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Mechanistic Investigation and Optimization of Photoredox Anti-Markovnikov Hydroamination

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ABSTRACT: The reaction mechanism and the origin of the selectivity for the photocatalytic intermolecular anti-Markovnikov hydroamination of unactivated alkenes with primary amines to furnish secondary amines have been revealed by time-resolved laser kinetics measurements of the key reaction intermediates. We show that backelectron transfer (BET) between the photogenerated aminium radical cation (ARC) and reduced photocatalyst complex (Ir(II)) is nearly absent due to rapid deprotonation of the ARC on the sub-100 ns time scale. The selectivity for primary amine alkylation is derived from the faster addition of the primary ARCs (as compared to secondary ARCs) to



s Supporting Information

alkenes. The turnover of the photocatalyst occurs via the reaction between Ir(II) and a thiyl radical; the in situ formation of an offcycle disulfide from thiyl radicals suppresses this turnover, diminishing the efficiency of the reaction. With these detailed mechanistic insights, the turnover of the photocatalyst has been optimized, resulting in a >10-fold improvement in the quantum yield. These improvements enabled the development of a scalable flow protocol, demonstrating a potential strategy for practical applications with improved energy efficiency and cost-effectiveness.

INTRODUCTION

Light-driven photoredox catalysis has emerged as a powerful strategy to perform organic synthesis under mild conditions by taking advantage of photons to generate highly reactive intermediates that are otherwise difficult to access with traditional methods.¹⁻⁷ Photoredox reactions, however, may confront back-reactions and undesired side-reactions as a result of the high reactivity of the photogenerated intermediates,⁸⁻¹¹ leading to a diminished energy efficiency.^{10,11} These backreactions must be overcome to enable the sustainable adaptation of photoredox methods, which includes the use of solar light as an energy input.^{12–14} Accordingly, photoredox catalysis performed under batch reaction conditions may require intense light sources (e.g., high-power LED lamps) and extended reaction times (e.g., days) to achieve appreciable yields of product.^{2–7} Therefore, flow setups are usually preferred^{15–17} to achieve high throughput for photocatalysis. As has been shown recently by our groups^{9-11,18,19'} and

others,²⁰⁻²⁴ detailed mechanistic studies provide critical insight for improving energy efficiency and the scope of photocatalysis methods. The formation of C-N bonds via intramolecular hydroamidation photocatalysis has particularly benefitted from the detection of reactive intermediates and an understanding of their chemistry.¹¹ Recently C-N bond formation has been achieved under mild photocatalytic conditions by hydroamination reactions between alkylamines and unactivated alkenes,^{25,26} demonstrating an atom-economic strategy to furnish both secondary and tertiary amine products. These photocatalytic hydroamination reactions have relied on photoexcited iridium complexes (Ir(III)) to oxidize amines, generating reduced photocatalyst complexes (Ir(II)) along

with aminium radical cations (ARCs). ARCs add to the alkenes in an anti-Markovnikov fashion to form product radicals²⁷ that then react with thiols through hydrogen atom transfer (HAT) to deliver the final product (Scheme 1).²⁸ The utility of this methodology has been demonstrated for the formation of tertiary amine products from their respective secondary amines with IrA (IrA = $[Ir(III)(dF(Me)ppy)_2(dtbbpy)]PF_6$ and





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dtbbpy = 4,4'-di-*tert*-butyl-2,2'-dipyridyl) as the photocatalyst (Figure 1C).²⁵ Strikingly, when the analogous reactions are



Figure 1. Product yields and selectivity achieved by different photocatalysts for photoredox hydroamination reactions starting from (A) primary amine 1 and (B) secondary amine 2. (C) Structures and redox potentials of IrA and IrB photocatalysts and HAT catalyst (TripSH). The redox potentials are referenced to Fc^+/Fc .

performed on primary amines with a stronger photooxidant IrB (IrB = $[Ir(III)(dF(CF_3)ppy)_2(4,4'-d(CF_3)bpy)]PF_6)$, the secondary amine products are selectively obtained with little over-reaction to produce tertiary amines (Figure 1A).²⁶ Such photocatalyst-dependent chemoselectivity is intriguing and provides an imperative for a detailed mechanistic understanding to improve the photochemical efficiency and enable a scalable protocol for large-scale synthesis.

Here, we present comprehensive mechanistic studies to uncover the origins of this chemoselectivity, as such insight aids in further reaction development, optimization, and application. We find that the chemoselectivity for the formation of secondary amine originates from the faster addition of the primary ARCs to the alkenes as compared to secondary ARCs. We have identified that rapid deprotonation of the ARCs, arising from their augmented acidity compared to the parent amine, is a significant nonproductive side-reaction. In addition, two critical intermediates (Ir(II) and thiyl radical) have been observed and found to be essential to the turnover of the photocatalyst and, hence, the overall reaction efficiency. With these mechanistic insights, an optimization strategy has been developed to improve the reaction efficiency, which enables relatively large-scale syntheses under scalable flow conditions for practical synthetic applications.

EXPERIMENTAL SECTION

General Considerations. All samples were prepared in a N_2 -filled glovebox unless otherwise stated. Solvents were dried with 3 Å preactivated molecular sieves. All commercial chemicals were purchased from Sigma-Aldrich or TCI Chemicals and used as received. Photoreagents and model substrates for mechanistic studies were synthesized (section A, Supporting Information) with their purity verified by NMR spectroscopy. For batch reactions, the solution was typically placed in a 2-dram glass vial, which was then sealed with electrical tape and illuminated with a single blue LED Kessil lamp (PR160-440 nm) under constant stirring and fan cooling (Figure S1A). The flow experiments were performed by using a custom flow setup with two Kessil lamps illuminating the reaction tubing from both sides (Figure S1B). UV-vis absorption spectra were obtained by using a Cary 5000 spectrophotometer (Agilent). NMR spectra were obtained by using a Bruker Avance Neo (400 MHz) spectrometer. The product yields were determined by gas chromatography (GC, Agilent 5975C) with dibenzyl ether as the internal standard. Isolated yields were obtained for large-scale reactions (section M, Supporting Information).

Quenching Studies. Steady-state emission spectra were measured by using a QM4 fluorometer (Photon Technology International). Steady-state quenching studies were performed by using the averaged steady-state emission intensity (*I*) ranging from 550 to 600 nm, with excitation at 400 nm. Dynamic quenching studies were based on lifetimes (τ) measured by the emission decay at 600 nm with pulsed excitation at 355 nm. The Stern–Volmer quenching constant ($K_{\rm sv}$) and quenching rate constant ($k_{\rm q}$) were obtained by using the relations I_0/I or $\tau_0/\tau = 1 + K_{\rm sv} \times$ [quencher] and $k_{\rm q} = K_{\rm sv}/\tau_0$, where I_0 and τ_0 are the emission intensity and emission lifetime, respectively, for a sample in the absence of quencher.

Electrochemical and Spectroelectrochemical Studies. All electrochemical studies were performed by using a Model 760D potentiostat from CH Instruments. Cyclic voltammetry (CV) measurements were undertaken by using a glassy carbon working electrode, Pt wire counter electrode, and Ag^+/Ag reference electrode on solutions purged with N₂. All CVs were referenced to the ferrocenium/ferrocene (Fc⁺/Fc) redox couple measured under the same conditions. Spectroelectrochemical measurements were performed in a N₂-filled glovebox and under similar conditions as above, except that a thin Pt mesh working electrode was placed into a 0.5 mm path length cuvette. The absorption spectra under an applied potential were obtained by using an Ocean Optics spectrometer and OceanView software.

Quantum Yield Measurement. The quantum yield (QY) was measured by using a custom setup. Monochromic light was generated by a Kessil lamp (PR160-440nm) and a 435 nm band-pass filter (FWHM = 10 nm). Passing through a lens (f = 40 nm), the light was focused onto the reaction solution (Figure 1A), which was contained in a 1 cm cuvette. The QY was determined via the following equation:

$$QY = \frac{\text{number of product molecules}}{\text{number of photons absorbed}} = \frac{cV}{\phi t}$$
(1)

where c is product concentration, V is the volume of the reaction solution, ϕ is the photon flux, and t is the reaction time. For each QY measurement, 1.2 mL of the reaction solution was used. The reaction time (t) varied from 30 to 300 min depending on the reaction rate. The photon flux was calibrated to be 2.56×10^{-7} mol/s (corresponding to a power of 62.1 mW) based on a published procedure.²⁹ The product concentration (c) was determined by GC with dibenzyl ether as an internal standard.

Time-Resolved Laser Spectroscopy. The laser spectroscopic setup was described in detail previously.³⁰ Excitation pulses at 355 nm were generated by a Quanta-Ray Nd:YAG laser (SpectraPhysics) with a repetition rate of 10 Hz and a pulse width of ~8 ns. Continuous white light, generated by a xenon-arc lamp (PTI, Model A1010), was used as the probe for the transient absorption (TA) measurements. To measure the time-resolved emission decay, the excitation laser beam was focused onto the sample contained in a 1 cm path length cuvette. The resulting emission was collected by a pair of lenses (f =20 cm), passed through a monochromator (Triax 320) to select the wavelength, and then detected with a photomultiplier tube (PMT). To measure the TA kinetics, the sample was flowed through a 2 mm path length micro flow cell (Starna Cells 583.65-Q-2/Z15), and both excitation and probe beams were focused onto the same spot on the sample. The transmitted probe beam was directed to the spectrometer and detected by the PMT. The signal of the PMT was recorded on a 1 GHz oscilloscope (LeCroy, Model 9384CM). To measure the broadband TA spectra, the probe beam passing through the spectrometer was detected by a CCD camera (Andor Technology).

Custom software was used for controlling the apparatus and data processing. Details of TA data analysis are provided in section B of the Supporting Information.

RESULTS

Hydroamination Selectivity. Figure 1A shows the results for the reaction between cyclohexylamine (1) and methylene-cyclopentane, with the **IrB** photocatalyst. As previously observed,²⁶ the secondary amine (2) is the predominant product. To further confirm this chemoselectivity, the secondary amine product (2) was subjected to the same photoreaction conditions with the **IrA** and **IrB** photocatalysts (Figure 1B). We note that the oxidizing power of the photoexcited ***IrB** relative to ***IrA** $(E_{1/2}(\text{IrB}(*\text{III}/\text{II})) = 1.27 \text{ V}$ and $E_{1/2}(*\text{IrA}(\text{III}/\text{II})) = 0.59 \text{ V})^{26}$ is greater, and thus ***IrB** should be able to photogenerate the secondary ARCs (step 1, Scheme 1) with greater facility. Nevertheless, the tertiary amine **3** is obtained in only 20% yield for **IrB**, whereas a product yield of 87% is obtained for the **IrA** photocatalysts (Figure 1B).

Quenching Rate and Solvent Dependence. To assess the reactivity of *IrB with primary and secondary amines (step 1, Scheme 1), Stern–Volmer quenching experiments were performed on IrB in various solvents in the presence of 1, 2, or TripSH (TripSH = 2,4,6-triisopropylbenzenethiol) (Figure 2A and Figures S2–S4). In 1,4-dioxane, 1 displays a quenching rate constant, k_{qr} comparable to that of TripSH, whereas 2 displays a k_q that is 2–3 times larger. In addition, quenching by



Figure 2. (A) Stern–Volmer quenching rate constant for the excited state ***IrB** by substrates **1**, **2**, and TripSH in benzonitrile (PhCN), 1,4-dioxane, and isopropyl acetate (ⁱPrOAc). Primary amine **1** exhibits an enhanced quenching rate in 1,4-dioxane and ⁱPrOAc. (B) ¹H NMR spectra of 20 mM substrate **1** in benzene- d_6 with various concentrations of 1,4-dioxane. The dashed gray box highlights the peak broadening and shift for the protons on the NH₂ group, indicating their H-bonding with 1,4-dioxane.

TripSH showed no appreciable increase in the presence of amine (Figure S5). Surprisingly, the quenching of primary amine 1 exhibits a solvent dependence whereas the secondary amine 2 and TripSH did not (Figure 2A). The 4-5-fold increase in k_q for the quenching of 1 from benzonitrile (PhCN) to 1,4-dioxane and isopropyl acetate (PrOAc) is also accompanied by a significant increase in the product yield of 2 (26% in PhCN, 76% and 79% in 1,4-dioxane and PrOAc, respectively) (Table S1, entries 1 and 2). To gain further insight into this solvent-dependent quenching behavior, ¹H NMR spectra of 20 mM 1 were measured in the presence of various concentrations of 1,4-dioxane. The broadening and shift of the NH₂ peak likely suggest a H-bonding interaction between 1 and 1,4-dioxane (Figure 2B). Under similar conditions, much less broadening and peak shift were observed for diethylamine (Figure S6). Nevertheless, the quenching of the *IrB by the secondary amine is higher than by the primary amine, suggesting that the secondary amine product may inhibit the primary amine reaction upon its formation in situ. To test this inhibition effect, we performed the primary amine hydroamination reaction with and without 20 mol % 2 as shown in Table S1. A dramatically attenuated initial rate was observed after 1 h of illumination in the presence of pre-added product 2 (35% yield compared to 64% yield without secondary amine product 2, entries 5 and 6, respectively).

Back-Electron Transfer, Deprotonation, and Addition. The stronger quenching of *IrB by 2 than by 1 (Figure 2A) suggests that the selectivity for the primary amine (Figure 1A) cannot result from the differences in the generation of the ARCs by excited-state electron transfer (step 1, Scheme 1). We therefore turned our attention to probing the back-electron transfer (BET) between the ARCs and the reduced photocatalyst, IrB(II), by examining the TA spectrum upon laser photoexcitation. Because of a weak long-lasting background signal after photoexciting IrB in 1,4-dioxane (Figure S7A), all TA spectroscopic studies were performed in ⁱPrOAc, in which *IrB decays completely to the ground state ($\tau_0 = 212$ ns) (Figure S7B) while maintaining similar yields and chemoselectivities as observed in 1,4-dioxane (Table S1, entry 2). Figure 3A shows the TA spectrum ($\lambda_{exc} = 355$ nm) when 200 mM substrate 1 or 100 mM substrate 2 is added to a 'PrOAc solution of 0.2 mM IrB. The high concentration of substrate ensures that *IrB is efficiently quenched, allowing a sufficient concentration of the quenching products to be captured in the TA spectrum. The formation of IrB(II) is observed immediately after initial quenching, indicating the oxidation of the amine substrates. However, TA features of ARCs $(1^{\bullet+} \text{ or }$ 2^{•+}) are not detected as these species absorb in the UV region $(<300 \text{ nm})^{31}$ which is beyond the detection range of our instrument. The spectrum of IrB(II) was confirmed independently by spectroelectrochemistry (Figure S8C). Surprisingly, IrB(II), probed at 520 nm, shows no appreciable decay up to 450 μ s after the initial quenching event (Figure 3A, inset). Similarly, when *IrA was quenched by the secondary amine 2, the resulting IrA(II) signal also remained for a long time (Figures S8C and S9). These results indicate that BET between IrA(II) or IrB(II) and the primary or secondary ARCs is insignificant.

The insignificant BET may result from a fast deprotonation of the ARCs. To further verify the deprotonation pathway, we performed a photoredox deuteration reaction using the conditions shown in Figure 3B based on a published method.³² We found 37% deuteration on the C_{α} of substrate 1 and 90%



Figure 3. (A) TA spectra at 2.5 μ s of a solution containing 0.2 mM **IrB** and 200 mM primary amine 1 (black) or 100 mM secondary amine 2 (blue). The inset shows the corresponding kinetic traces probed at 520 nm exhibiting nearly no decay, suggesting the absence of direct BET between photogenerated intermediates. (B) Deuteration reactions under photoredox conditions suggest that deprotonation can happen at the C_{av} where the deuterated product yields are shown accordingly. (C) TA spectra at 2.5 μ s of a solution containing 0.2 mM **IrB** and 200 mM substrate 1 in the absence (black) and presence (red) of 50 mM 1,1-diphenylethylene. The arrow highlights the TA feature centered at 329 nm, showing the intermediate after ARCs (1⁺⁺) add to 1,1-diphenylethylene. The addition kinetics (probed at 329 nm) are shown in the inset with various concentrations of 1,1-diphenylethylene. Different slopes (k_{prod}) suggest that 1⁺⁺ adds to alkenes more effectively than 2⁺⁺.

deuteration on both two C_{α} 's of substrate 2 based on the ¹H NMR spectra (Figure S10). In addition, on the basis of the oxidation potential and the bond dissociation energy (BDE), we estimated the $pK_a(NH)$ and $pK_a(C_{\alpha}H)$ of ARCs (Scheme S1 and section K in the Supporting Information). With ethylamine as an example, $pK_a(NH)$ and $pK_a(C_{\alpha}H)$ were calculated to be 14 and 6 in MeCN (Scheme S1A), respectively, significantly lower than the pK_a of ethylamnonium ($pK_a = 18$). For diethylamine, $pK_a(NH)$ and $pK_a(C_{\alpha}H)$ were calculated to be 20 and 15 (Scheme S1B), respectively, in contrast to a pK_a of 19 for diethylammonium.

The addition of ARCs to alkenes (step 2, Scheme 1) was probed by TA spectroscopy using solutions containing IrB, primary amine 1, and 1,1-diphenylethylene. Figure 3C shows the TA spectra obtained at 2.5 μ s for solutions containing 0.2 mM IrB and 200 mM 1 with and without 50 mM 1,1diphenylethylene. An additional TA feature at ~330 nm was observed for the solution with 1,1-diphenylethylene (Figure 3C, red) when compared to the one without (Figure 3C, black). This 330 nm feature is characteristic of the corresponding diphenylmethine radical³¹ resulting from the addition of ARC to the olefin (step 2, Scheme 1). Control experiments show that 1,1-diphenylethylene itself does not quench *IrB (Figure S11A) or contribute to the TA spectrum observed in Figure 3C (Figure S11B). To gain further kinetic information about the addition process, single-wavelength TA traces were monitored at 329 nm, where IrB(II) shows an isosbestic point with the spectrum of IrB(III) (Figure S8B). However, because of the residual signal of *IrB and potential scattering, the TA traces show a background signal up to ~ 200 ns (Figure S12, black trace). To remove this background signal, the TA trace for the solution without 1,1-diphenylethylene (0.2 mM IrB and 200 mM 1) was subtracted from the TA traces for similar solutions containing 1,1-diphenylethylene (Figure S12). The background-corrected TA traces are shown in the inset of Figure 3C. The product signal at 329 nm emerges at ~100 ns and increases with increasing concentrations of 1,1-diphenylethylene (12, 24, and 36 mM). However, no clear rising feature was observed before 100 ns (Figure 3C, inset). These results suggest that the deprotonation of the ARCs occurs extremely fast on the sub-100 ns time scale. Because of the fast deprotonation, residual signal of *IrB, and scattering, we were unable to measure the addition rate constant for the ARCs. Because deprotonation can occur from both $C_{\alpha}H$ and NH groups (Scheme S1), tert-butylamine, which does not possess C_{α} -hydrogens, was also used to study the addition process. Similar results were obtained showing that the product radicals emerged at ~ 100 ns (Figure S13) with no clear rising features below 100 ns. These results indicate that deprotonation occurs primarily from the NH group for primary amines.

Figure 3D plots the signal of the addition product (average signal from 200 ns to 2.0 μ s at 329 nm for traces in the inset of Figure 3C) as a function of the concentration of 1.1diphenylethylene. Linear fitting (Figure 3D, solid lines) allows for the extraction of the product radical formation rate constant (k_{prod}) as a function of concentrations of 1,1diphenylethylene, which effectively reflects the addition rate of the ARCs. As shown in Figure 3D, k_{prod} was found to be ~75 times higher for primary ARCs (1^{•+}, $k_{\text{prod}} = 166.5 \pm 5.3 \text{ mOD/M}$) than for secondary ARCs (2^{•+}, $k_{\text{prod}} = 2.2 \pm 0.2$ mOD/M). Therefore, the selectivity for primary amine (Figure 1A) correlates with a faster addition rate of the primary ARCs. Accordingly, any other photocatalyst that can oxidize primary amine should show a selectivity similar to that of IrB. Indeed, this is the case. When a metal-free organic photocatalyst, MesAcr (MesAcr = 9-mesityl-3,6-di-tert-butyl-10-phenylacridinium tetrafluoroborate and $E_{1/2}$ (MesAcr*/MesAcr⁻) = 1.68 V vs Fc⁺/Fc),³³ was used, the primary amine reaction proceeds with similar chemoselectivity as that observed for IrB photocatalyst (Table S1, entries 3 and 4).

Photocatalyst Turnover Mediated by a Thiyl Radical. To close a photocatalytic cycle, the reduced photocatalyst Ir(II) must return to Ir(III) (Scheme 1). To assess whether TripSH can facilitate the regeneration of the Ir(III) photocatalyst, TA studies were performed on a solution containing 0.2 mM IrB, 100 mM 2, and 30 mM TripSH (Figure 4). The TA spectrum at 200 ns in Figure 4A shows a prominent signal



Figure 4. (A) TA spectra of a solution containing 0.2 mM IrB, 100 mM substrate 2, and 30 mM TripSH. (B) TA kinetics probed at 520 nm for a solution containing 100 mM substrate 2, 30 mM TripSH, and 0.2 mM photocatalyst IrA or IrB. The faster decay for the solution with IrA compared to that with IrB indicates a faster photocatalyst turnover (see text). The scatter plots show the experimental data, and the solid lines show the model fittings (section B, Supporting Information), which allowed for the extraction of the rate constant ($k_{\rm ET}$) for the reaction between Ir(II) and TripS[•].

at 490 nm in addition to IrB(II) features at 385 and 520 nm. Laser excitation at 355 nm of a 15 mM $Trip_2S_2$ solution produces the same TA feature (Figure S14A), establishing $TripS^{\bullet}$ as the origin of the 490 nm transient absorption. Additionally, the IrB(II) features decayed significantly for the solutions containing TripSH (Figure 4A), in contrast to the case when TripSH is absent (Figure 3A). These results implicate the reaction of $TripS^{\bullet}$ with IrB(II), likely with a subsequent proton transfer to re-form IrB(III) and TripSH.²⁶ Accordingly, the reaction involving thiyl radical opens another pathway to turn over the photocatalyst, which would otherwise persist as IrB(II) (Figure 3A).

The decay of the TripS[•] at 490 nm occurs on a faster time scale than IrB(II) (Figure 4A). After 100 µs, TripS[•] completely disappears whereas ~28% IrB(II) remains. The faster decay of TripS[•] is likely due to its dimerization to form disulfide Trip₂S₂. When IrB is replaced with IrA (0.2 mM IrA, 100 mM 2, and 30 mM TripSH), similar spectral profiles are observed, albeit with faster decay kinetics (Figure S15). To compare the indirect BET between $\text{Trip}S^{\bullet}$ and the reduced photocatalyst (IrA(II) or IrB(II)), single-wavelength TA traces were probed at 520 nm (Figure 4B). Consistent with the spectral evolution, the TA traces show that IrA(II) decays faster than IrB(II). On a longer time scale (>100 μ s), the TA traces do not decay to zero (Figure 4A and Figure S15) as a result of the prevalence of Ir(II) resulting from the formation of the disulfide. To quantify the kinetics of the ET reaction between Ir(II) and TripS[•], TA studies were performed on a solution containing 0.2 mM IrB, 100 mM pyridine, and 30 mM TripSH (Figure S16), allowing us to determine the difference extinction coefficient ($\Delta \varepsilon$) of TripS[•] (Figure S16C and section B.1, Supporting Information). With a known $\Delta \varepsilon$ for TripS[•] and Ir(II) (Figure S8C), we extracted the ET rate constants $(k_{\rm ET})$ of $(2.1 \pm 0.1) \times 10^{10}$ and $(8.1 \pm 0.1) \times 10^{9}$ M^{-1} s⁻¹ for IrA(II) and IrB(II), respectively (section B.2, Supporting Information).

Disulfide Formation and Accumulation of Ir(II). The formation of disulfide has a significant impact on photocatalyst turnover if it cannot be reduced by Ir(II); in this case Ir(II) will accumulate and become the resting state. This is more likely to happen for reactions with IrB due to its mild reducing potential ($E_{1/2} = -1.18$ V vs Fc⁺/Fc), which is significantly lower than the half-wave reduction potential of $\text{Trip}_2 S_2$ ($E_{p/2}$ = -2.25 V vs Fc⁺/Fc) determined by CV (Figure S17C). The TA result of residual Ir(II) in the presence of disulfide, $Trip_2S_2$, can be recapitulated with UV-vis spectroscopy of reaction solutions of IrB, which quickly turn from yellow to dark red under blue light illumination (Figure 5, inset). To quantify this color change, UV-vis absorption spectra were monitored as a function of time for the standard reaction solution (Figure 1A) contained within a screw-capped cuvette (2 mm path length). As shown in Figure 5, the absorption spectra evolve over 40 min to furnish a profile with maxima at 385 and 520 nm, which match the absorption spectrum of IrB(II) (Figure S8B). This dark red color of the IrB(II) remains stable in the sealed cuvette once generated. Subsequently exposing the solution to air causes the prompt disappearance of the dark red color as a result of the aerobic oxidation of IrB(II).

To determine whether IrB(II) can react with $Trip_2S_2$, IrB(II) was generated photochemically (Figure 5) under standard reaction conditions (Figure 1A), after which 15 mM $Trip_2S_2$ was added to the photolyzed solution. The signature absorption of IrB(II) at 520 nm showed nearly no change after



Figure 5. UV-vis absorption spectra of the primary amine reaction solution during 40 min of illumination under blue light. The reaction solution changed from an initial yellow contour to dark red, as shown by the inset, due to the accumulation of **IrB(II)**. The reaction conditions were kept identical with those shown in Figure 1A, except that the solution was stored in a 2 mm path length screw-capped cuvette for UV-vis measurements.

several hours in the dark following the addition of Trip₂S₂ (Figure S18A, dark red and orange), suggesting little to no reaction between IrB(II) and Trip₂S₂ under the standard reaction conditions. IrB(II) was also generated by shining blue light on a solution containing 0.06 mM IrB and 50 mM 2 for 1 min (Figure S18B, dark red). Adding 15 mM Trip₂S₂ in the dark to this photolyzed solution resulted in no color change. Further illumination of this solution with additional disulfide results in the disappearance of the IrB(II) (Figure S18B, pink). In contrast, when a similar experiment was performed with IrA and 2 under standard conditions (Figure 1B), IrA(II) was not observed (Figure S18C). Alternatively, IrA(II) was generated photochemically by shining blue light on a solution containing 0.1 mM IrA and 50 mM 2 for 1 min (Figure S18D, blue). Adding 15 mM Trip₂S₂ to the illuminated solution resulted in an immediate disappearance of the IrA(II) signal (Figure S18D, orange). To further confirm the reaction between IrA(II) and $Trip_2S_2$, IrA(II) was chemically synthesized by the treatment of IrA(III) with sodium amalgam (section A.4, Supporting Information). The absorption spectrum of the resulting solution (Figure S19, blue) matched that of IrA(II) obtained spectroelectrochemically (Figure S8A, blue). When Trip₂S₂ was added to this IrA(II) solution, the signature absorption feature of IrA(II) at 530 nm disappeared (Figure S19, orange). Thus, $Trip_2S_2$ can be reduced by IrA(II) but not by IrB(II).

Reaction Optimization and Flow Chemistry. Recognizing that $TripS^{\bullet}$ dimerizes to $Trip_2S_2$, which IrB(II) is unable to reduce to regenerate the ground state IrB(III), an optimization strategy was focused on increasing the concentration of TripS[•]. Under the original conditions of 1 mM IrB (Figure 1A),²⁶ the maximum possible concentration of Trip₂S₂ is 0.5 mM. Because of the limited absorption of Trip₂S₂ in the visible region (Figure S14B), this concentration does not enable TripS[•] to be generated substantially in the standard reaction condition (Figure 1A). Accordingly, reaction conditions were examined with the addition of excess $Trip_2S_2$ with the desire to increase TripS[•] upon photocleavage of the disulfide. Figure 6 summarizes quantum yields (QYs) of the secondary amine product 2 with different concentrations of thiol and/or disulfide. The QY obtained for the standard conditions of 30 mol % (15 mM) TripSH is 0.20 ± 0.02%. Replacing 30 mol % TripSH with 30 mol % $Trip_2S_2$ causes a 3× increase in the QY



Figure 6. (A) Quantum yield (QY) measurements of the primary amine reaction as shown in Figure 1A. Varying the loading of TripSH and/or Trip₂S₂ results in significant increases in the QY. Standard deviations were obtained from experiments in triplicates. (B) Optimized reaction efficiency with additional disulfide allows for large scale (50 mL, 2.5 mmol) reactions to be performed under scalable flow conditions. A binary solvent of 1,4-dioxane and 'PrOAc (80:20 vol/vol) was used to solubilize IrB. Multiple substrates were tested on a large scale to demonstrate the general applicability of the optimized reaction strategy. Isolated yields were obtained via flash chromatography of the secondary-amine-product-derived benzamide. Yields in parentheses correspond to the secondary amines or their HCl salts, obtained from acid—base treatment of the postillumination reaction mixture (section M, Supporting Information).

(0.61 \pm 0.01%), which is also higher than that obtained for 60 mol % TripSH (QY = 0.44 \pm 0.01%). With both TripSH and Trip₂S₂ at 20 mol %, the QY further improved to 1.55 \pm 0.13%, reflecting that both TripSH and Trip₂S₂ are important to the reaction efficiency. Indeed, further boosting both the concentrations of TripSH and Trip₂S₂ to 30 mol % led to a QY of 2.43 \pm 0.04%, which is 12× greater than the original reaction conditions (Figure 1A) for this photoredox process.

Further optimization examined the effect of the absence and presence of additional disulfide with reduced loadings of photocatalyst and alkene (Table S2). Under the standard conditions of Figure 1A, decreasing the photocatalyst loading from 2 mol % to 0.5 mol % slightly reduced the product yield from 75% to 67% (Table S2, entries 1–3). Under similar conditions with the addition of 30 mol % (15 mM) disulfide, the product yield increased from 70% to 81% with a concomitant decrease in the photocatalyst loading (Table S2, entries 4–6). The slightly lower product yield observed with additional disulfide (Table S2, entry 4) when compared to that without (Table S2, entry 1) is possibly due to over-reaction



Figure 7. Complete reaction cycle for photoredox hydroamination. ET = electron transfer; BET = back-electron transfer; PT = proton transfer; HAT = hydrogen atom transfer.

after 20 h of blue light illumination. Significantly, the yield of product is maintained with 3-fold lower alkene loadings (2 equiv). Whereas a modest decrease in yield is observed in the absence of $Trip_2S_2$ (Table S2, entries 1 and 8), in the presence of Trip₂S₂, the yield increases from 70% to 78% (Table S2, entries 4 and 10). Interestingly, high yields hold for photocatalysts other than IrB. Using MesAcr at 4 mol % loading in the presence of Trip₂S₂ leads to appreciable product yield of the secondary amine (87%) with no detectable tertiary amine (Table S1, entry 4). These results together establish that the presence of disulfide allows the photoinduced hydroamination to be performed under reduced loadings of photocatalyst and alkene. Additionally, we also monitored the progress of the reaction with IrB in the presence of 30 mol % Trip₂S₂ and in the absence of TripSH. The photoreaction delivered the highest product yield of 2 (85%) in 7 h; further illumination resulted in a drop in yield of 2 from 85% to 69% with the concomitant formation of tertiary amine product 3 (Table S4).

The optimized conditions allowed the primary amine hydroamination reaction to be performed efficiently on larger scale under flow conditions. A flow reaction setup was designed comprising two Kessil lamps (440 nm) that illuminated both sides of a sample flowing through a PTFE tube (Figure S1B). The improved reaction efficiency induced by disulfide was verified for the flow setup (see section C in the Supporting Information). For the primary amine reaction (Figure 1A) performed in the presence of 30 mol % $Trip_2S_{24}$ 60% and 73% product yields were achieved in 5 and 10 min, respectively (Table S3). In contrast, only 11% and 14% yields were obtained after 5 and 10 min, respectively, for the photocatalysis under the original conditions (Figure 1A). Further illuminating the solution for 80 min delivered product in just 51% yield (Table S3). Large-scale synthesis was demonstrated by using the conditions shown in Figure 6B, top (section C, Supporting Information), where the photocatalyst loading was halved compared to the previously reported conditions.²⁶ Multiple primary amine and alkene subtrates were tested and showed moderate to high isolated yields (Figure 6B, bottom). All reactions were complete in 9 h on a 2.5 mmol (50 mL) scale. The flow setup may easily accommodate larger scale reactions if so desired.

DISCUSSION

A complete reaction cycle for the photoredox hydroamination reaction between primary amines and alkenes is proposed in Figure 7. The excited-state photocatalyst *Ir(III) oxidizes the amine to generate Ir(II) and ARC with a quenching rate constant approaching the diffusion-controlled limit (Figure 2A). The generation of Ir(II) is established by the transient absorption at 385 and 520 nm (Figure 3A). At this juncture, the ARC may react along three possible pathways: (A) addition to alkene in a productive reaction (Figure 7, left, productive cycle), (B) direct BET with Ir(II), and (C) deprotonation to form a neutral radical (Figure 7, right, nonproductive cycle). As previously elucidated, ARC propagating along pathway A establishes the productive hydroamination.^{25,26} The addition of ARC to the alkene is conveniently examined by using 1,1-diphenylethylene as its radical cation absorbs at 330 nm,³¹ which we have detected in the TA spectrum (Figure 3C). The resulting product radical cation can engage in a facile HAT reaction with TripSH ($\sim 10^8$ $M^{-1} s^{-1}$ ³⁴ to form the product ammonium cation and TripS[•], which then undergoes a reduction by Ir(II) and proton transfer to afford the desired product and regenerate both TripSH and Ir(III) (ET/PT reactions). The selectivity in this cycle originates from a difference in the kinetics between primary and secondary amines along pathway A. Pathway C enters an off-cycle reaction and is the determinant of photocatalyst turnover, which is specific to the redox properties of the Ir photocatalyst.

Origin of Chemoselectivity in the Primary Amine Reaction. A merit of this photoredox hydroamination method is its chemoselectivity toward the formation of secondary amine with minimal overalkylation.²⁶ Figure 1A reproduces the selectivity for this reaction of the primary amine by using IrB photocatalyst. To investigate the origin of this chemoselectivity, we examined the Stern–Volmer quenching of *IrB by the primary amine (1) and secondary amine (2). The enhanced quenching rate constant of IrB* by 2 as compared to 1 (Figure 2A) excluded the possibility that the chemoselectivity is associated with the initial quenching process (forward ET). TripSH was also observed to quench *IrB, but the quenching is insignificant considering its lower concentration (15 mM) as compared to that of the amine substrate

(50 mM) under the standard reaction conditions (Figure 1A). Even in the presence of amine substrate (1 or 2), the quenching by TripSH only increased slightly (Figure S5), suggesting that proton-coupled electron transfer (PCET) does not contribute to the initial quenching to any significant extent.^{19,35,36} The primary amine 1 shows a quenching efficiency 4-5-fold higher in 1,4-dioxane and ⁱPrOAc than in PhCN, likely due to the H-bonding interaction between primary amine and 1,4-dixoane as reflected by a peak shift and broadening of the NH₂ signal in the ¹H NMR spectra shown in Figure 2B. Considering the strong and potentially deleterious competitive quenching from 2 and TripSH (Figure 2A), this increased quenching for primary amine (1) may play an essential role in delivering the high product yields of 2 in 1,4dioxane (76% in Figure 1A) and PrOAc (79% in Table S1, entry 2).

Pathway B may engender selectivity for the primary amine if IrB(II) reacts with $2^{\bullet+}$ by back-electron transfer (BET) much faster than with $1^{\bullet+}$, hence extending the lifetime of $1^{\bullet+}$ for addition to the olefin (pathway A). However, the TA spectrum of IrB(II) persists over long times for both the primary and secondary amine quenching reaction (Figure 3A, inset, and Figure S9), indicating that BET is not a dominant reaction pathway and moreover is not the origin of chemoselectivity. These quenching results together suggest that chemoselectivity arises from differential addition rates of the primary versus secondary ARC to alkene. Indeed, as shown in Figure 3D, the primary ARC adds to the alkene at a rate (k_{prod}) that is ~76 times greater than that for the corresponding secondary ARC. Moreover, these results suggest that the chemoselectivity for the primary amine shown in Figure 1A and Table S1 (entry 2) is inherent to the primary ARC and is not photocatalystspecific. This contention is confirmed by the observation that chemoselectivity was maintained (Table S1, entries 3 and 4), when the primary amine reaction was performed by using the organic photocatalyst MesAcr in place of IrB.

Deprotonation of ARCs. ARCs are known to undergo facile deprotonations from NH or $C_{\alpha}H$ groups to form neutral radicals,^{27,37} as deduced primarily for secondary ARCs.³⁸ The pK_a calculations shown in Scheme S1 suggest that deprotonation is favored from both NH and $C_{\alpha}H$ groups for primary ARCs, and only from the $C_{\alpha}H$ group for secondary ARCs, indicated by the lower pK_a values of the ARCs than their corresponding ammonium cations. To probe if deprotonation from the $C_{\alpha}H$ group does occur, ARCs were generated under photoredox conditions in the presence of D₂O and TripSH. Deprotonation from the $C_{\alpha}H$ group is supported by the results of Figure 3B and Figure S10, which show 37% and 90% deuteration at C_{α} for primary amine 1 and secondary amine 2, respectively. These results are consistent with the pK_a calculations and confirm that deprotonation from the C_aH group indeed occurs.

TA spectroscopic studies suggest that deprotonation of the primary ARCs is faster than 100 ns. Figure 3C shows that the TA signal of the product radical cation appears promptly at 100 ns regardless of varying concentrations of 1,1-diphenylethylene (Figure 3C, inset). To determine if the fast deprotonation is associated with C_{α} H group or the NH group, TA kinetics studies were also performed by using *tert*butylamine, which is absent of C_{α} Hs. As shown in Figure S13, the product cation radical also appears in <100 ns, indicating that fast deprotonation occurs from the NH group. On the basis of these results, we conclude that primary ARCs pubs.acs.org/JACS

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predominantly deprotonate from the NH group on the sub-100 ns time scale, which is also consistent with previous reports of a short lifetime (40 ns) for primary ARCs.³⁹ The presence of fast deprotonation of the primary ARCs diverts the system to pathway C and also accounts for the absence of significant BET along pathway B in Figure 7. Additionally, the secondary ARCs are also short-lived under photoredox conditions based on similar observations showing the absence of direct BET after the initial quenching (Figure 3A, blue plots). This is in stark contrast to the reported lifetime of a few microseconds for the secondary alkyl ARCs in acidic solution³¹ and likely suggests that the secondary amine substrate significantly accelerates the deprotonation of ARCs under photoredox reaction conditions by acting as a base.

Pathway C diverts the system into a reaction off-cycle (Figure 7, right) because the neutral aminyl radicals formed after deprotonation are not observed to add efficiently to the alkene, as no additional rise in signal of the product radical is observed beyond 100 ns by TA spectroscopy (Figures 3C, inset, and Figure S13). This is in line with the several orders of magnitude slower addition reported for nucleophilic aminyl radicals when compared to electrophilic ARCs.⁴⁰ The carboncentered radical formed after deprotonation from the C_aH group should not react with alkene either, since the alkylation byproduct is not observed. Under the photoredox conditions shown in Figure 1A, the neutral aminyl and carbon radicals are expected to be reduced rapidly by TripSH via HAT (Figure 7, right cycle), as both reactions have been reported to proceed with rate constants of $\sim 10^8$ M⁻¹ s⁻¹.³⁴ Following HAT, TripS[•] and the starting materials (amines) are generated, the latter of which prevent side reactions from consuming the amine substrates.

Photocatalyst Turnover. Beyond its function as a HAT catalyst to facilitate product formation (Figure 7, left cycle) and the recovery of the amine substrate (Figure 7, right cycle), TripSH plays a critical role in mediating photocatalyst turnover.

For photoredox reactions involving IrB, TripSH provides a source of TripS[•] to drive photocatalyst turnover to IrB(III). The reaction between TripS[•] and IrB(II) was studied by observing the time evolution of the TA features for IrB(II) at 385/520 nm and TripS[•] at 490 nm, respectively (Figure 4A). Moreover, the reaction between IrB(II) and TripS[•] offers an ET/PT pathway for the photocatalyst to turnover as both IrB(II) and TripS[•] decay significantly (Figure 4), in contrast to nearly no decay of IrB(II) in the absence of TripSH (Figure 3A, inset). The TripS[•] radical can also dimerize to form a disulfide (Trip₂S₂), resulting in an accelerated decay of TripS[•] relative to IrB(II) decay and a residual TA signal for IrB(II) (Figure 4A). The formation of the $Trip_2S_2$ will negatively affect photocatalyst turnover if IrB(II) cannot react with Trip₂S₂. Indeed, photolysis of IrB(III) in the presence of primary amine, TripSH, and alkene leads to the generation of IrB(II) as monitored by UV-vis spectroscopy (Figure 5). Addition of $Trip_2S_2$ to this photolyzed solution of IrB(II) results in little change to the absorption profile, confirming the absence of reaction between IrB(II) and $Trip_2S_2$. However, as shown in Figure S18C, when the solution of IrB(II) and $Trip_2S_2$ was further subjected to illumination, IrB(II) can turnover due to the reaction between IrB(II) and the photogenerated thiyl radical. Therefore, for primary amine substrates, the reaction between IrB(II) and TripS[•] provides the only plausible path for photocatalyst turnover to IrB(III). To this end, the

regeneration of TripS[•] by $Trip_2S_2$ photocleavage²² is essential for the primary amine reaction. Figure S14 shows that $Trip_2S_2$ photocleavage is a facile process as the $TripS^{•}$ is formed promptly after laser excitation.

For photoredox reactions involving IrA, photocatalyst turnover may be driven by reaction with TripS[•] as well as by direct reaction with Trip₂S₂. Unlike the result in Figure 5 for IrB(II), IrA(II) does not build up for the photolysis of a solution containing IrA(III), secondary amine, TripSH, and alkene (Figure S18C). This result suggests superior turnover ability for IrA compared to IrB, as is observed for the faster TA decay kinetics of Ir(II) and TripS[•] for IrA (Figure S15) as compared to IrB (Figure 4A). Kinetic modeling of the decay signal at 520 nm for the two photoredox reactions yields the rate constants of $k_{\rm ET} = (2.1 \pm 0.1) \times 10^{10} \,{\rm M}^{-1} \,{\rm s}^{-1} \,{\rm vs} \,k_{\rm ET} = (8.1 \pm 0.1) \times 10^9 \,{\rm M}^{-1} \,{\rm s}^{-1}$, respectively (Figure 4B), for the ET/PT reaction following the generation of TripS[•] from TripSH by HAT. Moreover, unlike IrB(II), IrA(II) can directly react with Trip₂S₂ to furnish IrA(III) as was verified in Figures S18D and S19, where the disappearance of IrA(II) was observed when Trip₂S₂ was added to an IrA(II) solution prepared either photochemically (Figure S18D) or chemically (Figure S19). Hence, in IrA photoredox reaction with secondary amine substrates, the regeneration of TripS[•] from Trip₂S₂ via photolysis is not essential for photocatalyst turnover.

The differences in the turnover between IrA and IrB stem from the redox potentials of the reduced photocatalysts. Using CV (Figure S17), we determined IrB(II) to be much less reducing than IrA(II) ($E_{1/2} = -1.18$ and -1.80 V vs Fc⁺/Fc for IrB(III/II) and IrA(III/II), respectively). Hence, IrA(II) can react directly with Trip₂S₂ and also react with TripS[•] more efficiently than IrB(II) to result in photocatalyst turnover. We note that the half-peak potential for RSSR reduction (Figure S17), $E_{p/2} = -2.25$ V vs Fc⁺/Fc, is a poor approximation of the standard potential for disulfides. In disulfides, the reduction is accompanied by irreversible bond breaking that results in a shift of $E_{p/2}$ that is 300-600 mV more negative than the standard potential.⁴¹ Accordingly, as shown in Figures S18B and S18D, IrA(II) is able to reduce disulfide while IrB(II) is not and IrA(II) is able to turn over by direct reduction of the disulfide. This additional dark reaction for IrA(II) enhances turnover and accounts for the photocatalyst dependence in the secondary amine reactions (Figure 1B), where 87% tertiary amine product 3 was obtained by using IrA, in contrast to the 20% yield obtained by using IrB. Moreover, as demonstrated in Table S1 (entries 5 and 6), the pre-addition of 2 decreases the primary amine reaction efficiency. This inhibition is caused by the formation of the secondary amine product due to quenching of the *IrB photocatalyst (Figure S5), thus sending the system into the off-cycle pathway (Figure 7, right).

Mechanism-Informed Reaction Optimization. The detailed mechanism reveals that the efficiency of the primary amine hydroamination reaction by **IrB** is compromised by photocatalyst turnover, implying that a potential optimization strategy is to increase the concentration of thiyl radicals generated via photolysis of the disulfides. As shown in Figure 6, additional disulfide results in the improvement of the quantum yield by over an order of magnitude and allows for lower loadings of photocatalyst or alkene (Table S2). We note that a HAT catalyst that cannot undergo side reactions such as dimerization may also facilitate photocatalyst turnover though TripSH remains the best HAT catalyst known to date. This is likely due to the multiple roles served by thiol and disulfide

working in concert as HAT catalysts (Figure 7, left and right cycles). Though it has been shown that disulfide plays an important role in catalyst turnover in a number of radicalmediated transformations,²² thiol and disulfide together can enhance catalysis by working in concert. Whereas thiol is responsible for reducing the carbon-centered radical because of its rapid HAT dynamics (left cycle, Figure 7), the disulfide plays an essential role in turning over the photocatalyst. The benefit of thiol/disulfide cooperativity is apparent in the enhanced yield shown in Figure 6A (orange and dark green bar).

Batch reactions typically face challenges in scale-up using large reaction vessels⁴² because photoexcitation is confined to absorption of incident light at the surface of the reactor. The absorbance is particularly problematic for the primary amine reaction because of the accumulation of the IrB(II) (Figure 5), which absorbs light more strongly than IrB(III) (Figure S8B) and thus manifests a strong inner filter effect as the photoredox reaction proceeds. Under flow conditions, the inner filter effect may be attenuated by irradiating the same quantity of solution in unit time as a batch reactor but over a shorter path length. Additionally, the quantum yield of the overall reaction of IrB with primary amine is significantly increased with the addition of Trip₂S₂. This increased quantum yield allows the photoreaction to proceed with a shortened residence time under flow conditions as demonstrated in Table S3, which lists product yields of the photoredox reaction performed in the flow reactor for given time periods of irradiation. Together, the shortened path length enabled by the flow reactor and the increased QY with additional Trip₂S₂ permitted a relatively large-scale synthesis to be performed with reduced loading of the photocatalyst as shown in Figure 6B.

A detailed mechanistic study of the photoredox anti-Markovnikov hydroamination of alkenes reveals that the reaction selectivity for primary amines over their secondary amine products is inherent to the addition kinetics of ARCs to the alkene. For primary amines, the rate of addition is nearly 2 orders of magnitude faster than that of secondary ARCs. The BET between photogenerated species (Ir(II) complexes and ARCs) is circumvented by the fast deprotonation (<100 ns) of the ARCs. Instead, a reaction between Ir(II) and thiyl radical was discovered to be essential in facilitating photocatalyst turnover. This process is retarded by the formation of disulfide, which must be photolyzed to form thiyl radicals to turn over the photocatalyst. Finally, we optimized the photocatalyst turnover and achieved a quantum yield increase in excess of an order of magnitude compared to the previously reported conditions. This further allowed us to demonstrate efficient large-scale reactions under scalable flow conditions. Our results show that mechanism-informed optimization strategies can benefit practical applications of photoredox hydroamination of primary amines and potentially other hydrofunctionalizations as well.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c03644.

Materials and methods, data analysis, quantum yield measurements, photoredox catalysis setups, quenching

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studies, TA studies, pK_a calculations, controls and optimizations, product isolation (PDF)

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Notes

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