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General Strategy for Improving the Quantum Efficiency of Photoredox Hydroamidation Catalysis

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ABSTRACT: The quantum efficiency in photoredox catalysis is the crucial determinant of energy intensity and thus is intrinsically tied to the sustainability of the overall process. Here, we track the formation of different transient species of a catalytic photoredox hydroamidation reaction initiated by the reaction of an Ir(III) photoexcited complex with 2-cyclohexen-1-yl(4-bromophenyl)carbamate. We find that the back reaction between the amidyl radical and Ir(II) photoproducts generated from the quenching reaction leads to a low quantum efficiency of the system. Using transient absorption spectroscopy, all the rate constants for productive and non-productive pathways of the catalytic cycle have been defined, enabling us to establish a kinetically competent equilibrium involving the crucial amidyl radical intermediate that minimizes its back reaction with the Ir(II) photoproduct. This strategy of using an off-pathway equilibrium allows us to improve the overall quantum efficiency of the reaction by ×4. Our results highlight the benefits from targeting the back-electron transfer reactions of photoredox catalytic cycles to lead to improve denergy efficiency and accordingly improved sustainability and cost benefits of photoredox synthetic methods.

Introduction

Photoredox catalysis has emerged as a prominent methodology for highly selective, high throughput synthesis. A photoredox synthetic strategy allows for the straightforward generation of high energy and reactive radical intermediates resulting from electron transfer with a photocatalyst excited state, thereby unlocking reaction pathways that are difficult or even impossible to access using traditional routes.¹ As with any current methodological development, photoredox synthetic pathways are accentuated when the design effort incorporates sustainability.² To this end, the Process Mass Intensity (PMI = quantity of raw materials input (kg)/quantity of bulk active pharmaceutical ingredient output (kg)³ has been adopted as a metric for the implementation of green chemistry and engineering in modern synthetic design strategies. Whereas reagents and solvents are PMI targets of opportunity as raw materials inputs, the value of the energy input has been appreciated to a lesser extent even though it may be the overriding determinant of sustainability with regard to the environmental manufacturing footprint and the cost of the overall synthetic pathway. Accordingly, in addition to PMI, Energy Intensity (EI = total process energy (J)/mass of final product) is an emerging metric of importance in the design of new synthetic methods.^{4,5} In the context of EI, photoredox (as well as electroredox⁶) catalysis has the attractive attribute that its energy input may be a solar source,⁷ which by its nature has significant virtue with regard to sustainability, and in view of the declining cost of solar generation,^{8,9} has a cost benefit as well. However, to fully realize these attributes of a light energy input, the photoredox catalysis must occur at high quantum efficiency ($\Phi_{\rm P}$ = product out/photons in).

Whereas reaction scope and new methodologies for photoredox catalysis are rapidly expanding, quantum efficiencies to date have been typically overlooked and not optimized.¹⁰ Rational design principles to optimize Φ_P relies on extracting rate constants for photochemical steps and ensuing reaction rate constants pertaining to

rate-limiting and non-productive pathways, both of which will significantly affect the quantum efficiency of the reaction.^{11–13} Such rate constant data have not been characterized in most reports of photoredox catalytic systems to date; insight into reaction mechanisms have relied primarily on the redox potentials of the photocatalyst and reagents,^{14,15} bond dissociation energies^{16,17} and steady-state Stern-Volmer quenching rate constants,¹⁸ which provide information on the initial photoinduced redox event but not on ensuing reactions. Information pertaining to the productive pathways involving substrate and photoproduct intermediates, appearing after the initial photoinduced electron transfer, are the crucial determinants of the overall quantum efficiency of the synthetic method. In this regard, a major loss channel inherent to all photochemical processes and particularly to photoredox catalysis is back electron transfer (BET),^{19,20} which circumvents the forward propagation of the desired reaction sequence (see Scheme 1). Mechanistic insights pertaining to BET and other non-productive pathways may be furnished by time-resolved spectroscopy, which allows intermediates to be identified and rate constants to be determined. With this information in hand, competitive reaction pathways may be defined and subsequently manipulated.^{18,21-23} Such information is valuable for the rational optimization of the quantum efficiencies of photoredox catalytic reactions.

We now demonstrate an improved synthetic methodology for hydroamination by exploiting the knowledge garnered from comprehensively defining the reaction mechanism. Hydroamidation reactions are important but challenging transformations that generate C–N bonds from olefins with readily available amides, carbamates or ureas;²⁴ the functionalized amide and lactam products are omnipresent in pharmaceuticals, natural products and biological systems,^{25,26} and also appear in bulk commodity chemicals such as Nmethyl-2-pyrrolidone and N-vinyl-2-pyrrolidone, which are currently produced on kilotons scale for their applications as solvents or plastic precursors.²⁷ Successful hydroamidation methods typically invoke nitrogen-centered amidyl radicals as pivotal intermediates, as Journal of the American Chemical Society

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they can rapidly add to olefins in an anti-Markovnikov manner.^{28,29} However, the formation of the key amidyl radical intermediate is often nontrivial and involves the use of either synthetically challenging precursors such as chloroamides, thioamides, ^{30,31,32} aryloxy amides³³ or strong oxidants.³⁴ As pioneered by Knowles and co-workers,³⁵ photoredox catalysis has engendered a simple and reliable strategy to deliver the amidyl radical by photoinduced proton-coupled electron transfer (PCET)³⁶⁻³⁸ between the excited state of an Ir(III) photocatalyst and the corresponding amide in the presence of a dibutylphosphate base and a thiol hydrogen atom donor. This successful synthetic hydroamidation method applies to a wide range of amide, carbamates, ureas and olefin substrates but as we report here occurs at low efficiency owing to facile BET of the photogenerated amidyl radical. We now show that the entire hydroamidation cycle encompasses seven rate constants, two of which involve quenching the amidyl radical by BET with the Ir(II) photocatalyst and hydrogen atom transfer with the thiol. Both of these reactions return the amide starting reactant before cyclization of the amidyl radical may occur to produce the desired hydroamidation product. Using transient absorption spectroscopy, the rate constants of the complete hydroamidation cycle have been determined, allowing us to design an off-cycle equilibrium that traps the amidyl radical with a disulfide as schematically indicated in Scheme 1. The trapping reaction attenuates BET of the photogenerated amidyl radical, which may be returned to the catalytic cycle via the equilibrium. Knowledge of the cyclization rate constant in comparison to the rate constants for BET and HAT enables the equilibrium to be tuned to allow the cyclization reaction to prevail. Through this strategy, the photoinduced hydroamination reaction may be optimized to result in a significant increase in the quantum efficiency of the synthetic method.

Experimental

General Considerations. All reactions and samples were prepared in a N2-filled glovebox unless stated otherwise. Anhydrous solvents were obtained from drying columns and stored over activated molecular sieves.³⁹ NMR spectra were recorded at the Harvard University Department of Chemistry and Chemical Biology NMR facility on a Varian Mercury400 spectrometer operating at 400 MHz or a Varian Unity/Inova500 spectrometer operating at 500 MHz for ¹H acquisitions, and Varian Unity/Inova500C spectrometer operating at 126 MHz for ¹³C acquisitions. ¹H NMR chemical shifts are reported in ppm relative to SiMe₄ ($\delta = 0$) and were referenced internally with respect to the protio solvent impurity ($\delta = 5.32$ for CDHCl₂).^{40 13}C NMR spectra are reported in ppm relative to SiMe₄ $(\delta = 0)$ and were referenced internally with respect to the solvent (δ = 53.84 for CD_2Cl_2). Coupling constants are given in Hz. UV-vis spectra were recorded at 293 K in tightly sealed 1 cm quartz cuvettes on a Cary 5000 spectrometer (Agilent), and were blanked against the appropriate solvent. 2,4,6-Trimethylphenylthiol (MesSH) was purchased from Alfa Aesar or Santa Cruz Biotech and distilled before use. Tributylmethylammonium dibutyl phosphate (Pi^{Bu}₂) was purchased from Sigma Aldrich and dried under high vacuum for 24 h before use. 4-Bromophenyl isocyanate, cyclohexanol, sodium hydride, tetrabutylammonium hexafluorophosphate (TBAPF₆), and camphorquinone (CQ) were purchased from Sigma Aldrich and used without purification. $[Ir(dF(CF_3)ppy)_2(bpy)]PF_{6}$,⁴¹ 2-cyclohexen-1-yl(4-bromophenyl)carbamate 1a,42 2-cyclohexen-1-yl(4cyanophenyl)carbamate 1b,43 di(2,4,6-trimethylphenyl) disulfide44 (MesSSMes) and 2,4,6-trimethylbenzenesulfenyl chloride⁴⁵ were prepared according to literature procedures. The synthesis and characterization of cyclohexyl(4-bromophenyl)carbamate (3) and N-(2,4,6-trimethylphenylthyil)2-cyclohexen-1-yl(4-bromophenyl) carbamate (4) are detailed in the supporting information.

Quantum Efficiency Measurements. Typical photoredox hydroamidation reactions were performed using the procedure reported by Knowles and co-workers³⁵ with the appropriate amide substrates and $[Ir(dF(CF_3)ppy)_2(bpy)]PF_6(dF(CF_3)ppy = 2-(2,4$ difluorophenyl)-5-(trifluoromethyl)-pyridinyl, bpy = 2,2'-bipyridine) as a photoredox catalyst (PC) in a 2 mol% loading, $[OP(O)(OBu)_2]^-$ (Pi^{Bu}₂) as a base in a 20 mol% loading and 2,4,6trimethylphenylthiol (MesSH) as an H-atom donor or MesSSMes in a 10 mol% loading (unless stated otherwise) in CH₂Cl₂. All reactions were carried out under constant illumination provided by a A160WE Tuna Blue light source. The light source used for quantum yield measurements was a 150 W Xe arc lamp (Newport 67005 arc lamp housing) with a Newport 69907 universal arc lamp power supply. This latter light source was equipped with a a 310 nm long pass filter and a second Hg line filter (380 nm or 435 nm) to generate a wavelength-selective irradiation beam. Photon fluxes were determined by chemical actinometry against a potassium ferrioxalate standard (0.006 M for 380 nm and 0.15 M for 435 nm).⁴⁶ All measurements were conducted to an average conversion of 15%, and the illumination times were adjusted accordingly.

Electrochemical Studies. Electrochemical measurements were performed on a CH Instruments (Austin, Texas) 760D Electrochemical Workstation using CHI Version 10.03 software. Cyclic voltammetry (CV) experiments were conducted in a N2-filled glovebox on a CH2Cl2 solution at 293 K containing 0.2 mM of PC, 0.1 M tetrabutylammonium hexafluorophosphate (TBAPF₆) using a CH Instruments glassy carbon button working electrode (area = 0.071cm²), BASi Ag/AgNO₃ (0.1 M) reference electrode, and Pt wire counter electrode. TBAPF6 was dried prior to use. CVs were recorded with compensation for solution resistance and were referenced to the ferrocenium/ferrocene (Fc/Fc^{+}) couple by recording the CV of the complexes in the presence of a small amount of ferrocene. Spectroelectrochemical measurements were conducted in a small volume, 0.5 mm path length spectroelectrochemical cell equipped with a Pt mesh working electrode, a nonaqueous Ag/Ag⁺ reference electrode, and a Pt auxiliary electrode, all purchased from Bioanalytical Systems. A fiber-coupled light source (Ocean Optics DT-MINI-2GS) illuminated the sample and the transmitted light ACS Paragon Plus Environment

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59 60 was coupled into an optical fiber and sent to an Ocean Optics USB4000) spectrometer. Absorption spectra were recorded with OceanView 1.4.1 software.

Optical Characterization. Steady-state emission spectra were measured on a Photon Technology International (PTI) QM4 fluorimeter coupled to a 150 W Xe arc lamp as an excitation light source. The emitted photons were detected by a Hamamatsu R928 photomultiplier tube (PMT) cooled to -70 °C. Samples were placed in tightly sealed 1 cm path length quartz cuvettes. Steady-state Stern-Volmer (SV) quenching experiments monitored the emission intensity at 500 nm generated by excitation at 370 nm, while dynamic quenching experiment followed emission decay at 500 nm after laser excitation at 355 nm. For all SV quenching experiments, the sample contained PC (25 μ M), Pi^{Bu₂} (0.25 mM) and different concentration of quenchers 1a and MesSH. Before each series of experiments, the lifetime of PC was measured in absence of quencher; the lifetime of PC^{*} varied from $\tau_0 = 1.70$ to 1.82 µs, in good agreement with previously reported lifetimes for analogous iridium polypyridyl complexes.⁴⁷ Stock Pi^{Bu2} solutions of PC and quencher were prepared and mixed to give the desired concentration of quencher (with the concentration of PC held at 25 µM). All Stern-Volmer experiments were conducted under identical experimental conditions in less than 1 h, ensuring that oxygen contamination was minimized (as verified by the minimal variation in τ_0).

Detailed information about the nanosecond transient absorption (TA) spectroscopy setup has been provided previously.⁴⁸ Briefly, an Quanta-Ray Nd:YAG laser (SpectraPhysics) provides 3rd harmonic laser pulses at 355 nm with a repetition rate of 10 Hz and maximum output of 3 W. The laser output was directed to a MOPO (SpectraPhysics) to produce tunable pump pulses from the UV to the visible spectral region. The excitation energy at the sample was set to 1 mJ/pulse. White light generated by a 75 W Xe-arc lamp (Photon Technologies Incorporated A1010 arc lamp) was partly selected with a pinhole to serve as probe light. Both pulses were focused and overlapped on the sample with a crossing angle of ~15°. Samples were flowed through a 1 cm path length flow cell (Starna Cells) to avoid photodamage. The transmitted probe was directed to a spectrometer (Triax 320) and detected either by a PMT (Hamamatsu) or a CCD camera (Andor Technology). Single-wavelength TA traces were recorded by the PMT coupled to a 1 GHz oscilloscope (LeCroy 9384CM), while spectra were acquired by the CCD camera. All setups were synchronized either to the TTL pulse of the Qswitch signal or the pump pulse detected by a photodiode. Time delays were generated by an SRS DG535 delay generator (Stanford Research Systems). The solution used to record kinetic traces typically contained PC (0.1 mM), Pi^{Bu2} (1 mM), the amide substrate (10 mM), and when necessary, MesSH or MesSSMes (2 mM). The experiments were conducted in succession to ensure the same experimental conditions. The pump wavelength was set to 355 nm or 440 nm to ensure exclusive absorption by PC. The fitting procedures of the kinetic traces are detailed in the SI.

DFT Calculations. Quantum mechanical calculations were performed using density functional theory (DFT) as implemented in Gaussian 16.⁴⁹ All geometry optimizations were carried out at the UB3LYP/cc-pVTZ level of theory in combination with the conductor-like polarizable continuum model (C-PCM) to implicitly account for solvation of the molecules in CH₂Cl₂. Transition states were obtained with the QST3 algorithm and intrinsic reaction coordinate calculations (IRC, backward and forward direction) resulted in the expected reactant and product species. In all cases, geometry ACS Paragon Plus Environment

Scheme 2



optimizations were carried out on an ultrafine grid with the convergence criterion: RMS(Force) < 3×10^{-6} (iop1/7 = 30). Frequency calculations verified the nature of the optimized structure; local minima displayed no negative frequencies, while transition states indicated one negative frequency associated with the excepted IRC. Gibbs free energies for each compound were obtained at T = 298.15 K and the corresponding cyclization rates were approximated by transition-state theory according to the following,

$$k_c = \frac{\mathbf{k}_{\mathrm{B}}T}{\mathbf{h}} \exp\left(-\frac{\Delta G^{\mathrm{t}}}{\mathbf{k}_{\mathrm{B}}T}\right) \tag{1}$$

where k_B is Boltzmann's constant, *T* is temperature, h is Planck's constant and ΔG^{\dagger} is the Gibbs free energy barrier for cyclization.

UV-vis absorption transitions for $1a \cdot and 2a \cdot were computed us$ ing time-dependent DFT (TD-DFT) in Gaussian 16⁴⁹ at the samelevel of theory. The number of excited states included in the calculation was set to 8.

Results

Photoredox Hydroamidation Quantum Yield. The photoredox hydroamidation of 1a was performed using the procedure reported by Knowles and co-workers (Scheme 2).³⁵ In this cycle, the $[Ir(dF(CF_3)ppy)_2(bpy)]^+$ photocatalyst (PC) is quenched by the amide to produce the amidyl radical. This quenching reaction occurs by PCET, and hence is promoted by the presence of the dibutylphosphate base, Pi^{Bu2}. After cyclization, MesSH serves as a hydrogen atom donor to the cyclized radical intermediate to furnish the final product. Using a ferrioxalate actinometer ($\lambda_{exc} = 380 \text{ nm}$), we find that the desired cyclized carbamate product 2a is obtained in 86% yield with a quantum efficiency of 4.7(4)% ([MesSH] = 2 mM). The influence of the arylthiol concentration on the quantum efficiency was evaluated by conducting the photoredox hydroamidation of 1a in the presence of various concentrations of MesSH (0.2, 1, and 4 mM), which furnished quantum yields of 2.1, 3.4 and 6.5%, respectively. The hydroamidation of para-cyano substrate 1b into product **2b** under standard conditions proceeded with a quantitative yield and showed an increase in quantum yield to 5.8(4)%, as expected as a result of the presence of an electron-withdrawing group (EWG), which leads to faster cyclization rate through destabilization of the electrophilic amidyl radical intermediate.³⁴

The hydroamidation of **1a** with MesSSMes in place of MesSH proceeds in 91% yield and with an enhanced quantum efficiency of Environment





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Figure 1. Emission spectra of PC (25 μ M) without (—) and with Pi^{Bu₂} (2 mM) (—). Emission profile obtained upon the addition of 20 mM TBAPF₆ (—). Inset: Emission decay of PC (25 μ M) without (—) and with Pi^{Bu₂} (2 mM) (—). Decay trace (—) obtained upon the addition of 20 mM TBAPF₆.

11.9(8)%. When the excitation wavelength was changed to $\lambda_{exc} = 435$ nm, a similar quantum yield of 13.9(10)% was measured. The constancy between the quantum yields at these different wavelengths ensures that the increased quantum efficiency observed for MesSS-Mes is not a result of its direct photolysis, as MesSSMes has no absorption at 435 nm (Figure S11). The photoredox hydroamidation of **1a** with both MesSH (10 mol%) and MesSSMes (10 mol%) proceeds with a quantum efficiency (13.5(10)%) similar to that of MesSSMes alone (Table S1). As observed previously for the paracyano substrate **1b**, the quantum efficiency for hydroamidation increases (to 20.0(9)%) when MesSH is replaced with MesSSMes.

Quenching Studies. Stern-Volmer (SV) quenching experiments were conducted to evaluate the reaction of PC* with Pi^{Bu2}, MesSH and the amide substrate.

The presence of Pi^{Bu_2} nominally affects the photophysics of PC*. Addition of base prompts the appearance of fine structure on the PC* emission profile (Figure 1), though the overall integrated emission intensity is unchanged. The lifetime of PC increases marginally from 1.78 (black trace, Figure 1 inset) to 2.01 µs (red trace, Figure 1 inset) with the addition of 2 mM Pi^{Bu₂} (Figure 1, inset). The emission intensity and lifetime do not change for the addition of Pi^{Bu₂} concentrations down to 0.5 mM (Figure S4). These results are suggestive of ion-pair formation, PC:Pi^{Bu₂}, as has been observed to occur when cationic polypyridyl complexes are in the presence of monoanionic species such as chloride. ⁵⁰ Addition of an excess TBAPF₆ to a solution of PC and Pi^{Bu₂} recovers the native lifetime of PC (blue trace, Figure 1 inset), and the fine structure on the emission profile of PC is lost, consistent with the separation of a PC:Pi^{Bu₂} ion pair at increased ionic strength of the solution.

An ion-pair complex is reflected in the ¹H NMR spectrum of PC in the presence of increasing concentrations of Pi^{Bu2} in dichloromethane. Addition of Pi^{Bu2} to PC causes a shift in the CH ligand resonance at 8.61 ppm (Figure S1a). The equilibrium constant for the binding between Pi^{Bu2} and PC may be obtained from the chemical shift (δ) of this resonance upon titration of PC by Pi^{Bu2}, using the relationship,

$$\frac{[\mathbf{p}_i^{\mathbf{B}\mathbf{u}_2}]}{\Delta\delta} = \frac{1}{K\Delta\delta_{max}} - \frac{[\mathbf{p}_i^{\mathbf{B}\mathbf{u}_2}]}{\Delta\delta_{max}} \tag{2}$$

where $\Delta \delta = \delta(PC) - \delta_{obs}$, and $\Delta \delta_{max}$ is the maximum value of $\Delta \delta$. Specifically, the equilibrium constant, K (= slope/intercept), is provided ACS Paragon Plus

from a plot of $[Pi^{Bu_2}]/\Delta\delta$ against $[Pi^{Bu_2}]$.⁵¹ The retrieved value for the binding constant between PC and Pi^{Bu_2} is $K = 549(24) M^{-1}$ (Figure S1b). Additionally, a shift in the NH resonance of **1a** is observed upon increasing concentrations of Pi^{Bu_2} , suggesting association of Pi^{Bu_2} to **1a** via a hydrogen bonding interaction (Figure S1c). The equilibrium constant for the interaction between Pi^{Bu_2} and **1a** may be obtained from similar titration studies, furnishing a binding constant of $K = 25(1) M^{-1}$ (Figure S1d).

The association of **1a** to Pi^{Bu2} is consequential to excited state quenching. 1a alone does not quench the excited state of the PC,³⁵ however, in the presence of Pi^{Bu2}, a steady-state SV quenching constant of K_{SV} = 939 M⁻¹ was observed (Figure S5), in agreement with Knowles' previous studies.³⁵ Moreover, a similar K_{sv} value of 890 M⁻¹ is obtained from dynamic quenching measurements (Figure S5). These quenching results are consistent with a shift in the redox potential of 1a upon its association to Pi^{Bu2}, as confirmed by cyclic voltammetry measurements. The cyclic voltammogram (CV) of 1a alone shows an irreversible wave at +1.3 V (Figure S2a). In the presence of base, a new cathodic peak appears at +0.77 V (Figure S2b). With an oxidation potential for PC* of +0.85 V (based on the standard potential of the redox couple PC/PC⁻ and the maximum emission wavelength of PC* of 500 nm),¹⁵ whereas the direct oxidation of 1a by PC* is not possible, the oxidation of 1a associated to Pi^{Bu2} is thermodynamically accessible.

MesSH is also capable of quenching PC* in the presence of Pi^{Bu}₂. Steady-state and dynamic SV quenching measurements yield $K_{sv} = 229 \text{ M}^{-1}$ and 232 M⁻¹, respectively (Figure S6). Based on the relative K_{SV} of **1a** as compared to that of MesSH, we deduce that 10 mM of **1a** will quench the PC* emission by 89.9%, and thus **1a** is the primary quencher under the experimental synthesis conditions. As $K_{SV} = k_q \tau_0$ where τ_0 is the natural (unquenched) lifetime of PC* (τ_0 (PC*) = 1.7 and 1.82 µs, respectively), the rate constants for quenching by **1a** and MesSH are $5.2 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ and $1.3 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, respectively. The former represents rate for the PCET reaction (k_{PCET1}) of the amide with PC*.

Transient Species. The PCET reaction between $PC^* + Pi^{Bu_2} + 1a$ generates the amidyl radical $1a \cdot$, HPi^{Bu_2} and the reduced Ir(II) species PC^- . Transient absorption (TA) spectroscopy was undertaken to characterize these species and their reaction rate constants. TA spectra of photocycle intermediates were generated from the two initial quenching photoevents: $PC + 1a + Pi^{Bu_2}$ and $PC + MesSH + Pi^{Bu_2}$, as the quenching studies (*vide infra*) showed that both 1a and MesSH can react with PC^* in the presence of Pi^{Bu_2} .

Figure 2A (black trace) shows the TA spectrum at 2.5 µs after photoexcitation ($\lambda_{exc} = 355 \text{ nm}$) of PC + 1a + Pi^{Bu₂} in CH₂Cl₂. At this time delay, PC⁻ and **1a**• only contributes to the TA signal, as PC* is removed by quenching and the base shows no visible absorption. Both the absorption spectra of PC⁻ and **1a**• may be determined independently. Because the CV of PC (Figure 3, inset) shows a reversible PC/PC⁻ redox couple a wave at -1.64 vs Fc/Fc⁺, the absorption spectrum of PC⁻ may generated by spectroelectrochemistry (Figure 3, red spectrum). As both PC and PC⁻ are present in the TA spectrum, the spectrum of consequence is the difference spectrum of PC and PC⁻ (Figure 3, orange spectrum), which is provided by subtracting the PC absorption profile of Figure 3 (black spectrum) from the PC⁻ absorption profile of Figure 3 (red spectrum). The absorption spectrum of 1a. may be determined independently with the use of the radical initiator camphorquinone (CQ) to generate 1a. by HAT between CQ* and 1a, as the excited state CQ* is known to abstract hydrogens from a variety of substrates.⁵² The advantage of CQ as a Environment

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Figure 2. A TA spectrum (—) taken 2.5 µs after photoexciting ($\lambda_{exc} = 355 \text{ nm}$) a CH₂Cl₂ solution of PC (0.1 mM), Pi^{Bu₂} (1 mM) and **1a** (10 mM). TA spectrum (—) taken 20 µs after photoexciting (460 nm) a CH₂Cl₂ solution of camphorquinone (CQ) (10 mM), Pi^{Bu₂} (1 mM) and **1a** (10 mM). The absorption spectrum of PC⁻ (—), generated by spectroelectrochemistry (see Figure 3). The spectrum shown in red (—) is generated by adding the spectrum at 2.5 µs (—). B TA spectrum (—) taken 5.2 µs after photoexciting (440 nm) a CH₂Cl₂ solution of PC (0.1 mM), Pi^{Bu₂} (1 mM) and MesSH (10 mM). TA spectrum (—) obtained after photolysis ($\lambda_{exc} = 355 \text{ nm}$) of a CH₂Cl₂ solution of MesSSMes (1 mM). The absorption spectrum of PC⁻ (—), generated by spectroelectrochemistry (see Figure 3). The spectrum shown in red (—) is generated by adding the spectrum of PC⁻ (—), generated by spectroelectrochemistry (see Figure 3). The spectrum (—) taken 5.2 µs after photoexciting (440 nm) a CH₂Cl₂ solution of PC (0.1 mM), Pi^{Bu₂} (1 mM) and MesSH (10 mM). TA spectrum (—) is generated by adding the spectrum of PC⁻ (—), generated by spectroelectrochemistry (see Figure 3). The spectrum shown in red (—) is generated by adding the spectrum of PC⁻ (—) and MesS• (—); this spectrum reproduces the TA spectrum at 5.2 µs (—).

photosensitizer is its weak excited state absorption together with the weak absorption of the CQH• photoproduct in the 400 to 600 nm spectral range (Figure S7), thus allowing for baseline-free detection of the radical signature of **1a** \cdot at $\lambda_{max} = 435$ nm (Figure 2A, green line). To further confirm that the spectral feature has N• parentage, we examined the photoreaction of CQ with 3, which is an analog of 1a without the olefin functionality, for which the cyclization step is impossible (Scheme 3). The TA spectrum recorded after 2.5 µs laser excitation ($\lambda_{exc} = 355 \text{ nm}$) of a solution of either PC + Pi^{Bu2} + 3 (Figure S8a) as well as CQ + Pi^{Bu_2} + 3 (Figure S8b) is the same as that obtained when 1a is the substrate, confirming that the spectral feature at 435 nm belongs exclusively to the amidyl radical species. As shown in Figure 2A, the sum (red line) of the PC/PC⁻ difference spectrum (Figure 2A, orange line) and the 1a. spectrum (Figure 2A, green line) matches the TA spectrum (Figure 2A, black line) obtained for solutions of PC, Pi^{Bu2} and 1a, confirming that PC* reacts with 1a in the presence of base by photoinduced electron transfer to form PC⁻ and **1a**.

Figure 2B shows the results of a similar series of experiments for



Figure 3. UV-vis spectroelectrochemistry of PC and reduced PC⁻ in CH₂Cl₂. Applying a potential of -1.66 V vs Fc/Fc⁺ converts PC (—) into PC⁻ (—). The difference extinction coefficient (—) between PC and PC⁻ is shown according to the right axes. Inset: CV of a solution of PC (0.2 mM) in CH₂Cl₂ with 0.1 M TBAPF₆ at a scan rate 0.01 V s⁻¹ and referenced vs Fc/Fc⁺.



the PC + MesSH + Pi^{Bu}₂ quenching reaction in CH₂Cl₂. The TA spectrum for the MesS• (Figure 2B, purple line) was independently obtained from laser excitation (λ_{exc} = 355 nm) of di-(2,4,6-trime-thylphenyl) disulfide, MesSSMes, in CH₂Cl₂ (Figure 2B); the absorption at λ_{max} = 493 nm is characteristic of arylthyil radicals.^{53,54} The sum (Figure 2A, red line) of the PC/PC⁻ difference spectrum (Figure 2B, orange line) and the MesS• absorption spectrum (Figure 2B, purple line) perfectly matches the TA spectrum (Figure 2B, blue line) obtained for PC + Pi^{Bu}₂ + MesSH, confirming that PC* in the presence of base is quenched by MesSH in an photoinduced electron transfer event.

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Figure S9 summarizes the absorption spectra of the key photoredox intermediates, PC⁻, **1a**• and MesS• and shows their difference molar absorptivity coefficients, which are valuable for modelling transient absorption kinetics (*vide infra*). The difference extinction coefficient for PC⁻ was determined from the spectroelectrochemical spectrum in which a sufficient number of Coulombs were passed to ensure complete conversion to PC⁻. The difference extinction coefficient for **1a**• was determined from TA spectrum at 2.5 µs after photoexcitation ($\lambda_{exc} = 355$ nm) of a solution of PC + **1a** + Pi^{Bu2}. At this early time, PC⁻ and **1a**• are generated in equimolar amounts by the PCET quenching. Therefore, the difference extinction coefficient of **1a**• is provided by deconvoluting the signal into the signal of PC⁻ and **1a**•, and then referencing to the molar absorptivity of PC⁻. The same method furnishes the difference extinction coefficient for MesS• shown in Figure S9.

Figure S10 displays the TA spectra recorded on solutions containing PC + $Pi^{B\upsilon_2}$ + MesSH in the presence of either 1a or 3. At long times after excitation (21.5 μs), a significant signal arising from MesS• is observed. The Stern-Volmer quenching results indicate that the amount of MesS• generated by quenching PC* with MesSH is insignificant (owing to the dominance of substrate quenching arising from its higher concentration ([1a] = 10 mM, [MesSH] = 2

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Figure 4. Single wavelength kinetic traces recorded at 425 nm after photoexcitation (355 nm) of a solution of PC, Pi^{Bu}₂ and **3** in the absence ($^{\circ}$, experimental data; —, fit) and presence ($^{\circ}$: experimental data, —: model fit) of MesSH, compared to a solution of PC, Pi^{Bu}₂, substrate **1a** in the absence ($^{\circ}$: experimental data, —: model fit) and presence ($^{\circ}$: experimental data, —: model fit) and presence ($^{\circ}$: experimental data, —: model fit) of MesSH. Inset: early time dynamics. Note, the orange and green traces are overlapped with each other.

mM) and larger quenching rate constant k_q). Accordingly, the observation of MesS• at long times is indicative of reactions subsequent to the substrate quenching reaction with PC*. It is noteworthy that the production of MesS• is more prevalent when the substrate is 1a than 3, presaging its important role in the complete photoredox hydroamidation process.

Kinetics Rate Constants for the Photoinduced Catalytic Hydroamination Cycle. Because substrate 3 eliminates the possibility of cyclization, it isolates the reaction kinetics for generation of the amidyl radical and its return to the amide reactant by BET or HAT (with MesSH). The single wavelength kinetic trace of the amidyl radical **3**• monitored at 425 nm after photoexcitation ($\lambda_{exc} = 355$ nm) of a solution of PC + Pi^{Bu_2} + 3 was measured first in the absence of MesSH to allow the BET kinetics between the amidyl radical and PC⁻ to be defined without interference of cyclization. The monitoring wavelength of 425 nm was selected slightly to the blue of the maximum absorption of the radical so as to be outside the window of residual PC* emission. In the absence of a hydrogen atom donor, the decay of the TA signal in Figure 4 (red trace) is a result of the BET reaction between PC⁻ and 3• and accordingly is governed by bimolecular kinetics. Fitting the decay trace (see SI) furnishes $k_{BET} =$ $7.4 \times 10^9 \,\mathrm{M^{-1} s^{-1}}$. The green trace in Figure 4 is the observed decay of the amidyl radical when MesSH is added to the reaction mixture. The faster disappearance of the amidyl radical 3. in the presence of MesSH is a consequence of HAT between the amidyl radical and MesSH to produce 3 and the thiyl radical MesS• species. The retrieved rate constant of $k_{\text{HAT1}} = 7.9 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ is in the range of reported values for HAT between amidyl radicals and thiols.⁵⁵ We note that though k_{HAT1} is two orders of magnitude slower than k_{BET} , the former reaction pathway is manifest in the photocycle owing to the high concentration of MesSH (2 mM) in the reaction mixture.

Next, we explored the contribution of the cyclization reaction (in the absence of MesSH) to the decay kinetics by examining the kinetic trace at 425 nm of a solution of PC + Pi^{Bu_2} + 1a. We observe a marginally faster decay signal compared to the same solution containing substrate 3. This difference is attributed to the presence of the cyclization reaction pathway, which also consumes 1a• (Figure 4, blue trace). Kinetics analysis with the added contribution of the unimolecular cyclization reaction furnishes a cyclization rate constant $k_c = 2.4 \times 10^4 \text{ s}^{-1}$.

After cyclization, the radical product 2a. can engage in two reactions: (i) HAT with MesSH to give the hydroamidation product 2a and MesS•, and (ii) PCET with PC⁻, HPi^{Bu2} to regenerate PC:Pi^{Bu2} and produce 2a. We were able to extract the rate of HAT between 2a and MesSH by following the appearance of MesS•, which was fitted to a value of $k_{\text{HAT2}} = 1.8 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$. Although this rate is subject to error because of the low signal of MesS. at the later stages of the reaction, the fitted number is consistent with reported rate constants of HAT between thiols and secondary alkyl radicals, which are well documented to be in the order of 10⁸ M⁻¹ s⁻¹.⁵⁶ We cannot determine the rate of the PCET between PC⁻, HPi^{Bu2} and **2a** • because **2a** • does not exhibit an appreciable visible absorption signature. Nonetheless, we believe that the this PCET reaction is minor as compared to HAT because the concentration of PC⁻ is significantly lower than that of MesSH, such that $k_{PCET3}[PC^{-}] \ll k_{HAT2}[MesSH]$. In evidence of the insignificance of this pathway, no product is observed in the absence of MesSH.

The MesS•, generated from both HAT reactions involving **1a**• and **2a**•, may react with PC⁻ and HPi^{Bu}₂ by PCET to complete the photocycle. Fitting the decay of MesS• formed after photoexcitation ($\lambda_{exc} = 355 \text{ nm}$) of a solution of PC + Pi^{Bu}₂ + **3** + MesSH yields a rate constant of $k_{PCET2} = 5.4 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ for the reaction of MesS• with PC⁻ in the presence of HPi^{Bu}₂.

The orange trace in Figure 4 shows the decay at 425 nm of the complete system, i.e. PC + Pi^{Bu₂} + **1a** + MesSH and as a reference in the absence of cyclization, PC + Pi^{Bu₂} + **3** + MesSH (Figure 4, green trace). The decay traces for both solutions are identical, a result that is in line with a cyclization rate constant that is small as compared to k_{BET} and k_{HAT1} . The rate constants and standard deviations from fits of the time-dependent data are listed in Table S2.

DFT Calculations. Further support for the assignment of the visible absorption features observed in the nanosecond transient absorption measurements is offered by time-dependent density functional theory (TD-DFT). Figure 5 shows the absorption line spectrum of **1a**• calculated from TD-DFT. After Gaussian broadening (see methods) and scaling of the simulated spectrum of **1a**• by a factor of 0.47, we observe excellent agreement with the experimentally deduced absorption spectrum. As expected for an aliphatic carbon radical, cyclized radical **2a**• absorbs almost exclusively in the UV spectral region, inaccessible to our laser excitation wavelength (Figure 5). We can therefore confidently exclude cyclized radical signatures in our transient absorption data and subsequent photoinduced chemistry of the cyclized radical species.

The cyclization reaction of **1a**• to **2a**• was also investigated using DFT calculations (Figure 6A). The product radical **2a**• is lower in energy by $\Delta G_{\text{stab}} = 3.5 \text{ kcal mol}^{-1}$ compared to **1a**•, indicating a thermodynamically favorable reaction. However, the transition state for the cyclization is energetically uphill by $\Delta G^{\dagger} = 12.57 \text{ kcal mol}^{-1}$, which translates to a cyclization rate constant of $k_{c,\text{DFT}} = 3.75 \times 10^3 \text{ s}^{-1}$, in good agreement with the experimental value of $2.4 \times 10^4 \text{ s}^{-1}$ as measured by TA kinetics. The associated rate constants for the reverse cyclization (**2a**• \rightarrow **1a**•) computes to 10.2 s^{-1} , rendering the intramolecular cyclization essentially irreversible. To examine the effect of the para substituent on the cyclization rate, the activation barriers were calculated for the following para-substituted groups: – NO₂, –CN, –CF₃, –H, –Br and –OMe and correlated with the corresponding Hammett parameter, i_p (Figure 6B, top).⁵⁷ We find a gen



Figure 5. Simulated absorption line spectrum for **1a**• and **2a**• (orange and blue, respectively, right y-axis) overlaid with the experimentally retrieved **1a**• spectrum (black, left y-axis). Simulated absorption line spectra were scaled by 0.47 and broadened to 0.25 eV (2016 cm^{-1} , at half-width half height) to match the amplitude of the experimentally retrieved **1a**• spectrum (orange and blue shaded, left y-axis).

eral decrease in ΔG^{\dagger} for increasing strength of the electron withdrawing substituents. The decreased activation barrier directly translates into a faster cyclization rate with the fastest calculated rate constant for NO₂ ($k_c^{NO_2} = 2.2 \times 10^5 \text{ s}^{-1}$) and the slowest calculated rate constant for OMe ($k_c^{OMe} = 3.2 \times 10^1 \text{ s}^{-1}$). The observed trend for the activation barrier is mirrored in the trend for the stabilization Gibbs free energy of the product radical compared to the substrate radical (Figure 6B, bottom).

Disulfide Trapping. With the insights provided by the kinetics measurements, we sought to trap the photogenerated amidyl radical to minimize its back reaction with PC⁻. Energetic considerations led us to deliver a masked MesS• to amidyl radical **1a**• by reacting MesSSMes with **1a**• to form the thioamide species **4** via the equilibrium depicted in Scheme 4. DFT calculations show that the energy difference for the reaction between **1a**• and MesSSMes to produce **4** and MesS• is slightly favorable at $\Delta G^0_{DFT} = -1.19$ kcal mol⁻¹. A more favorable reaction is obtained for **1b** ($\Delta G^0_{DFT} = -2.59$ kcal

Scheme 4



mol⁻¹) indicating the thioamide to be a stronger trap with an equilibrium that remains thermally accessible. We therefore investigated the photoredox hydroamidation cycle employing MesSSMes in place of MesSH.

The single wavelength kinetic trace at 425 nm after photoexcitation (λ_{exc} = 440 nm) of a solution of PC + Pi^{Bu}₂ + MesSSMes + **1a** showed a higher concentration of both **1a**• and MesS• after 21.5 µs (Figure 7). Photoexcitation was conducted at 435 nm or 440 nm to avoid direct photolysis of MesSSMes; unlike photoredox cycles relying on direct photolysis of the disulfide,²¹ direct photolysis is negligible at 380 nm. Indeed, based on the extinction coefficients of PC and MesSSMes at 380 nm (Figure S11), only ~5% of the incident photons are absorbed by MesSSMes and at 435 nm, MesSSMes does not absorb light. In view of the similar quantum efficiencies for 435 nm (13.9%) and 380 nm (11.9%) excitation, direct photolysis of disulfide is not responsible for the production of MesS• observed in Figure 7.

To define the role of thioamide **4** in the photocycle, the photoredox chemistry was performed with **4** as the only potential source of amidyl radical. The thioamide was prepared through the sequence of reactions consisting of deprotonation of **1a** with 1 equiv of NaH followed by addition of MesSCl. When solutions of PC + MesSH + **4** were photolyzed, **1a** and **2a** are quantitively produced (in a 1:0.2 ratio). Direct irradiation of **4** in the presence or absence of PC leads to an intractable mixture of products over hours with negligible formation of **2a**, thereby confirming that the amidyl radical/thioamide equilibrium of Scheme 4 results in a clean conversion cycle.

The reaction between PC⁻ and MesSSMes was examined as a possible side reaction. Figure S3 shows the CV for the electrochemical reduction of PC in the presence of MesSSMes. A S-waveform is



Figure 6. Calculated cyclization reaction properties. (a) Reaction diagram depicting the cyclization $1a \rightarrow 2a$ with associated optimized structures. Values in parentheses are relative Gibbs free energies in kcal mol⁻¹. The inset illustrates the ring-delocalization of the nitrogencentered radical in the singly-occupied molecular orbital. (b) Computed Gibbs free energy activation barriers (top, black circles) and linear fit (top, orange, dashed) and product stabilization Gibbs free energies (bottom) for different para-substituents on the phenyl ring correlated with the Hammett parameter, σ_p . The R² values for the linear fits are also shown. ACS Paragon Plus Environment



Figure 7. TA decay trace (—) recorded at 425 nm after photoexciting (λ_{exc} = 440 nm) a solution of PC (0.1 mM), Pi^{Bu₂} (1 mM), **1a** (10 mM) and MesSSMes (1 mM). The normalized blue trace (—) is from Figure 4, which results from photoexciting (λ_{exc} = 355 nm) a solution of PC (0.1 mM), Pi^{Bu₂} (1 mM) and **1a** (10 mM). Inset: TA spectra taken at 21.5 µs after photoexcitation.

observed, characteristic of a rate-limiting catalytic reaction that is not limited in substrate.⁵⁸ For this case, the plateau current directly yields the reaction rate constant ^{59,60} from,

$$i = FSC_P^0 \sqrt{D} \sqrt{kC_A^0}$$
(3)

where *i* represent the plateau current, F the Faraday constant, S the electrode surface, C_P^0 the PC concentration, D the diffusion coefficient of PC, *k* the rate constant of the reaction and C_A^0 the concentration of MesSSMes. The diffusion coefficient D of PC was calculated using,

$$i_p^0 = 0.446FSC_P^0 \sqrt{D} \sqrt{\frac{F\nu}{RT}}$$
(4)

where i_p^0 represent the peak current of PC in the absence of MesSS-Mes, v the scan rate, R the gas constant, and T the temperature. Rate constants were determined from eq (3) for CVs taken at scan rates of 0.02 V s⁻¹ for solutions containing PC (0.2 mM) + MesSSMes at concentrations of 2, 5, 10 mM; the averaged rate constant of $k_{cat} = 48(3) \text{ M}^{-1} \text{ s}^{-1}$ is too slow to account for the fast kinetics observed in transient absorption experiments. Thus, the observed transient and kinetics observed in Figure 7 is a direct result of the amidyl radical/thioamide equilibrium.

Discussion

Scheme 5 shows the complete photoredox hydroamidation cycle. The solid black pathway was originally identified by Knowles and co-workers,³⁵ and the results described herein are in complete agreement with this pathway. The electrochemical, quenching and transient kinetics studies reported in this study allow us to further elaborate the cycle with the addition of the red, blue and dotted pathways and all rate constants for the primary photoredox event and subsequent reactions of intermediates. The photoredox hydroamidation of substrate **1a**, despite being quantitative, proceeds with a low quantum efficiency of 4.7% (\pm 0.4) (Figure 8). Critical to the overall efficiency of the photoredox cycle are the red reaction pathways involving the photogenerated amidyl radical and its subsequent reaction kinetics.

Overall there are five critical reaction intermediates (i.e. PC* (Ir(III) photosensitizer), PC⁻ (Ir(II) photoproduct), **1a**•, **2a**• and MesS•), characterized by 7 rate constants, that define the complete catalytic cycle comprising the following steps: (i) absorption of a photon by PC to produce the excited state PC*, and (ii) PCET between PC* and the amide that is hydrogen bonded to Pi^{Bu_2} to yield an amidyl radical, HPi^{Bu_2} and the reduced species PC⁻. At this branchpoint, three separate reaction paths are available to the primary photoproducts: (iii) BET between the amidyl radical, HPi^{Bu_2} and the reduced species pC⁻ to regenerate the starting reagents, (iv) HAT between the amidyl radical and MesSH to produce the amidyl radical and MesSH species reduced radical.

Scheme 5



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Figure 8. Quantum yield values for the photoredox hydroamidation of substrates **1a** and **1b** in different reaction conditions. Pink bars correspond to non-optimized conditions (PC (2 mol%), Pi^{Bu_2} (20 mol%), MesSH (10 mol%)), while blue bars depict optimized conditions (PC (2 mol%), Pi^{Bu_2} (20 mol%), MesSSMes (10 mol%)). Error bars correspond to one standard deviation.

cycle is closed by (vii) PCET among PC⁻, HPi^{Bu2} and MesS• to regenerate PC:Pi^{Bu2} and MesSH. Alternatively, the cycle is closed directly by the PCET reaction of the C-centered radical with PC⁻ and HPi^{Bu2}. We now progress through each step of the catalytic cycle, beginning with the PCET quenching step.

Based on measured redox properties, PC* is not capable of oxidizing the substrate alone but can oxidize the amide when hydrogen bonded to a base such as Pi^{Bu2}. Such hydrogen-bonded PCET events are common for a multitude of redox-based organic transformations.^{61–64} Both steady state and dynamic quenching experiments indeed show that the PCET quenching between PC* and **1a** is efficient only when Pi^{Bu2} is present, and the PCET quenching event proceeds with a rate constant of k_q (= k_{PCET1} in Scheme 5) = 5.2 × 10⁸ $M^{-1} s^{-1}$. Additionally, the PCET nature of the quenching event is confirmed by transient absorption spectra, which shows the decay of PC* with the attendant formation of PC⁻ and the prompt formation of PCET product **1a**• upon the laser excitation of a solution of PC + Pi^{Bu2} + **1a** (Figure 2A). Importantly, the high rate of quenching confirms that the low quantum efficiency of the system is not limited by the initial photoredox event.

After photoinduced electron transfer, the amidyl radical may react by BET, HAT and cyclization defined by rate constants k_{BET} , k_{HAT1} and k_{c} , respectively, in Scheme 5. In determining these rate constants, substrate 3, which cannot cyclize, is useful as it allows the bimolecular BET reaction to be isolated. Bimolecular kinetics analysis of the red trace in Figure 4 (section G1 in SI) gives $k_{\text{BET}} = 7.4 \times$ 10⁹M⁻¹s⁻¹. When MesSH is present, back reaction to the amide starting material is enhanced by HAT, as shown by the faster decaying green trace in Figure 4. With the value of k_{BET} in hand, kinetics analysis (section G2 in SI) of the decay of the transient absorption signal for solutions of PC + $3 + Pi^{Bu_2} + MesSH$ (green trace, Figure 4) yields $k_{\text{HAT1}} = 7.9 \times 10^7 \,\text{M}^{-1} \text{s}^{-1}$. By switching to substrate **1a**, the cyclization reaction kinetics is introduced into the system. This additional kinetics pathway is reflected in a faster decay rate (blue trace, Figure 4) as compared to that for substrate **3** (red trace, Figure 4). Analysis of the blue trace using k_{BET} (section G3 in SI) directly furnishes the rate of cyclization, $k_c = 2.4 \times 10^4 \text{ s}^{-1}$. The slow intramolecular cyclization rate is a consequence of the delocalization of the unpaired electron over the phenyl group of the aniline in the amidyl radical 1a., as

highlighted by the singly-occupied molecular orbital (SOMO, Figure 6A, inset). Following cyclization, product 2a is most easily formed by HAT between 2a. and MesSH. To determine this rate constant, we monitored the transient absorption decay of a solution of PC + Pi^{Bu_2} + 1a + MesSH (orange trace, Figure 4). As the presence of the cyclization reaction consumes 1a. to form 2a., a faster decay might be expected for the system when 1a is present vs 3 (green trace, Figure 4). However, we observe almost identical decays for these two systems. This result is due to the fact that there is additional absorption arising from the presence of MesS• that is produced by HAT between the cyclized radical 2a. and MesSH. Fitting the kinetics of the decay of the orange trace with the known k_{BET} , k_{HAT1} and k_{c} rate constants (section G4 in SI) furnishes $k_{\text{HAT2}} = 1.8 \times$ $10^8 \text{ M}^{-1}\text{s}^{-1}$. Finally, the cycle is closed by PCET between PC⁻, HPi^{Bu}₂ and MesS• to regenerate PC:Pi^{Bu2} and MesSH. The kinetics for this reaction is provided by the observed decay of MesS• in the transient absorption experiment of a solution of PC + Pi^{Bu_2} +3 and MesSH. The observed decay renders a value of $k_{PCET2} = 5.4 \times 10^9 \,\text{M}^{-1} \text{s}^{-1}$ (section G2 in SI).

The rate constants of the complete photoredox cycle reveal the BET and the HAT reactions as the major non-productive pathways. The rate constants allow the concentration profiles for the intermediate species formed during the reaction to be simulated, including the product radical **2a**•. If no BET or HAT1 were present, 100% conversion of **1a**• to **2a**• is expected. When the BET pathway is added into the simulation (i.e., k_{BET} and k_c added to the simulation), we observe that only 29.6 % of **1a**• converts to **2a**•; 71.4% of **1a**• engages in BET reaction. With the addition of the HAT1 pathway to the simulation, the overall conversion yield of **1a**• to **2a**• is further reduced to 8.4%. Thus, the combination of BET and HAT1 pathways consume 91.6% of **1a**• after the initial PCET quenching event. Noting that the initial quenching event has a yield of 89.9%, the upper limit for the photoredox product quantum yield is 7.6%.

With the major loss pathways of BET and HAT1 established, we explored optimization strategies aimed at minimizing these reactions. Because the cyclization rate for 1a. is slow as compared to the BET and HAT rates (Scheme 5), we first sought to use substrates with faster cyclization rates that could kinetically compete with the fast BET and HAT reactions. The para substituent of the aniline group of **1a** provides a straightforward handle on the cyclization rate of the corresponding amidyl radical, since electron-withdrawing groups (EWG) lead to faster cyclization rate through destabilization of the π -delocalized amidyl radical.⁶⁵ DFT calculations indeed support that cyclization rates correlate with the nature of the para substituent on the aniline group, with stronger EWG groups leading to increasingly faster cyclization rates due to smaller activation barrier (Figure 6B). The quantum yield for hydroamidation of the para-cyano substrate 1b into product 2b under standard photoredox conditions does indeed show an increase from 4.7(4)% to 5.8(4)% (Figure 8). However, as reflected in this modest increase in efficiency, cyclization alone is too slow to kinetically compete with the BET and HAT1 reactions.

Of the two pathways, BET is the most important to the overall efficiency of the photocycle as (i) the rate constant for this reaction is highest and (ii) it is effectively enhanced because the primary photoproducts may geminately recombine within a solvent cage.^{11,66} Accordingly, we turned our attention to directly intruding on this reaction path to markedly increase the efficiency of the photoredox cycle. In the initial quenching reaction, the concentrations of the initial photoproducts are equal and small (sub-micromolar). Since the Environment

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BET reaction is bimolecular, further reduction in the concentration of PC⁻ or amidyl radical can markedly affect the rate of the reaction. We settled on a strategy to intercept the amidyl radical by reversibly trapping it, and in doing so, removing it from the solvent cage of the primary photoproducts, thereby disrupting BET. We found that MesSSMes does not react with PC⁻ ($k = 48 \text{ M}^{-1}\text{s}^{-1}$) and is thus available to successfully trap the transient amidyl radical 1a. to form thioamide 4 via the equilibrium reaction shown in Scheme 4. Diffusion of the thioamide 4 away from PC⁻ impedes the bimolecular BET reaction. Because of the nearly thermoneutral amidyl radical/thioamide equilibrium, the amidyl radical may be released at a later stage to re-enter the catalytic cycle and undergo productive cyclization. In support of this contention, the transient absorption decay of a solution of PC, Pi^{Bu2}, MesSSMes and 1a shows a higher concentration of both 1a. and MesS. at later stages of the reaction (Figure 7). We note that independently prepared thioamide 4 in the presence of MesS. (generated by irradiation of PC and MesSH) promptly and cleanly produces a mixture of 1a and 2. Conversely, irradiation of thioamide 4, whether in the presence or absence of PC, leads to an intractable mixture of products over hours, thereby establishing that 1a. can only be cleanly generated from thioamide 4 when MesS. is present. These results further support the reversibility of the amidyl radical/thioamide reaction. By perturbing BET with the side-equilibrium involving the amidyl radical, when MesSSMes is introduced in place of MesSH, the hydroamidation quantum yield of 1a is increased to 11.9(8)%; for the faster cyclizing para-cyano substrate 1b, a quantum efficiency of 20.0(9)% is achieved.

Conclusion

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The reactions governing the quantum efficiency of the photoredox hydroamidation of olefins are elucidated by transient laser and electrochemical methods. Determination of the rate constants for the reactions involving five intermediates in the cycle identify the energy-wasting and non-productive back reaction of the photogenerated amidyl radical with the reduced photosensitizer and hydrogen

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ASSOCIATED CONTENT

Supporting Information

Synthetic details for compounds 3 and 4, ¹H NMR binding studies, additional details on quantum yield measurements, laser experiments, fitting strategies and a complete author list for ref. 49.

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Notes

The authors declare no competing financial interest.

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