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Singlet Photoredox Catalysis via Supramolecular Host-Guest Interactions

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ABSTRACT: Photocatalysts most often leverage long-lived triplet excited states to promote valuable reactivity in organic synthesis. Consequently, many potential photosensitizers remain unviable for catalytic applications due to kinetic constraints of diffusion-controlled intermolecular electron transfer. Supramolecular mechanisms can obviate this constraint through ground-state association with a reactant, enabling species with short-lived excited state lifetimes to engage in synthetically relevant transformations. Thus far, the instability of host architectures towards open-shell intermediates has limited their use as photoredox catalysts. Through the synthesis of an oxidatively robust Ge^{IV} catecholate cage, ($E_{p/2} = 0.357$ V vs. Fc/Fc⁺), we have enabled the (4+2) synthesis of isoquinolones via *singlet* photoredox catalysis. These results establish supramolecular pre-organization as a generalizable platform for harnessing the unique redox potentials of singlet excited states in organic synthesis.

INTRODUCTION

Figure 2. Visible-light supramolecular photoredox catalysis (a) Previous work in our laboratory has established **Host I** as a competent photoredox sensitizer for the rearrangement of encapsulated cinnamyl ammonium salts. (b) This work: Supramolecular photoredox catalysis via singlet excited states to synthesize isoquinolones. (c) Supramolecular host design to furnish **Host III**, with improved catalytic properties.

Photoredox catalysis has emerged as a powerful tool for organic synthesis, enabling the rapid construction of complex molecular architectures under mild reaction conditions^{1,2}. Traditional photoredox catalysts often rely on organic and organometallic species capable of accessing long-lived

triplet excited states, which are necessary to ensure dynamic quenching of their excited states (**Fig. 1a**)³. A photosensitizer that can react via its singlet excited state offers unique modes for substrate activation, obviating the need for intersystem crossing to provide larger redox potential and higher quantum yield^{4,5}.

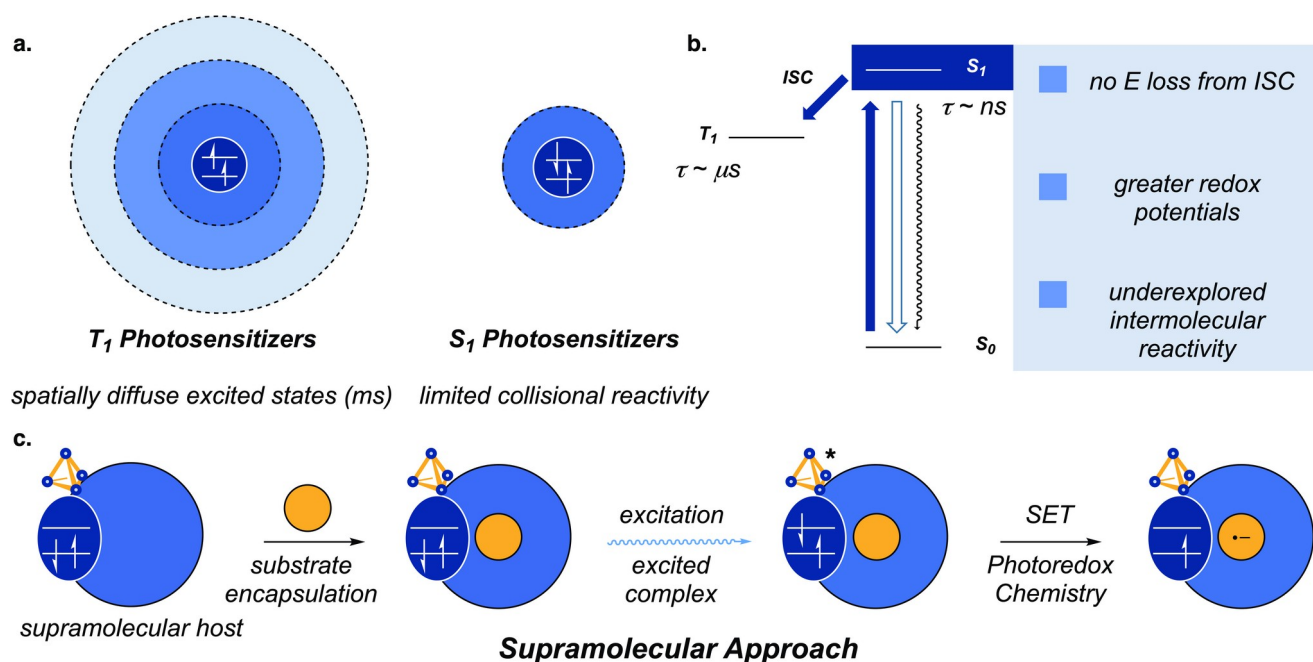


Figure 1. S_1 Photoredox Catalysis through Supramolecular Mechanisms (a) Effective concentrations of photosensitizers are typically limited by collisional reactivity. (b) Jablonski schematic for a photoredox catalyst, showing increased energy in the S_1 versus the T_1 state as well as inherent advantages of the S_1 state. (c) Supramolecular encapsulation promotes pre-association of the substrate with the photocatalyst, promoting SET from transient lifetimes.

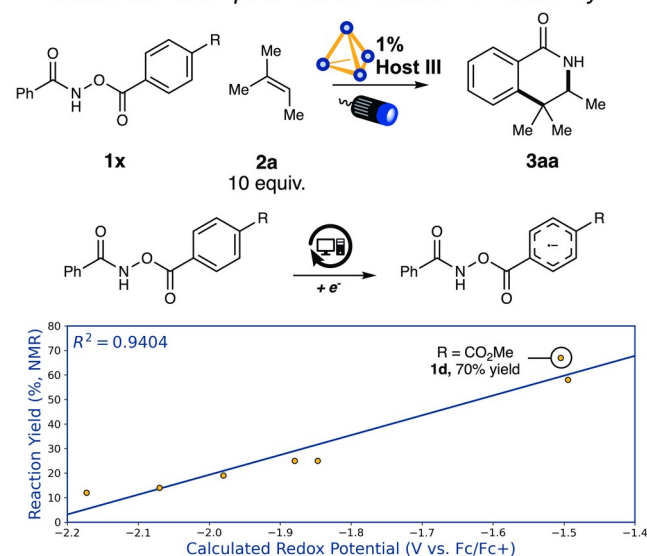
However, the ultrashort lifetimes of the singlet excited state typically preclude its intermediacy in intermolecular photocatalysis due to diffusion-controlled rate limitations (**Fig. 1b**).

Supramolecular chemistry can address these constraints through preassociation between the substrate and photosensitizer, increasing the effective concentration of the excited state encounter complex to promote intermolecular reactivity^{6–15}. (**Fig. 1c**) Despite recent advances in photosensitization under confinement, these materials most often leverage triplet excited states to enable energy transfer^{16–22} or single electron transfer^{23–25}. Previous work from our laboratory has demonstrated highly reducing excited states for tetrahedral Ga-catecholate coordination cages for the rearrangement of cinnamyl ammonium guests (Ga^{III}₄Lnaph₆ **I**, Lnaph = N,N'-bis(2,3-dihydroxybenzoyl)-1,5-diaminonaphthalene) (**Fig. 2a**)¹³. While our protocol established Host **I**¹² as a potent reductant in its excited state and Host **I**¹¹ a capable ground state oxidant, catalytic applications of this mechanism were limited due to the strongly bound product inhibiting turnover.

Building on previous work in the Raymond, Bergman and Toste groups,^{26–30} synthetic engineering of metal-catecholate tetrahedra should promote this excited state redox chemistry, increase guest exchange rates, and resist decomposition from oxidizing intermediates. A novel coordination cage, Ge^{IV}₄Lpyr₆ (**III**, Lpyr = N,N'-bis(2,3-dihydroxybenzoyl)-1,6-diaminopyrene) was synthesized, exhibiting greater redox stability than its Ga congener (Ga^{III}₄Lpyr₆, **II**). Additionally, Host **III** exhibits a red-shifted absorption spectrum compared to Host **I**, enabling visible light excitation. Hydroxamate esters are widely utilized precursors to amidyl radicals via single electron reduction.^{31–33} Hypothesizing that the excited state of Host **III** is sufficiently reducing to conduct SET to an encapsulated N-aryl-hydroxamate, the reactivity of amidyl radicals could be harnessed by the supramolecular scaffold.

Herein, a novel synthesis of isoquinolones is disclosed via a formal (4+2) cyclization between aryl hydroxamates and olefins catalyzed through visible light irradiation of a supramolecular host. (**Fig. 2b**) High turnover numbers are observed due to the oxidative stability imparted by the comparatively stable octanionic character of the supramolecular scaffold relative to its dodecaanionic congener. Furthermore, the red shift in the photophysical transition enables excited state chemistry with less ionizing radiation. (**Fig. 2c**) Various substituted aryl hydroxamates and electron rich olefins are shown to

a. Substrate redox potential correlates with reactivity



b. Optim

Entry	
1	
2	
3	
4	
5	
6	
7	

Figure 3. Reaction discovery and optimization (a) Effect of O-acyl-substitution on hydroxamate and resulting yield for the isoquinolone synthesis. See supporting information for details. (b) Reaction conditions: hydroxamate (25 μ M, 1.0 equiv.), Host **III** catalyst (1 mol%), light-emitting diodes (LEDs), r.t., 16 h. ^b ¹H NMR yield was determined using 1,3,5-

participate in the reaction. Photophysical, electrochemical, and computational studies reveal that non-covalent binding between the substrate and supramolecular host accelerates electron transfer from a singlet excited state.

RESULTS

Establishing and optimizing photocatalytic reactivity with supramolecular Host **III**.

Irradiation (440 nm) of a solution of N-(benzoyloxy)benzamide (**1a**), excess 2-methylbut-2-ene (**2a**), and 1 mol% of Host **III** furnished the desired isoquinolone (**3aa**) in 17% yield. Previous work has shown that more electron deficient aromatic substituents on the O-acyl substituent can effectively modulate its redox potentials while producing identical products.³³ A series of hydroxamates with varying substituents at the O-acyl arene were tested, which furnished increasing reaction yields according to the electron withdrawing ability of the substituent (**Fig. 3a**). This trend correlated strongly with the substrates' calculated reduction potentials, as confirmed via cyclic voltammetry (CV) for a subset of the calculated structures. Indeed, substrate **1d** exhibited an experimental reduction potential significantly less negative than **1a** ($E_{p/2} = -2.03$ to -1.67 V vs. Fc/Fc⁺) and afforded the desired product **3aa** in 70% yield (**Fig. 3b, entry 1**).

With optimized substrate **1d** in hand, further studies were conducted to understand how modifications of the supramolecular scaffold influenced observed reactivity. Conducting the reaction with Host **I**, under both 390 nm and 440 nm irradiation, provided 0% yield of the desired product (**Fig. 3b, entry 2**). While Host **I** does not show appreciable absorption at 440 nm, all reactivity with 390 nm irradiation led to rapid decomposition of the host scaffold without detectable formation of **3aa**. Attempts to leverage Host **II**, Ga^{III}₄L₆pyr, resulted in only 19% yield of the desired product (**Fig. 3b, entry 3**). With the more oxidatively robust Host **III**, no product was observed in the absence of visible-light irradiation (**Fig. 3b, entry 4**). Monitoring the reaction by ¹H NMR shows limited degradation of the supramolecular scaffold over the course of the reaction. (See Supporting Information, Figure S24) Critically, irradiation of a catalytic loading of deprotonated ligand resulted in a complete suppression of reactivity, demonstrating that the ligand alone is insufficient to enable turnover (**Fig. 3b, entry 5**). To probe for encapsulation as a requirement for reactivity, a high affinity binder was included in the reaction medium, (Cp*)₂CoPF₆ (K_a = 1.16 × 10⁴ M), to compete for the cavity and inhibit reactivity. With only 10 mol % competing guest significant inhibition was observed with only 4% yield of isoquinolone produced (**Fig. 3b, entry 6**). In assessing the competency of other known photoredox catalysts, Ir(ppy)₃ can likewise catalyze this reaction albeit with slightly lower efficiency (**Fig. 3b, entry 7**).

Elaborating reaction substrate scope.

The substrate scope of our isoquinolone synthesis was then explored. First the electronic character of the putative amidyl radical was assessed for reaction efficiency (**Fig. 4**). Across an array of *N*-substituted benzoyl hydroxamates, (**1e-1k**) electron donating substituents favored desired reactivity with the olefin whereas electron withdrawing substituents led to undesired side reactivity. With all substrates, full consumption of the hydroxamate starting material was observed via the production of benzamide. This likely forms due to hydrogen atom abstraction from the solvent, methanol. In assessing the competency of various olefin coupling partners, only olefins that produce a stable radical resulted in desired reactivity. Pleasingly, a variety of 1,1-disubstituted, trisubstituted, and tetrasubstituted alkyl olefins furnished desired isoquinolones **3ab-3af**. Various α-olefins and internal olefins resulted in little to no product formation. (See

SI, Fig. S18) Vinyl ethers were also effective substrates, exemplified by **3ag**. Assessing the functional group tolerance of the reaction, esters, alcohols, and even less electron rich olefins were well tolerated (**3ah-3ai**) We explored additional substrate scope to understand whether the supramolecular scaffold influences the product distribution within the catalytic cycle. In the case of hydroxamate **1k**, the intermediate alkyl radical can cyclize to form **3ka-1** or **3ka-2** depending on the position on the arene that undergoes cyclization. Minimal perturbation of selectivity was observed compared to solution-phase photocatalytic methods (2.3:1 for Host **III** vs. 2.0:1 for Ir(ppy)₃), implying that the supramolecular scaffold is not significantly influencing the intramolecular cyclization of the alkyl radical. Furthermore, when using olefin **2k** no isoquinolone formation was observed. Instead, the oxidation of the benzylic radical was favored with addition of methanol to quench the resulting carbocation, which is consistent with previously reported reactivity in photoredox catalysis³³. During the reaction an equivalent of 4-(methoxycarbonyl)benzoic acid is produced as a side product. We found that the addition of exogenous 4-(methoxycarbonyl)benzoic acid had little effect on catalytic efficiency, with buffered aqueous solutions providing slightly diminished yields with increasing pH (See SI, Fig. S19).

Interrogating reaction mechanism using host photophysical and electrochemical properties.

To understand the mechanism of this transformation, further characterization of Host **III** was conducted to assess its excited state electrochemical and photophysical properties. The CV of Host **III** reveals an irreversible oxidation wave, E_{p/2} = 0.357 V vs. Fc/Fc⁺ (See SI, Fig. S16). Absorption and emission spectra of Host **III** allowed for the assignment of the S₀-S₁ excitation energy (E_{0,0}) at 2.90 eV (See SI, Fig. S10). From these data, the complex's excited state oxidation potential was calculated to be -2.55 V vs. Fc/Fc⁺. This potent reducing potential is capable of exergonic electron transfer to substrate **1d**. To confirm that the S₁ state was the photoredox active intermediate experimentally, the fluorescence lifetime of our catalyst was measured to be 9.81 ns, characteristic of a singlet excited state (See SI, Fig. S12)³⁴. In contrast, the unmetallated ligand exhibits a lifetime too short to be well resolved by our instrumentation (<1 ns, See SI, Fig. S13). Further characterization efforts are ongoing to understand

the electronic transitions that precede SET from the excited state and what additional effects the supramolecular structure imparts on the photophysical properties of the ligands.

Host-guest interactions enable SET from transient excited states..

Figure 4. Reaction scope of supramolecular photoredox catalyzed isoquinolone
1.0 equiv.), **Host III** (1 mol %), olefin (10 equiv.), 4:1 MeOH:H₂O, 50 mM, 440 nm
was determined using 1,3,5-trimethylbenzene as the internal standard. Yields are t

Investigations of the host-guest adduct began with encapsulation studies. Addition of ten equivalents of substrate **1d** to a solution of Host **III** showed only modest changes in the host's ¹H NMR signals corresponding to the pyrene walls. Signals which correspond to encapsulated protons of **1d** were also observed but were insufficiently resolved to confidently establish a ground state binding constant. As a surrogate with more diagnostic NMR signals we conducted encapsulation studies with substrate **1i** to find definitive evidence of encapsulation via concentration dependent shifts in the ¹⁹F signal of the substrate. These data reveal the binding constant between Host **III** and **1i** to be $116 \pm 37 \text{ M}^{-1}$ (**Fig. 5a**)³⁵.

To further elucidate the reaction mechanism, kinetic experiments via in-situ via LED-NMR were conducted. Combining varying concentrations of supramolecular Host **III**, hydroxamate **1d**, and 2-methylbut-2-ene (**2a**) under continuous monitoring by ¹H NMR provided a rich data set from which we could extract the contribution of each component to the rate of the

reaction. Utilizing Bures' variable time normalization analysis,³⁶ first-order dependence on Host **III** was observed (See SI, Fig. S7).

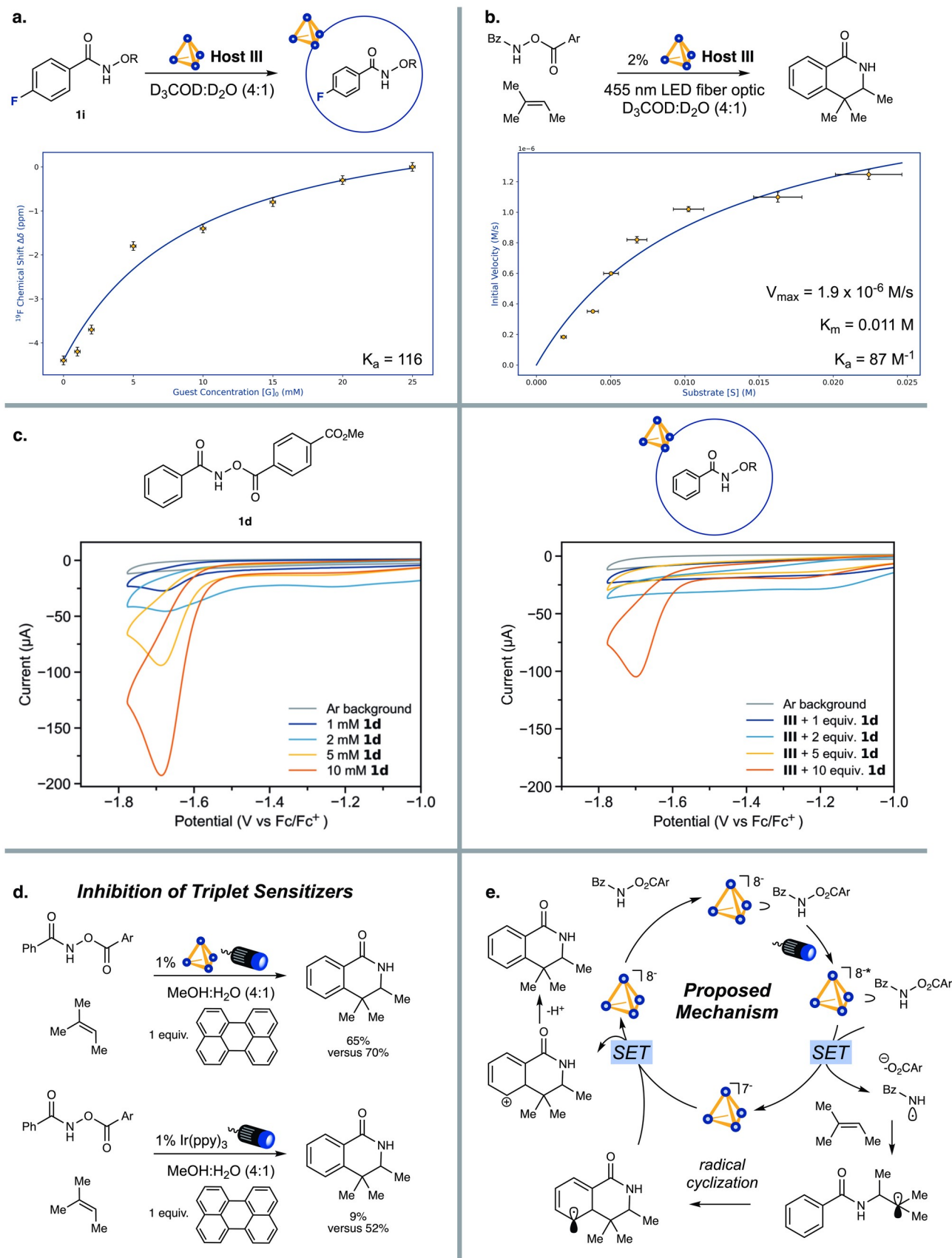


Figure 5. Mechanistic investigations and proposed catalytic cycle (a) Binding studies by ^{19}F NMR using substrate **1i**. (b) LED-NMR kinetics of the host catalyzed reaction. (c) CV studies of varying concentration of **1d** with and without host **III** under Ar; Conditions: 1–10 mM **1d** and 1 mM **III**, scan rate 100 mVs $^{-1}$, 0.1 M NaClO $_4$ in MeOH. (d) Triplet quenchers inhibit triplet photosensitizers but not host **III**, a singlet photoredox catalyst. (e) Proposed mechanism for the host catalyzed isoquinolone synthesis.

Similarly, cyclic voltammetry was conducted to identify the half-peak reduction potential of substrate **1d**. The room-temperature CV collected in MeOH under Ar displays an irreversible reduction feature at $E_{p/2} = -1.67$ V vs Fc/Fc⁺. When equimolar amounts of **1d** and supramolecular host were combined, complete silencing of the redox behavior of **1d** was observed. Upon further addition of an excess of **1d** up to ten equivalents, the reduction feature returns. This behavior has been identified in previous studies of host-guest complexes exhibiting encapsulation-sensitive redox behavior.³⁷ This attenuation in current is attributable to the encapsulation of **1d**, rendering it electrochemically inactive, with the restored signal at excess equivalents reflecting the unbound species in solution. A negligible 13 mV negative shift in the reduction half-peak potential was observed, reinforcing our conclusion that the host does not significantly perturb the redox properties of the guest (**Fig. 5c**).

Furthermore, steady state luminescence quenching of Host **III** with **1d** reveals a quenching rate constant of $1.11 \times 10^{10} \text{ M}^{-1}\text{s}^{-1}$ (See SI, Fig. S11), according to Host **III**'s excited state lifetime (9.81 ns). This value exceeds the diffusion limit for collision quenching in the solvent mixture, (4:1 MeOH:H₂O, $5.6 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$, See SI, pg. 18) indicating that static quenching via pre-association is the operative mechanism. These data all reinforce a model in which binding of our substrate within supramolecular Host **III** precedes photoexcitation. To further probe the character of the excited state in the reaction under study, an equivalent of perylene was added to the reaction mixture, a known triplet quencher (35.3 kcal/mol).³⁸ With Host **III** little impact on the overall efficiency of catalysis was observed, with significant inhibition of reactivity with Ir(ppy)₃ as a catalyst (**Fig. 5d**). This difference in reactivity is ascribed to our catalyst's inability to achieve significant population of its triplet excited state, with Ir(ppy)₃ undergoing competitive quenching with SET from a long-lived triplet excited state. To further investigate competing excited state quenching mechanisms, the triplet excited state energies of a series of various O-benzoyl hydroxamates were calculated. No trend was discernable between the substrates' triplet excited state energies and the yield of the desired isoquinolone (See SI, Fig. S21).

With sufficient characterization, the following mechanism is proposed (**Fig 5e**). Initial encapsulation of hydroxamate **1d** in the supramolecular Host **III** promotes SET from the complex's singlet excited state to **1d**. N-O bond scission from the reduced species extrudes a carboxylate and produces an amidyl

radical. This radical reacts with an electron-rich olefin such as **2a**, to form a more stable tertiary alkyl radical. Intramolecular cyclization of this alkyl radical to the pendant arene furnishes a cyclohexadienyl radical, which undergoes oxidation by Host **III**⁷⁺, regenerating Host **III**⁸⁺, and a carbocation. This undergoes elimination with 4-(methoxycarbonyl)benzoate acting as a base to form the desired isoquinolone **3aa**.

In conclusion, supramolecular mechanisms enable a formal (4+2) couplings of aryl hydroxamates and electron-rich olefins. Reaction kinetics, photophysical investigations, and electrochemical characterization support the necessity of supramolecular encapsulation with transient singlet excited states to promote SET reactivity. While this strategy did not impart regio- or stereochemical control over the reactive intermediates, efforts are ongoing to leverage the chiral microenvironment of the supramolecular host to induce stereoselectivity in open-shell intermediates generated via photoredox catalysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedure and data for all products, computational procedures, and supplementary discussions. (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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