalysis, König and co-workers recently designed a photocatalytic system that drives challenging reductive SET events using the energy of two photons rather than one. This consecutive photon-induced electron transfer (conPET)[24,25] strategy relies on a catalytic photooxidant and sacrificial reductant that, upon irradiation, result in a potent radical anion photoreductant (Figure 1B). Despite its mechanistic complexity, this approach is practical and operationally simple; it leverages inexpensive and safe LEDs to accomplish reactions that otherwise require UV photoreactors or harsh chemical reductants. Following proof-of-concept aryl halide reductions,[24,26−33] this approach has enabled photochemical alternatives to alkali metal reductants in reactions such as Birch reductions[34] and sulfonamide cleavage.[35]

In contrast to the progress in photoreductions, oxidations driven by the consumption of multiple photons have remained elusive. We suspect that this is the consequence of two inextricable challenges: (1) the catalyst must be a competent photocatalyst in both the closed shell and radical cation states[5,25] and (2) the terminal oxidant must efficiently activate the catalyst but not otherwise interfere with the reaction (Figure 1C).[36] Given the difficulty applying multiple photons toward a challenging SET oxidation, photoredox reactions initiated by SET oxidation are typically limited to electron-rich hydrocarbon substrates.[6,37−42]

We questioned whether conventional photoreductants, which typically possess persistent radical cation states, could be repurposed as strong photooxidants using a conPET strategy.[43] We hypothesized photochemical conditions designed to drive these photocatalysts toward their oxidized congeners could reveal potent photooxidation behavior. To probe this hypothesis, we targeted cyclic triarylamine photoreductants. These are a well-established and modular family of photocatalysts[21,44] and photophysical studies conducted by Wasilewski and co-workers indicate that their radical cation congeners exhibit photochemical activity.[45] Furthermore, intriguing studies from Wagenknecht and co-workers have implicated photoexcitation of triarylamine radical cations formed via SF_6 reduction in alkene pentafluorosulfonylation processes.[46,47] We envisioned that photochemically accessing these radical cations using a bystanding oxidant would offer an ideal avenue to explore the potency of these radical cation photooxidants.

We selected the Nicewicz-type[41] oxidative coupling of arenes and *N*-heterocyclic nucleophiles as a model reaction. This synthetically valuable transformation is representative of the general challenges in oxidative photoredox catalysis. It has been predominantly limited to electron-rich arene substrates, such as anisole derivatives[48] and also requires a bystanding terminal oxidant. Difficult to oxidize arene substrates, such as benzene, typically mandate high energy UV light (UVB or shorter)[18] or strong ground state oxidants (e.g., DDQ) that absorb visible light.[49,50] Recent progress by Lambert and co-

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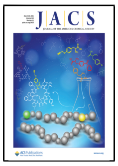

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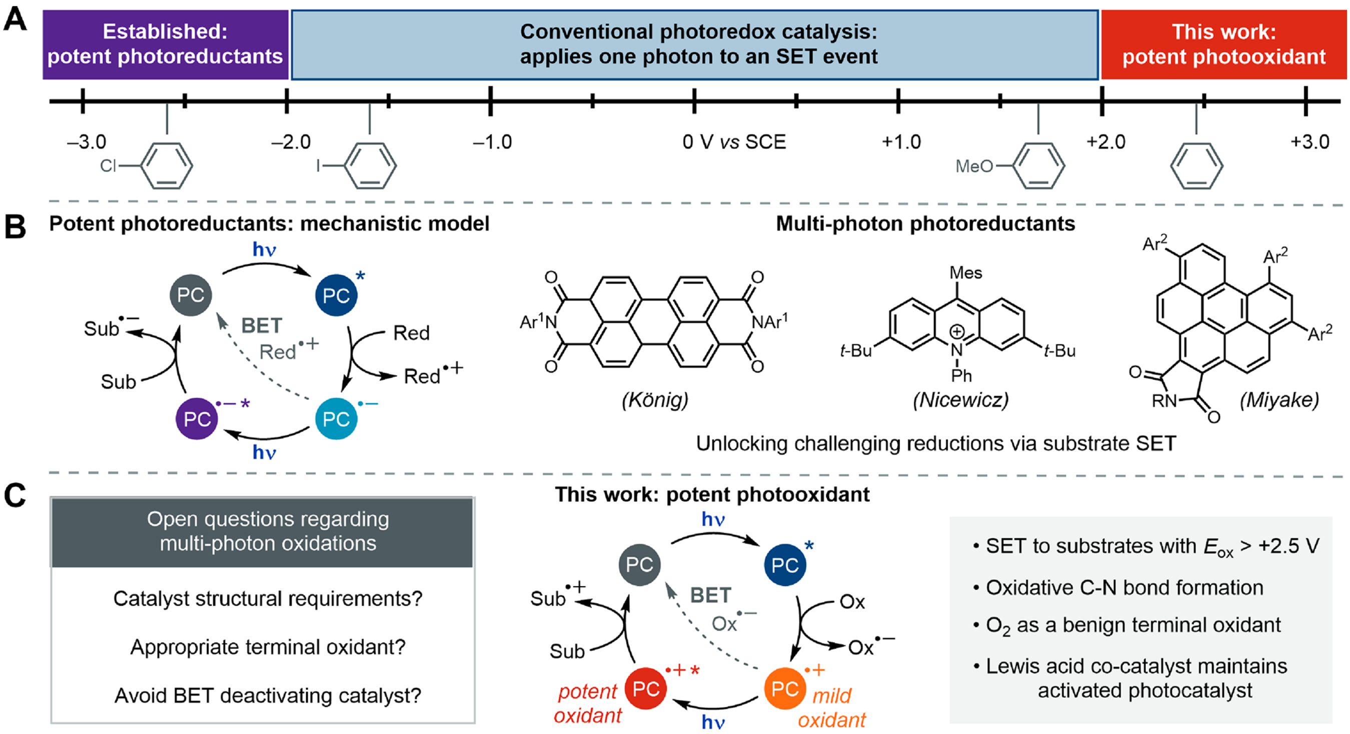
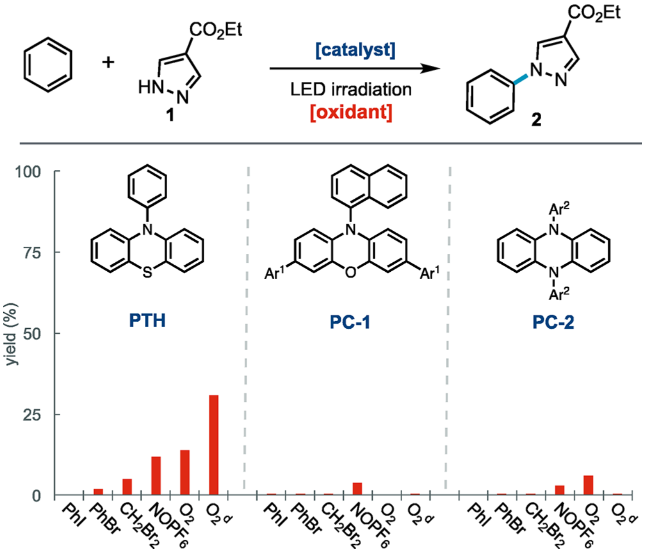


Figure 1. (A) Overview of redox potentials in photoredox catalysis. (B) Overview of multiphoton photoreductants. Full catalyst structures available in SI. (C) Overview of research described herein.

Table 1. Survey of Oxidants and Photoreductants[a−d]



[a]Reactions were conducted on a 0.05 mmol scale in 1:1 MeCN:PhH for 24 h, unless noted otherwise, using 2 equiv oxidant or 1 atm O_2. Ar^1 = 4-biphenyl. Ar^2 = 2-naphthyl. [b]**PTH** irradiated using 390 nm Kessil lamp. [c]**PC-1** and **PC-2** irradiated using Tuna Blue Kessil lamp. [d]1:1 TFE:PhH.

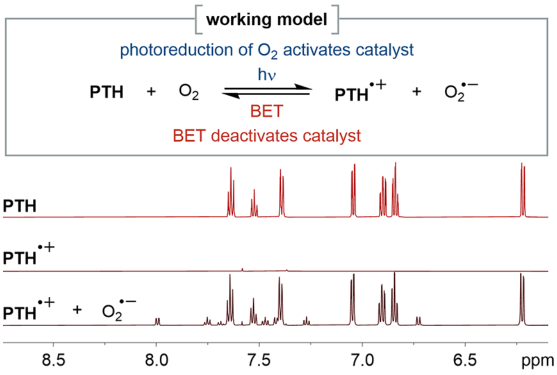
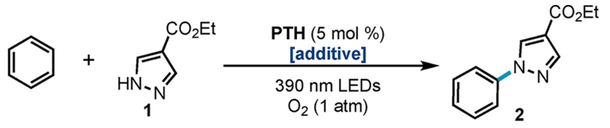


Figure 2. ^{1}H NMR spectroscopic evidence supporting the working model for catalyst deactivation pathways.

workers has introduced an alternative electrophotocatalytic approach that employs electrochemistry and photochemistry in concert to accomplish this energetically demanding oxidation.[51−53] However, while electrophotocatalysis is an exciting emerging area of research,[51,52,54−63] these reactions require specialized electrochemical equipment (e.g., divided cells, electrodes, and power supplies) and are technically complex relative to purely photochemical processes.[64] Thus, we envisioned that promoting this transformation using a bench stable and commercially available photocatalyst simply with inexpensive LEDs would be a synthetically useful complement to existing methods. Accordingly, this constitutes an appealing context for our proof-of-concept experiments.

First, we examined three distinct photoreductants[21,6566,] and a range of oxidants for activity in the oxidative coupling of benzene (E_{ox} = 2.5 V vs SCE)[67] and pyrazole **1** (Table 1). We initially aimed to generate the catalyst radical cation congener via photoreduction of reagents that undergo irreversible decomposition after SET to avoid catalyst deactivation via back electron transfer (BET). Excitingly, these data revealed that *N*-phenylphenothiazine (**PTH**), the most reducing photocatalyst of the series, could promote this challenging oxidative coupling in low yield using organohalides as the oxidant. A sufficiently strong oxidant to oxidize each catalyst to the corresponding radical cation without additional energy from light, NOPF$_6$,[68] provided low yield of benzene oxidation

Table 2. Reaction Optimization[a]



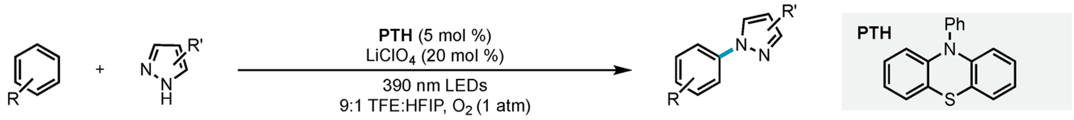
entry	additive	yield (%)
1	none	31
2	KO_2 (5 mol %)	<2
3	$LiClO_4$ (1 equiv)	86
4	$LiClO_4$ (20 mol %)	73
5	*n*-Bu_4NClO_4 (20 mol %)	29
6	$LiPF_6$ (20 mol %)	64
7	LiOTf (20 mol %)	56
8	$LiClO_4$ (20 mol %)[b]	**89**
9	**PC-1** (5 mol %), $LiClO_4$ (20 mol %)[b,c]	<2
10	**PC-2** (5 mol %), $LiClO_4$ (20 mol %)[b,c]	<2
11	$Ir(ppy)_3$ (1 mol %), $LiClO_4$ (20 mol %)[b,c]	<2

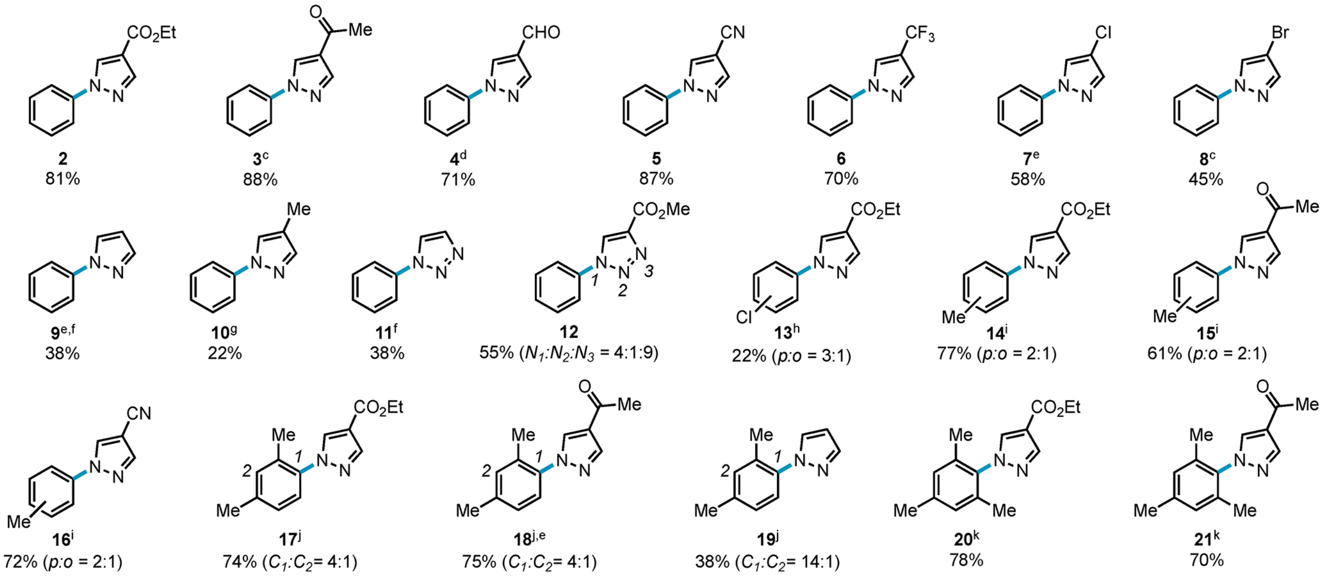
[a] Reactions were conducted on a 0.05 mmol scale in 1:1 TFE:PhH for 24 h. See SI for details. [b] 9:1:10 TFE:HFIP:PhH solvent mixture. [c] Tuna Blue Kessil lamp irradiation.

products using all three catalysts. However, under 1 atm of O_2, **PTH** promoted oxidative coupling in promising yield (14%). Given the enhanced stability of radical cations in fluorinated alcohol solvents,[19,53,69−71] we substituted MeCN for trifluoroethanol (TFE). This resulted in a modest increase in reaction yield with **PTH** but only traces of product with the other two catalysts. Of note, while most photoredox catalysts undergo rapid intersystem crossing to a long-lived triplet,[5,13] **PTH** is a singlet excited state reductant.[72] This property circumvents photocatalyst deactivation by triplet−triplet annihilation with O_2.

We suspected that BET between **PTH** radical cation and superoxide[73] might attenuate reactivity under these conditions (Figure 2).[74] Indeed, when synthetically prepared **PTH** radical cation is treated with KO_2, we observe a rapid color change and reformation of **PTH** by ^1H NMR. Given that superoxide generation is inextricable from aerobic catalyst activation, this observation could account for the modest reactivity of this catalytic system (Table 2, entry 1). As expected, addition of 5 mol % KO_2 to the reaction mixture completely suppressed product formation (entry 2). We hypothesized that additives capable of sequestering or scavenging this inhibitor would enhance the observed reactivity. Guided by this model, we found addition of one equivalent of an inexpensive, redox innocent Lewis acid, $LiClO_4$, dramatically improved the yield of oxidative coupling product (entry 3). Reduction of the $LiClO_4$ loading to a substoichiometric quantity (20 mol %) retained the benefits of the additive, suggesting a cocatalytic role for $LiClO_4$ rather than it purely sequestrating stoichiometric byproducts (entry 4). In principle, the lithium cocatalyst could mitigate BET by promoting superoxide disproportionation.[75,76] Consistent with this proposed Lewis acidic role, alkylammonium salts had no impact on the reaction (entry 5), whereas other Lewis acidic lithium salts retained the catalytic effect (entries 6 and 7). Final tuning of the reaction parameters revealed adjusting the solvent mixture to include a small amount of hexafluoroisopropanol (HFIP) delivered the desired product in 89% yield (entry 8). Substitution of **PTH** with other triarylamine photoreductants or a classic metal-based photoreductant, $Ir(ppy)_3$, resulted in only trace yield of

Table 3. Scope of Arene C−H Amination[a,b]





2 81%

3[c] 88%

4[d] 71%

5 87%

6 70%

7[e] 58%

8[c] 45%

9[e,f] 38%

10[g] 22%

11[f] 38%

12 55% (*N*1:*N*2:*N*3 = 4:1:9)

13[h] 22% (*p*:*o* = 3:1)

14[i] 77% (*p*:*o* = 2:1)

15[i] 61% (*p*:*o* = 2:1)

16[i] 72% (*p*:*o* = 2:1)

17[j] 74% (*C*1:*C*2= 4:1)

18[j,e] 75% (*C*1:*C*2= 4:1)

19[j] 38% (*C*1:*C*2= 14:1)

20[k] 78%

21[k] 70%

[a] Reactions conducted using 0.4 mmol of heterocycle, 8 mL of arene, and irradiated with two 390 nm Kessil lamps for 24 h with fan cooling. See the SI for further experimental details. [b] Isolated yields. [c] 20% $LiPF_6$. [d] 1:1 HFIP:PhH solvent. [e] NMR yield. [f] 0% r.s.m. [g] 31% r.s.m. [h] 10% r.s.m. [i] 1:1:2 MeCN:HFIP:arene solvent with 10% *t*-dodecyl mercaptan. [j] 10 equiv arene, 0.1 M in 1:1 MeCN:HFIP, 10% *t*-dodecyl mercaptan. [k] 5 equiv arene, 0.1 M in 1:1 MeCN:HFIP, 10% *t*-dodecyl mercaptan.

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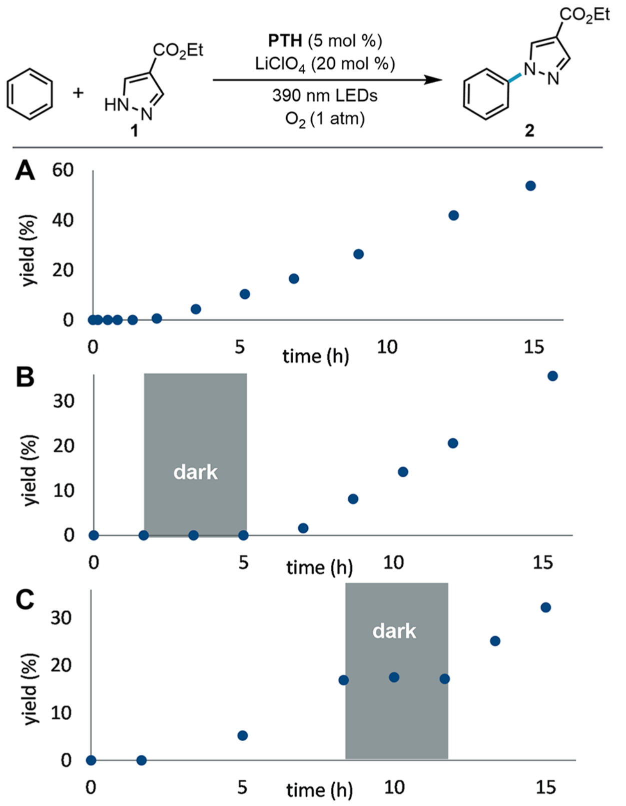
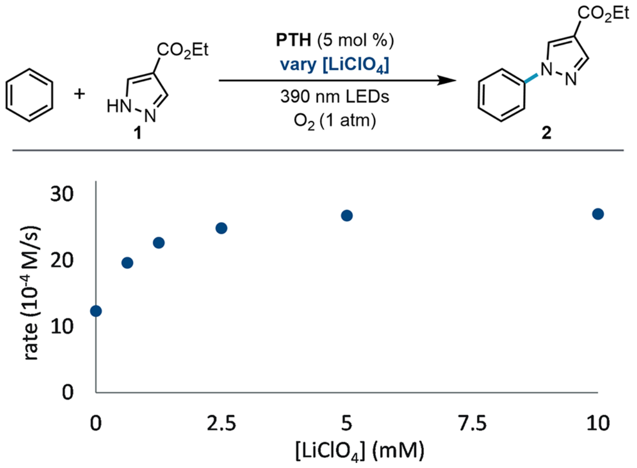
Scheme 1. Light-Dependence on Induction Period and Product Formation Regimes: (A) Standard Reaction Profile with Continuous Irradiation; (B) Suspended Irradiation during Induction Period; (C) Suspended Irradiation during Product Formation[a]



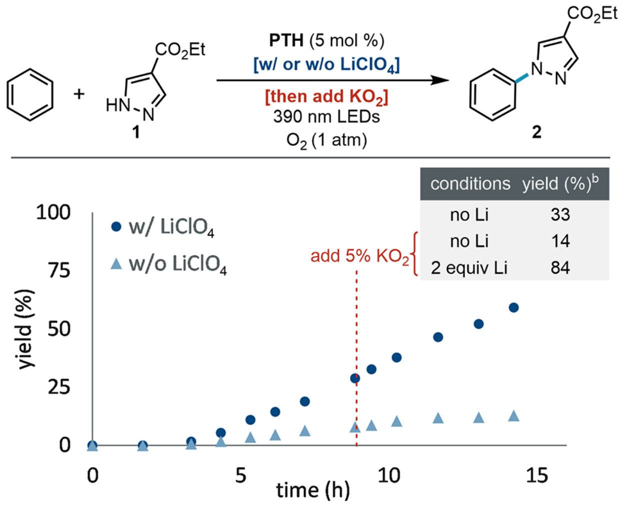
[a]Reactions were conducted on a 0.05 mmol scale in 9:1:10 TFE:HFIP:PhH. See the Supporting Information (SI) for overlays of total irradiation time.

Scheme 2. Saturation in Lithium Cocatalyst[a]



[a]Reactions were conducted on a 0.05 mmol scale in 9:1:10 TFE:HFIP:PhH.

Scheme 3. Impact of Added Substoichiometric KO_2 on Rate with and without $LiClO_4$[a]



[a]Reactions were conducted on a 0.05 mmol scale in 9:1:10 TFE:HFIP:PhH. See the Supporting Information (SI) for further details. [b]Final yield after 22 h.

oxidation product under these otherwise optimal conditions (entries 9−11).

Having identified a promising catalytic system, we examined the scope of this new process (Table 3). Pyrazole nucleophiles bearing a range of electron-withdrawing moieties, including ketones (**3**), aldehydes (**4**), nitriles (**5**), and trifluoromethyl groups (**6**) were oxidatively coupled to benzene. Halogenated pyrazoles (**7** and **8**) were also productively coupled despite the fact that **PTH** is a potent photoreductant. Prior approaches capable of oxidizing benzene have not been readily amenable to the arylation of neutral heterocyclic substrates.[77] In contrast, we observed coupling of both parent pyrazole (**9**) and even an electron-rich analogue (**10**), albeit in diminished yield relative to the electron deficient heterocyclic coupling partners. In addition to pyrazole derivatives, we found that 1,2,3-triazoles (**11** and **12**) were amenable to oxidative coupling with benzene. Even an exceptionally challenging to oxidize electron-deficient arene, chlorobenzene, could be engaged in productive C(sp^2)−N coupling via arene photooxidation (**13**). To probe the limits of what this catalytic system can oxidize, we evaluated acetophenone as an arene substrate and detected at most traces of oxidative coupling products. This result indicates that this arene is too electronically deactivated for oxidation under these conditions. We recognized that benzylic C−H bonds could be a liability under these aerobic conditions; however, we found reasonable C(sp^2)−N coupling yields could be obtained from toluene using our standard conditions and these yields could be further improved by tuning the reaction conditions to mitigate benzylic oxidation processes.[78] Under these modified conditions, **PTH** promoted the photochemical coupling of toluene, *m*-xylene, and mesitylene with pyrazole derivatives in high yield (**14**−**21**). The oxidation of *m*-xylene and mesitylene could be achieved using a smaller excess of arene, presumably due to the significantly lower oxidation potential relative to benzene.[79] Of note, while the scope and reagent stoichiometries required for this approach are similar to prior electrophotocatalytic systems, these photocatalytic conditions exclusively require commercially available catalysts and no specialized equipment outside of LED lamps. Furthermore, this simple photocatalytic system delivers coupling products with substantially shorter reaction times.[80] Overall, these data illustrate that the scope of this photochemical process described herein is on par with complementary electrophotocatalytic approaches.[51,52]

Next, we aimed to uncover preliminary mechanistic insight into this new and unusually oxidizing photocatalytic system. First, we collected the full reaction profile by monitoring the yield of coupling product **2** as a function of time (Scheme 1A). These data revealed an induction period, wherein only a trace amount of product is formed, followed by zeroth order formation of product that continues until nearly all of the pyrazole is consumed (see SI for complete reaction profile). If irradiation is temporarily suspended during the induction period, the onset of product formation is correspondingly delayed (Scheme 1B). Similarly, when irradiation is halted during the product-forming regime, the reaction ceases until irradiation resumes (Scheme 1C). Overall, these data are consistent with a mechanism involving an initial photochemical catalyst activation step (e.g., photooxidation of **PTH** to the radical cation) followed by a product-forming regime with either rate-limiting catalyst oxidation or benzene oxidation, given both benzene and O_2 are present in excess throughout the reaction. Additionally, we determined the O_2 stoichiometry of the reaction by measuring gas consumption within a sealed reaction vessel equipped with a pressure transducer (Figure S16).[81] These data indicate that just over 2 equiv of O_2 are consumed over the course of the reaction, consistent with O_2 acting as only a one-electron oxidant.[82] As anticipated, we found that only minimal oxygen is consumed during the induction period.

Given the initially unanticipated cocatalytic role of $LiClO_4$ in this system, we next carefully investigated the origin of its impact on the reaction. Omission of this additive resulted in a modest elongation of the induction period and, subsequently, slower product formation (see SI for details). Systematic variation of the concentration of $LiClO_4$ revealed that the impact of this reaction component on rate saturates at roughly 20 mol % (Scheme 2). These data are consistent with our working model wherein $LiClO_4$ catalytically scavenges inhibitory reactive oxygen species produced through photochemical O_2 reduction. Once the inhibitor is scavenged at a sufficiently rapid rate, its steady state concentration will approach zero and additional increase in cocatalyst loading is expected to have no impact on the process. When the reaction is charged with 5 mol % KO_2 shortly after the induction period, we observe that the reaction halts thereafter in the absence of $LiClO_4$. In stark contrast, a reaction containing 2 equiv of $LiClO_4$ was unperturbed by direct addition of this inhibitor (Scheme 3).[83]

On the basis of the data presented herein, we have constructed a plausible mechanistic model, which involves: (1) initial oxidative activation of **PTH** via photoreduction of O_2; (2) photoexcitation of a triarylamine radical cation to oxidize the arene substrate;[84,85] (3) trapping of arene radical cation with pyrazole nucleophile. While lithium salts are not mechanistically necessary to promote the photocatalytic transformation, we suspect that these Lewis acidic cocatalysts accelerate the reaction by promoting the disproportionation of superoxide, an inhibitor inextricably formed in the aerobic catalyst activation step. We envision the lithium cocatalyst is turned over by protonation of Li_2O_2 by HFIP.[86]

Overall, we have identified a catalytic system that unlocks potent photooxidant behavior from one of the most reducing conventional photoredox catalysts, **PTH**. This approach enables oxidative C(sp^2)−N coupling via photooxidation of arene substrates outside of the redox window of reported photoredox approaches. Preliminary mechanistic studies are fully consistent with photocatalyst activation via photoreduction of O_2. Intriguingly, we found that Lewis acid cocatalysts could promote and maintain catalyst activation. Beyond providing the first example of purely photochemical benzene oxidation using inexpensive LEDs, this study provides a roadmap to exploit known photocatalysts in new and unconventional ways. We anticipate that continued examination of reaction conditions that force photocatalysts into destabilized oxidation states will dramatically expand the scope of oxidative photoredox catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c00399.

Experimental procedures, characterization data, and spectra (PDF)

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Notes

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