Ultrafast photoactivation of C–H bonds inside water-soluble nanocages

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Light energy absorbed by molecules can be harnessed to activate chemical bonds with extraordinary speed. However, excitation energy redistribution within various molecular degrees of freedom prohibits bond-selective chemistry. Inspired by enzymes, we devised a new photocatalytic scheme that preorganizes and polarizes target chemical bonds inside water-soluble cationic nanocavities to engineer selective functionalization. Specifically, we present a route to photoactivate weakly polarized sp3 C–H bonds in water via host-guest charge transfer and control its reactivity with aerial O2. Electron-rich aromatic hydrocarbons self-organize inside redox complementary supramolecular cavities to form photoactivatable host-guest charge transfer complexes in water. An ultrafast C–H bond cleavage within ~10 to 400 ps is triggered by visible-light excitation, through a cage-assisted and solvent water–assisted proton-coupled electron transfer reaction. The confinement prolongs the lifetime of the carbon-centered radical to enable a facile yet selective reaction with molecular O2 leading to photocatalytic turnover of oxidized products in water.

INTRODUCTION
Photon-mediated activation of chemical bonds has long been regarded as an efficient method to trigger chemical reactions (1–4). Since the fundamental time scale of photon absorption is in femtoseconds, the ensuing nonequilibrium nuclear dynamics on the excited-state potential energy landscape can lead to facile and efficient chemistry. However, due to the ultrafast rates of photon-energy redistribution within the various internal molecular degrees of an excited molecule, carrying out photoactivated bond-selective chemistry has remained a challenge (5). In recent times, it has been realized that preorganization of reactants preceding light excitation can be a key for controlling photoactivated reactions (6–8). Enzymes provide a powerful inspiration in this context as they lower the activation barrier of chemical reactions by orienting the substrates appropriately in their active sites for bond-selective polarization and reactivity (9). To mimic the concept of bond polarization by preorganization, chemists have designed synthetic active sites by constructing supramolecular cavities to host chemical reactions that are usually difficult to carry out in free solution (10–12). With the design of diverse cavities having tunable shapes, confinement sizes, and electronic properties, remarkable discoveries of new reactions and difficult chemical cascades have been made possible (13, 14). Here, we show that the concept of supramolecular host-guest preorganization can be harnessed to selectively photoactivate benzylic sp3 C–H bonds and enable its controlled reaction with molecular oxygen to achieve photocatalytic turnover of oxidized products.

Activation of weakly polarized C–H bonds has remained a grand synthetic challenge in organic chemistry (15–17). Natural enzymes carry out C–H bond activation inside their hydrophobic cavities with precise positioning of the hydrocarbon substrate near the H atom abstraction site, via preorganization. In the enzyme cytochrome P450, the O2 activation site that generates reactive metal-oxo species is capable of abstracting a hydrogen atom from the requisite C–H bond (9). Synthetic transition metal complexes successfully mimic the generation of high-valent metal-oxo species (18–21), although they often undergo self-degradation concurrently with the diffusive C–H functionalization reaction. Recent template-based C–H activation methodologies have been able to alleviate the lack of preorganization in the activation step (22–24), although the additional steps of attachment and removal of the template increase the cost of functionalization. Alternatively, supramolecular cavities have shown tremendous potential for orienting the substrates in the right reactive configuration and for kinetically stabilizing on-pathway reactive intermediates. Fujita and co-workers (25, 26) had demonstrated that tertiary C–H bonds of adamantane can be activated by ultraviolet (UV) light excitation inside a porous Pd6L412+ nanocage where adamantyl hydroperoxide and its tertiary alcohol were formed as products. Although the cage-induced C–H bond reactivity was promising, a lack of an industrially viable catalytic methodology and limited understanding of the reaction mechanisms made it difficult to access a wide range of hydrocarbon substrates.

To activate a C–H bond via H atom abstraction reaction inside a water-soluble cavity, a host-guest photoactivation scheme, which should be universal in its operation, will be efficient. We recently reported an ultrafast (few picoseconds) light-induced H atom abstraction reaction via proton-coupled electron transfer (PCET) (27–29) inside a cationic Pd6L412+ nanocage (30) by preorganizing ionizable N–H or O–H bonds with proximal solvent water molecules (31). The incipient acidity of the photoexcited N–H or O–H polar groups in the radical cation state was exploited to generate long-lived neutral radicals (31). We therefore hypothesize that a mild yet green catalytic method for selective C–H functionalization can be established by combining light activation with substrate preorganization inside a water-soluble supramolecular cavity (Fig. 1). Previously, PCET cascades (32, 33) or hydrogen atom transfer reactions (34, 35) have been used to indirectly activate C–H bonds in photoredox catalysis (36). In addition, Mayer and co-workers (37) have recently shown that C–H bonds can be cleaved or formed in free solution via multisite concerted proton-electron transfer by suitably prepositioning a carboxylate base near to the requisite C–H bond within the substrate. This reaction strategy is promising, although it suffers from a diffusion-limited activation of C–H bonds in the presence of stoichiometric amounts of chemical oxidants or reducers. Consequently, inspired by these ideas, here, we postulate that

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ArCH$_2$ radicals (Ar = aryl) can be photogenerated in confinement by triggering the PCET reaction (Fig. 1) directly at the benzylic C–H site of ArCH$_3$ whose acidity can be substantially altered in the radical cation state (pK$_a$ can be $<-10$ for the radical cation) (38–41). Thus, the ultrafast photogeneration of a long-lived carbon-centered neutral radical species inside a supramolecular cavity is expected to ensure temporal segregation of the subsequent O$_2$-dependent functionalization steps, thereby enabling an almost enzyme-like execution of organic oxidation reactions in water.

**RESULTS AND DISCUSSIONS**

**Photoinduced host-guest charge transfer creates radical cations and long-lived neutral radicals inside the Pd$_6$L$_4^{12+}$ nanocage**

To validate our biomimetic host-guest paradigm for metal site-independent C–H bond oxidation, we chose three alkyl-aromatic substrates: 9-methylantracene (9-MA; 1), 1-methylnaphthalene (1-MeNap; 2), and toluene (Tol; 3), which have varying degrees of aromaticity and distinct redox potentials. Incarcerating these electron-rich aromatic guest molecules inside a water-soluble Pd$_6$L$_4^{12+}$ nanocage (figs. S2 to S4) (30) resulted in the generation of color in the solution emanating from new charge transfer (CT) bands in the visible part of the spectrum (Fig. 2A, inset). The CT absorption band for 1 ⊂ Cage is broad with a peak maximum at 475 nm (Fig. 2A). However, 1-MeNap and Tol that have smaller ring sizes compared to 9-MA show blueshifted CT transitions for their respective incarcerated complexes, i.e., 2 ⊂ Cage and 3 ⊂ Cage, relative to that of 1 ⊂ Cage. These emergent CT features were absent in the absorption spectra of both free guest molecules dissolved in organic solvents and the aqueous solution of the empty Pd$_6$L$_4^{12+}$ cage (figs. S5 and S8). Incarceration of the guest molecules was confirmed by the observation of upfield $^1$H NMR (nuclear magnetic resonance) spectral shifts of guest protons (figs. S6, S9, and S11) due to hydrophobicity of the cavity and aromatic ring currents of the triazine ligands in the walls. We could quantify from the NMR peak area integration that two of 9-MA molecules, three of 1-MeNap, and four to five of Tol molecules have occupied the cage cavity. For 9-MA, the large size of the anthracene ring (long axis is ~9.3 Å) allows only two guests per cavity since the cage diameter is roughly around ~20 Å (fig. S6). The steady-state spectroscopy on the host-guest complexes therefore predicts that radical cationic states of guest molecules can be photogenerated in confinement.

To track the photogenerated radical cation and neutral radical states of the guest molecules inside the cavity, we carried out femtosecond transient absorption measurements. Figure 2B shows the radical cation signatures for the incarcerated guests, 1, 2, and 3, after an ultrafast electron transfer reaction (<100 fs) to the nanocage, which forms a corresponding radical anion (25, 26), all recorded at 1 ps subsequent to photoexcitation. For both 9-MA and 1-MeNap, we observed sharp features in the 675- to 750-nm region, while for Tol, a sharp peak at 450 nm was observed. Notably, the radical cation features for all the three molecules were slightly redshifted by ~10 to 20 nm from their respective free-solution absorption maxima, providing evidence for confinement of the radical cations (42, 43). The cage-incarcerated radical cationic state of the aromatic substrates was observed to decay in a picosecond time scale to form the corresponding neutral benzyl radical after donating a proton to the solvent water molecule since it is an exergonic process (41). The neutral radical states of these alkyl aromatics are typically characterized by their substantially low molar absorption cross section (44). Exponential fits of the radical cation decay kinetics for the signature spectra observed at 714 nm for 2 ⊂ Cage (Fig. 2C) revealed a time constant of 354 ± 25 ps for the generation of the long-lived neutral radical signal. Although the cavity-incarcerated Tol radical cation of 3 ⊂ Cage complex also decays with a monoexponential rate, the time scale is an order of magnitude faster for the deprotonation step. We observe a radical cation decay time scale of 46 ± 4 ps for the formation of neutral benzyl radical (PhĊH$_2$) for 3 ⊂ Cage subsequent to photoexcitation of the weak CT band at 400 nm (fig. S32). In contrast, the incarcerated 9-MA radical cation gets deprotonated with two distinct time constants of 14 ± 0.8 ps and 47 ± 9 ps, respectively (figs. S28 and S29). The large variation in guest deprotonation rates, from tens to hundreds of picoseconds, indicates that the cavity preorganizes the sp$^3$ C–H bond differently in the case of Tol, 9-MA, and 1-MeNap for proton transfer (PT) to solvent water. The PT reaction from a benzylic –CH$_3$ becomes facile because of substrate polarization in the photoexcited host-guest CT state. We therefore assign this as a stepwise ET-PT or bidirectional PCET, one of the classes within the generalized PCET reactions (27, 28, 45).

The disparity in PCET reaction time scales motivates us to probe the differential positioning of the reactive methyl group with respect to the proton-accepting water molecule for the three alkyl-aromatic substrates. To understand the buried nature of the methyl group, its dynamic mobility inside the cavity, and the corresponding heterogeneity of the guest population, we compared the $^1$H NMR linewidth of sp$^3$ methyl protons in all the three alkyl-aromatic substrates. We have performed temperature-dependent $^1$H NMR measurements on the host-guest complexes to identify conformational heterogeneity of the guest inside the cage. At room temperature (fig. S7), we find that, in the case of 9-MA ⊂ Cage, the $^1$H NMR linewidth is ~10 times broader than that for 1-MeNap (6.5 Hz; fig. S10) and Tol (7 Hz; fig. S11) inside the cage and two distinguishable conformers of 9-MA coexist. We observe two distinct peaks [$\delta$ 0.44 and $\delta$ 0.34 parts per million...
(ppm)] buried under the broad envelope, which is prominently revealed by lowering the temperature to 5°C. We could therefore expect two distinct deprotonation time scales representative of two major populations with altered solvent exposure. However, the extremely large upfield shift (δfree = 2.78 ppm to δcaged = −0.13 ppm) of methyl protons for 1-MeNap suggests that the C▬H is highly shielded through its proximity to triazine walls and possibly positioned away from the interfacial water molecules. Temperature-dependent 1H NMR on the 2 ⊂ Cage complex shows a single peak throughout the temperature range (25° to 5°C) with gradual broadening at low temperatures, dictating that one kind of conformation predominantly exists in the ground state (fig. S10).

**Solvent-assisted sequential PCET reactions for confined alkyl-aromatic substrates**

Convincing proof for water-assisted substrate deprotonation of the radical cation leading to neutral alkyl-aromatic radical formation was obtained by measuring the H/D kinetic isotope effect (KIE) of the radical cation decay rates in H2O and D2O. We find that the substrate deprotonation time scales are altered by a D2O/H2O solvent exchange. For instance, the C–H deprotonation in D2O for nanocage-confined 1-MeNap (Fig. 2C) takes longer (456 ± 35 ps) than in H2O (354 ± 25 ps), indicating that the secondary KIE value of 1.29 arises from a closely interacting solvent water molecule. In the case of nanocage-confined Tol, we find a slightly higher KIE value of 1.44 than in 1-MeNap. The KIE again confirms the formation of a neutral benzyl radical state. The decay of the cage-confined 9-MA radical cation state shows biphasic deprotonation kinetics such that both of the steps [fast (14 ps) and slow (47 ps)] show secondary KIE values of 1.43 and 2.32, respectively (figs. S28 and S29). We summarize the secondary KIE values for all the three substrates in Fig. 2D to highlight the distinguished role of the water solvent in the primary step of −CH3 deprotonation.

To further dissect the proton removal reaction at the substrate end, we studied the C▬H versus C▬D cleavage reaction rates in 9-MA (figs. S30 and S31). The observation of clear primary isotope effects in proton abstraction steps show that the C–H bond cleaves with the assistance of a water molecule or water cluster and that the
rate-limiting step involves both the radical cation and solvent H₂O/D₂O. Primary KIE values for both steps with deuterated d₁₂–9-MA show a lower value of 1.37 and 1.6, respectively (fig. S31), than the secondary KIE values obtained for the D₂O exchange experiment (1.43 and 2.32; figs. S28 and S29). Such a distinction in KIE values suggest that the bidirectional PCET reaction is solvent-assisted, presumably through a water cluster around the sp³ C–H bond. We hypothesize that the variation in KIE values for the three alkyl-aromatic substrates results from a combination of differential excited-state proton acidities, substrate packing inside the cavity, and differential solvent (H₂O) accessibility to the reactive –CH₃ functionality.

We next mapped the exposure of the –CH₃ group in our confined alkyl-aromatic substrates to the water cluster independently by measuring the solvation time scale (46–48) of the excited CT state. All the three host-guest complexes explored here show a specific coupled CT state (31, 48) with an optical transition in the near-infrared region between 850 and 1100 nm, obtained from transient absorption (fig. S33). Previous studies have established the dynamical blueshift observed for this coupled CT feature as a representative of the solvent rearrangement time scale in the photogenerated CT state (48). We find that, in 9-MA c Cage, solvent reorganization takes place in a biphasic manner with two time scales of ~900 fs and 4.2 ps (fig. S34), which we assign as local and bulk solvent relaxation time scales of the CT state, respectively. In contrast, for 1-MeNap, we find solvent relaxation time scales of 1.3 and ~34 ps, respectively. The 10-fold slower time scale for bulk water rearrangement in 1-MeNap compared to that in 9-MA hints at the buried nature of the methyl protons with respect to the bulk water. Therefore, the sluggish time scale (~34 ps) for the bulk rearrangement of the water shell around the photoexcited 2 c Cage complex finally leads to the slowest bidirectional PCET reaction.

We deduced the lifetime of the radical cation and neutral radical population in 2 c Cage and 3 c Cage by analyzing the time-resolved absorption data with a two-species sequential model, as shown in Fig. 2E. The picosecond time scales (14 to 350 ps) for deprotonation reactions reported here are slower than the solvent water reorganization time of 4 to 34 ps around the cationic nanocage. Although we find that the solvent reorganization time scale is critical to the radical cation deprotonation rates, we believe that other factors including molecular dynamics inside the cavity also contribute to the efficiency of the neutral radical generation rates. The directly measured rate of the neutral radical generation rates. The directly measured rate of the radical cation deprotonation rates, we believe that other factors including molecular dynamics inside the cavity also contribute to the efficiency of the neutral radical generation rates. 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**9-MA undergoes facile photooxidation inside nanocage**

To test the reactivity of the photogenerated and cage-stabilized alkyl-aromatic neutral radicals, we carried out photooxidation of all three guests, 1, 2, and 3, with molecular oxygen by forming stoichiometric host-guest complexes (figs. S6, S9, and S11) with the Pd₆L₄¹²⁺ nanocage, as summarized in Fig. 3, A to C. Resonance excitation to the CT state with green light centered at 530 nm leads to complete oxidation of 9-MA within 5.5 hours under ambient conditions (figs. S35 and S36A). After 1.5 hours of reaction, the photoproducts primarily include quinones and hydroxylated compounds, i.e., 9,10-anthraquinone (40%), hydroxyquinone (30%), 9-anthracenealcohol (9-AnCH₂OH; 15%), and 9-methyl-10-hydroxyanthracene (15%) (figs. S37 and S38). At a higher O₂ pressure of ~1.5 atm, the product distribution substantially changes with ~10-fold faster reaction rates (figs. S36B and S39). The reaction was made photocatalytic by loading 2 mole percent (mol %) of the cage in the aqueous phase with excess solid powder of 9-MA (fig. S41). The product distribution obtained for the catalytic reaction shows that the flux favors the hydroxylated products at the expense of the anthraquinone product. Since anthraquinone formation requires multi-e⁻/H⁺ removal steps, substrate turnover steps during catalysis limit the over-oxidation of the anthracene framework by shortening the residence time of the pathway intermediates or products inside the cavity.

To confirm the influence of residence times on the product distribution of 9-MA photooxidation, we separately carried out the photoreaction on the cage-loaded 9-AnCH₂OH, which is an intermediate in the 9,10-anthraquinone formation pathway. In this case, we observe sole formation of the anthraquinone product (fig. S42B), demonstrating that the residence time of the primary alcohol formed in the cavity during the oxidation of 9-MA directly influences reaction selectivity. Our proposed reaction sequence was also confirmed through ¹H NMR experiments, where we found that the loss of the 9-AnCH₂OH product correlated with the increase of the quinone formation (fig. S42A). The formation of an anthraquinone photoproduct from both 9-MA and 9-AnCH₂OH is not entirely surprising since the middle ring in the anthracene moiety has a diene character, thereby enabling the electrophilic addition of O₂ at the 9,10 position. The identity of the chemical products that we obtain from the nanocage-mediated photoreaction (for plausible mechanism, see scheme S2) matches exactly with the enzyme-catalyzed oxidation products of 9-MA and 9-AnCH₂OH (52). In essence, we find that our methodology of photoinduced PCET activation and subsequent oxidation for 9-MA inside the cage mimics the enzyme-mediated reaction conceptually without the direct involvement of a conventional metal-based catalyst.

**Nanocage enables selective photooxidation of 1-MeNap and Tol**

For 1-MeNap and Tol, the reduced number of fused benzene ring prohibits a direct 1,4 addition of O₂, thereby reducing the possibilities of para-quinone formation. Blue-light illumination [460-nm light-emitting diode (LED)] on the host-guest complex of 2 c Cage for 7.5 hours yields 1-naphthaldehyde in 60% and 7.8-diol in 40% yield (Fig. 3B and figs. S43 and S44). The higher selectivity for C–H photooxidation to yield aldehyde and alcohol without any naphthoquinone formation demonstrates the generality of our host-guest photoactivation paradigm. Photocatalysis was performed with 5 mol % of the cage while maintaining the product ratios. In contrast, the enzymatic oxidation of naphthalenes by naphthalene dioxygenases usually produce ring-degraded products after the formation of aromatic diols, aldehydes, and quinones (53). The emergence of selectivity toward –CH₃ oxidation by our host-guest CT paradigm indicates that specificity toward the primary C–H bond can be amplified by tuning the delocalization of the substrate cation radical. Separately, we observed that 1-naphthaldehyde forms from the photooxidation of 1-naphthylalcohol, thereby confirming that the aldehyde product is exclusive if the intermediate alcohol is formed. Since we do not isolate any intermediate alcohol from 1-MeNap photoreaction, we conjecture that 1-naphthaldehyde formation can proceed via a concerted 4e⁻/4H⁺ pathway (54) after C–H photoactivation. Alternatively, we...
can also rationalize that alcohol, being more reactive toward oxidation, can have a very small steady-state concentration, making it difficult to identify in the photoprduct mixture.

Tol, due to its single benzene ring, has a more spatially localized π-electron cloud and shows a blueshifted CT band relative to 9-MA or 1-MeNap after incarceration (Fig. 2A). By using the PCET trigger operated at 400-nm LED illumination for 3 ⊂ Cage, the photo-generated long-lived benzyl radical inside the cavity reacted with molecular O₂ to give benzaldehyde as a single product. When the photoreaction was carried out under an average stoichiometry of...
~4 Tol molecules per cage, we obtained 60% yield for the reaction and 100% selectivity for benzaldehyde in 8.5 hours (Fig. 3C). Extending this remarkable result to catalytic conditions, we found that, when operated with 5 mol % loading of the cage, 93% of Tol molecules converted to benzaldehyde with 100% selectivity in 40 hours, as shown in the gas chromatography–mass spectrometry (GC-MS) trace in Fig. 3D (fig. S46). No other side products such as benzyl alcohol or benzoic acid or ester were observed. To the best of our knowledge, this PCET-mediated photocatalytic route is a novel methodology for selective chemical synthesis of benzaldehyde from toluene under ambient conditions in water with high conversion efficiency. Note that, although both stoichiometric and catalytic conversions for selective benzaldehyde formation have been targeted previously (55, 56), these methods have not been optimized for industrial scalability. In addition, the industrial method of Etard oxidation for benzaldehyde synthesis requires high temperatures and use of caustic solvents (57). Apart from these forays, metal-oxide cages have also been used as photocatalytic containers, although the reactions examined were mostly in the heterogeneous phase with activation at a metal site. In contrast, our method relies on the green chemistry principle, i.e., usage of water as a solvent and light and oxygen as reagents, without direct involvement of a metal center in the bond activation while the entire photocatalysis is carried out at room temperature.

Radical stability is increased by alky substitution on the methyl group

Since the photocatalytic Pd6L412+ nanocage cavity mimics an enzyme active site, the displacement of the photoproduct, benzaldehyde, by fresh Tol is essential for maintaining catalytic turnover (see the photocatalytic cycle in Fig. 3F). Since PCET activation of substrate C•H bonds is much faster than the product formation time scale, the residence time of the benzaldehyde inside the cavity is crucial for determining the catalytic turnover rate. Because of the presence of a polar –CHO functional group, benzaldehyde has higher free energy of solvation in water than Tol, causing facile displacement of benzaldehyde from the cavity by excess Tol after single turnover. Since there were no intermediates observed during conversion of Tol to benzaldehyde, we hypothesized that the neutral benzyl radical upon reaction with O2 and subsequent electron and proton recombination step forms the organic hydroperoxide. Previous works on benzyl radical oxidation by O2 gas or chemical oxidants (55, 58, 59) has also shown benzaldehyde formation along with other oxidized side products. We found out that, depending on the intrinsic stability of aromatic benzylic hydroperoxide, kinetic partitioning via either heterolytic cleavage I or heterolytic cleavage II of the O–O bond can occur (see the schemes in fig. S49). Although our cage-confined benzyl radical reaction with molecular O2 has similarity to literature precedents, we demonstrate temporal and chemical control on the obtained oxidized products. To elucidate the mechanism for benzaldehyde formation inside the cavity, we used isopropyl-benzene or cumene, 4, as a mechanistic probe (see Fig. 3E and fig. S49). Since the isopropyl group can form a stable tertiary radical after the PCET reaction, the photogenerated organic hydroperoxide (4c, 28%) and the corresponding tertiary alcohol (4b, 36%) are stable as compared to their primary analogs, thereby allowing their observation in the GC-MS traces along with the one carbon-removed product, acetophenone (4a, 35%). These stable hydroperoxides at the tertiary carbon of adamantine were also reported previously by Fujita and co-workers (25). We therefore demonstrate that the lifetime of the organic hydroperoxide plays a critical role in directing the selectivity of products formed by also photocatalytically (3 mol % cage) converting ethylbenzene to acetophenone (93%), with a minor population of secondary alcohol (7%) (fig. S48).

**Nanocage-confined alkyl-aromatic substrate reactivity is altered by substitutions on the phenyl group**

We rationalized that the photocatalytic rates of benzaldehyde formation from Tol could be tuned by systematically introducing electron-donating and electron-withdrawing substituents on the phenyl ring of Tol. To this end, we compared substrate conversion rates and product yields for three different Tol derivatives, namely, methyl (–CH3), methoxy (–OCH3), and fluoro (–F) derivatives with substitution at the para position (in Fig. 4, A and B). While methyl and methoxy groups are electron-donating substituents, the fluoro group has a strong electron-withdrawing effect. We find that, for methyl substitution in para-xylene [for one-dimensional (1D) and two-dimensional (2D) NMR characterization; figs. S17 and S18], the substrate conversion rate increases by twofold relative to Tol, thereby demonstrating a modest extent of reaction tunability induced by this particular phenyl ring substituent through stabilization of the radical cation state (fig. S50). On the other hand, in the fluoro-derivative case (for 1D and 2D NMR characterization; figs. S23 and S24) the reaction does not proceed beyond 70% in 40 hours, demonstrating that the electron-withdrawing substitution in the ring not only slows down the conversion rate by 1.3 times but also affects the turnover step due to additional noncovalent interactions via the –F site (fig. S54). Unexpectedly, the electron-donating –OMe substitution (for 1D and 2D NMR characterization; figs. S21 and S22) also shows slower reaction rates but with high conversion percentages (~94%) and exclusive product selectivity (97%) (fig. S53). Presumably, in the case of para-OMe substitution, both the electronic effects and intermolecular interactions caused by substrate packing in confinement drive product selectivity and catalytic rates.

To understand the dependence of sp2 C–H bond oxidation on the position of the CH3 substituent in the phenyl ring, the reaction rates of positional regioisomers, meta-xylene (for 1D and 2D NMR characterization; figs. S19 and S20) and ortho-xylene (for 1D and 2D NMR characterization; figs. S15 and S16), were compared to that obtained for para-xylene. For meta-xylene, we observe slower rates of conversion relative to para-xylene and pure Tol oxidation (fig. S52), while ortho-methyl substitution led to conversion rates that were slightly faster than the parent Tol but slower than para-xylene rates (fig. S51). The decrease in rates from para- to ortho- to meta-presumably enunciates strong influence of regioisomeric ring substitution effects on C–H bond oxidation. However, the packing of the substrates are also slightly different for the three xylene derivatives (figs. S16, S18, S20, and S25). The chemical shifts of the –CH3 protons in 1H NMR spectra for the three xylene derivatives correlate well to their catalytic rates of oxidation (fig. S55). The observed chemical shifts from the NMR data indicate faster oxidation reaction rates when the methyl protons are toward the open pore/interfacial water (closer to pyridine H3/H4) rather than orienting to the core triazine ring (C3N3) of the cavity ligand walls. Although two equivalent methyl groups are available for the photooxidation reaction in the xylene derivatives, we find only single –CH3 oxidation, reinforcing high regioselectivity for the exposed C–H bond. The anomalous
reaction rates for para-OMe and para-Fluoro substituents can be explained by the differential packing of these substrates in the cage cavity, as highlighted by the clear changes observed in the chemical shifts and cross-correlation peak intensities in both 1D $^1$H NMR and 2D $^1$H-$^1$H ROESY (rotating frame nuclear Overhauser effect spectroscopy) NMR spectral data. We find lower integrated peak volumes for cross-peaks arising between $\text{▬CH}_3$ protons of the guest and the triazine protons ($H_\beta$ and $H_\alpha$ on the pyridine) of the cage in para-OMe and para-Fluoro substituent compared to all the xylene-incarcerated complexes (table S2). In Fig. 5C, the data indicate greater distances between substrate $\text{▬CH}_3$ protons and cage pyridine-$H_\alpha$/pyridine-$H_\beta$ for para-OMe and para-Fluoro substituent compared to all the xylene-incarcerated complexes (table S2). In Fig. 5C, the data indicate greater distances between substrate $\text{▬CH}_3$ protons and cage pyridine-$H_\alpha$/pyridine-$H_\beta$ for para-OMe and para-Fluoro substituent compared to all the xylene-incarcerated complexes (table S2). In Fig. 5C, the data indicate greater distances between substrate $\text{▬CH}_3$ protons and cage pyridine-$H_\alpha$/pyridine-$H_\beta$ for para-OMe and para-Fluoro substituent compared to all the xylene-incarcerated complexes (table S2).

The nanocage as a prototypical photoenzyme: Tunable cage electronics and cavity size as evolutionary strategies for controlling reaction kinetics

By combining the enzyme-like substrate encapsulation behavior of the nanocage with light activation, we have introduced a modular photocatalytic method, robust and general enough for a diverse range of alkyl-aromatic substrate oxidation reactions. The cationic Pd$_6$L$_4$ nanocages can be thought to evolve like an enzyme to modulate the catalytic rate of Tol oxidation. Figure 4C compares the reaction time course of photocatalytic Tol oxidation inside two different Pd$_6$L$_4^{12+}$ nanocages, Encage and Bipycage, being plotted.

**Fig. 4. Tuning the substrate and cavity electronics for photocatalytic oxidation of Tol.** (A) Product distribution for Tol and each of the Tol derivatives at 5 mol % catalyst loading of the Pd$_6$L$_4^{12+}$ nanocage and under high O$_2$ pressure (~1.5 atm) with 400-nm LED illumination. All the reactants showed benzaldehyde as the major product with >94% yields. Minor products of alcohol and acid are also observed for certain derivatives. (B) Comparison of photocatalytic reaction time (gray bars) and percentage conversion (orange bars) for Tol, para-methoxy Tol, para-Fluoro Tol, para-xylene, meta-xylene, and ortho-xylene inside the Encage. (C) Reaction rates for conversion of Tol to benzaldehyde using two different Pd$_6$L$_4^{12+}$ nanocages, Encage and Bipycage, are plotted.
in ~40 hours with 93% conversion, while for the Bipycage, the conversion is slower (in ~56 hours with ~90% conversion) although with equal product selectivity (fig. S56). Note here that the reaction proceeds via a lag phase, which is independent of the nanocage used and possibly reflects the initial encapsulation dynamics of the guest inside the host necessary to trigger the catalytic reaction. For another variant of the nanocage, where the external ligand of Pd^{2+} is TMEDA (N,N,N′,N′-tetramethylethylenediamine), we observe a prominent selectivity change in the Tol photocatalytic oxidation reaction (fig. S57). After 26 hours of photocatalysis, while 53% of Tol is converted into products, ~20% of the product mixture comprises benzyl alcohol, ortho-cresol and para-cresol, and the rest is benzaldehyde. These “mutations” of the cavity therefore ensure that the nanocages studied here can be evolved by a change of Pd ligands, thereby making these supramolecular structures excellent mimics of natural enzymes. We thus view the Pd_{6}L_{4}^{12+} nanocage as a prototypical “photoenzyme” (61), which can oxidize organic substrates in water with the help of molecular oxygen and can be evolved in an enzyme-like fashion.

**Preorganization of Tol assists polarization of methyl C–H bonds inside a nanocage**

One of the notable features of the artificial photooxidase system presented here is that the sp^{3} C–H bond activation occurs without any direct interaction with a metal center. However, the cage itself is made up of six Pd^{2+} metal ions in octahedral symmetry where each ion is coordinately saturated within a symmetric square-planar geometry. We estimated the spatial proximity of the –CH_{3} group in Tol to the Pd^{2+} sites in the cavity through detailed ¹H–¹H correlation 2D NMR experiments. As shown in Fig. 5A, the ROESY experiment provides direct evidence for spatial proximity (~5.1 Å; table S1) of the Tol CH_{3} protons to the β protons of the triazine pyridine rings that form the cavity walls. In addition, the aromatic protons of Tol also exhibit spatial coupling, albeit with lower strength (r ~ 5.7 to 6.7 Å), indicating that the benzene ring is closer to the central ring of the triazine wall. These spatial constraints allow us to estimate the average separation of the Tol CH_{3} protons from the Pd site to be ~6.7 Å (see model in Fig. 5B, fig. S13, and table S1). NMR data thus provide evidence that there is no direct interaction of the sp^{3} C–H center with Pd^{2+}. On the other hand, the electrostatic field generated by the six Pd^{2+} ions may still be strong enough to possibly prepolarize the alkyl-aromatic substrates. These strong fields can potentially influence both the π-electron density of aromatic ring and the σ density on the C–H bonds. We used Raman spectroscopy to directly probe any ground-state prepolarization effects on the substrate arising from nano-confinement in the presence of strong electric fields (E-fields). Ground-state Raman spectroscopy (λ_{ex} = 532 nm) enumerated guest-specific C–H bond stretching frequencies for both the methyl sp^{3} C–H bond and the sp^{3} C–H bond in the benzene ring. In Fig. 6A, the incarcerated Tol molecules (3 c Cage) show two distinct C–H stretches at 2952 cm⁻¹ (phenyl C–H) and 2849 cm⁻¹ (methyl sp^{3} C–H), which are remarkably redshifted by 105 and 73 cm⁻¹ respectively, relative to their values observed for bulk-free Tol. The large redshift in the C–H bond stretching frequency cannot be explained by [C–H•••O] H-bonding as these effects are limited to modest shifts of 15 to 20 cm⁻¹ (62). However, solvent-induced E-fields can produce large Stark shifts [with a tuning rate of ~0.4 cm⁻¹/(MV/cm)] in vibrational frequencies for the polarizable C–O bond (63). We therefore believe that the Raman
data hint at an overall ground-state electrostatic polarization of the C–H bonds inside the charged cavity. For the unpolarized C–H bond, the Stark tuning rate of the cavity E-fields is expected to be much larger than that for the C–O oscillator.

E-fields inside the cavity lead to bond polarization

To capture the effect of C–H bond polarization due to static E-fields, we computed the electronic structure of a free Tol molecule under field strengths, varying from 0 to 25 V/Å and along two distinct directions. For an E-field orientation parallel (↑↑) to the phenyl-methyl bond along the −CH₃ symmetry axis, we find (Fig. 6B) that the methyl C–H stretching mode frequencies (fig. S58) undergo marked redshifts relative to their values in the absence of an E-field. The frequencies are found to increase monotonically with the field strength. The E-field–dependent shift is not mode sensitive at lower E-fields (<10 V/Å) but becomes mode sensitive at higher E-fields. For the ↑↑ E-field direction, a field strength of 10 V/Å reproduces the experimentally observed redshift of 73 cm⁻¹ for the sp³ C–H stretches (Fig. 6B and fig. S58). We find (fig. S58C) that the character of the modes is retained (i.e., modes remain purely methyl modes) over the entire range of E-field strengths spanning from 0 to 25 V/Å. Our calculations further show that the C–H bond frequency shifts are highly sensitive to the direction of the E-field. The application of an anti-parallel (↑↓) E-field to the phenyl-methyl bond, along the −CH₃ symmetry axis, leads to a blueshift in the methyl C–H stretch mode frequencies (relative to zero field values) initially at low field strengths (<5 to 6 V/Å), but it is reversed to a redshift at higher field strengths (Fig. 6B). Further analysis (fig. S59) reveals that higher ↑↓ E-field strengths (>5 to 6 V/Å) result in admixture of methyl and phenyl C–H stretch modes and produce mode-selective frequency shifts. Notably, for the ↑↓ E-field direction, higher field strengths >15 to 25 V/Å are required to produce the experimentally observed redshift (~73 cm⁻¹). For both ↑↑ and ↑↓ E-field directions, field strengths that reproduce the experimental C–H stretch redshifts do not alter the molecular geometry (fig. S60) but rather polarize the molecular orbitals (Fig. 6C) in a direction-sensitive manner. Using a point charge description of the bare cationic nanocage, we found an E-field strength of ~5 to 6 V/Å inside the cavity at a distance of ~7 Å from the Pd²⁺ sites. Together, our experimental and computational investigations indicate a substantial prepolarization of the ground-state methyl C–H bonds induced due to the E-field within the cavity.

Our model of bond prepolarization inside the nanocage resembles enzyme-mediated catalysis, which is also driven by confined E-fields generated by active site residues (64). Our results above suggest that changes in the substrate ring aromaticity, which alter the delocalization of molecular orbitals, may further tune the prepolarization of the methyl C–H bonds by E-fields. To examine the effect of the aromatic ring structure on the E-field–induced shifts in

![Fig. 6. Ground-state polarization of the preorganized sp³ C–H bond.](image)

(A) Steady-state Raman traces for free Tol (top, blue) and caged Tol (bottom, black) along with the fit (red line) after an excitation at 532 nm. Phenyllic and methyl C–H stretches are both redshifted because of cage confinement. (B) Ground-state Raman frequency shifts (zoomed in) of methyl C–H stretches (three modes are color-coded) in the presence of E↑↑ (top, E-field parallel to the C₃ axis of the Tol molecule) and E↑↓ (bottom, E-field opposite to the C₃ axis of the Tol molecule) full spectra are presented in figs. S58 and S59. (C) Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of Tol are plotted in the absence (first column) and presence of E↑↑ (at 10 and 25 V/Å) (middle pair of columns) and E↑↓ (at 5 and 25 V/Å) (last pair of columns) to show the polarization effect on the frontier orbitals due to an external E-field. a.u., arbitrary units.
methyl C–H stretch frequencies, we compared ↑↑ E-field–induced (5 to 15 V/Å) shifts on mode frequencies of 9-MA and Tol (fig. S61). We find that the change in substrate aromaticity distinctly alters the C–H stretch mode frequency shifts due to the applied E-field. While the ↑↑ E-field–induced shifts in methyl C–H stretches for Tol are not mode sensitive (fig. S61, D and E), the ↑↑ E-field–induced shifts for 9-MA show pronounced mode sensitivity. For instance, all three Tol sp^3 C–H stretch modes show experimentally relevant redshifts (~73 cm^−1) at E-field strengths of ~10 V/Å. In contrast, three C–H stretches of methyl in 9-MA show distinct E-field–dependent shifts (fig. S61B). While two of the modes (blue and green) show a redshift (~73 cm^−1) at E-field strengths <10 V/Å, the third mode (red) shows the similar shifts at values >10 V/Å. The different aromaticity of 9-MA and Tol leads to different extents of E-field–induced MO polarizations (fig. S61F and Fig. 6C), which tune the response of the methyl C–H stretch frequencies and therefore the ground-state prepolarization of C–H bonds by the cavity E-fields. It has not escaped our attention that, apart from E-fields, the polarization induced due to emergence of the new host-guest CT states should also affect the C–H bond stretching frequency.

CONCLUSIONS
The cationic nanocage presented here is a prototypical photooxidase that mimics natural enzymes by encapsulating organic substrates in water and photocatalytically generates oxidized products in the presence of molecular oxygen. Using the nanocage, we have developed a modular general approach for redox-activated reactions, which can be diversified by a suitable and rational choice of guest and its complementary host. In addition, our work enunciates the critical role of E-fields in driving reactions under nano-confinement. Tailoring the E-field features should enable selective bond polarization in complex polyatomic molecules trapped inside nano-hosts. The success of our prototypical photoenzyme is further highlighted by our ability to tune cavity electronics along with molecular packing to control both catalytic reactivity and selectivity. We anticipate that our paradigm will lead to the development of new prototypical photoenzymes for redox-activated C–C or C–N bond coupling reactions and that, through these green methodologies, the environmental impact of chemical industries can be alleviated.

MATERIALS AND METHODS
Materials
9-MA (98%), 1-MeNap, ethylbenzene (anhydrous, 99.8%), iso-propylbenzene (cumene), para-substituted Tol derivatives, and 2,4,6-tri(4-pyridyl)-1,3,5-triazine were purchased from Sigma-Aldrich and TCI Chemicals Pvt. Ltd., respectively. We used high-performance liquid chromatography–grade (HPLC) Tol (99.7% purity) for all the photoreactions. Solvents and other reagents were purchased from SD Fine Chemicals and Sigma-Aldrich. Deuterated water (D$_2$O; 99.9 atom %D) was procured from Sigma-Aldrich. The Pd$_4$L$_4$ cage was synthesized following the reported protocol and discussed in supporting information. All the incarceration strategies are discussed in the Supplementary Materials.

Resonance Raman spectroscopy
For resonance Raman measurements, we used an excitation wavelength of 532 nm, which was generated from a frequency-doubled diode-pumped solid-state (DPSS) yttrium-aluminum-garnet–Nd (Nd:YAG) laser (WITec) and coupled to the Alpha 300R confocal Raman microscope (WITec GmbH, Ulm, Germany). A 100-µm optical fiber was used to collect the backscattered light where a lens-based ultrahigh throughput spectrometer (UHTS300) with 1800 grooves/mm grating was used and coupled to a back-illuminated charge-coupled device camera (CCD, 1024 × 128 pixels, Peltier-cooled to ~65°C) for detection. The spectral resolution of the spectrograph was ~2 cm^−1. The laser was focused into the solution flowing through a flow cuvette (path length is 2 mm) using a 10× objective. The power of the laser source (532 nm) was 3 to 4 mW at the sample stage.

Transient absorption measurements
All pump-probe measurements were executed using an ultrafast transient absorption spectrometer, located in the ultrafast biophysics and photomaterials laboratory of the Department of Chemical Sciences, Tata Institute of Fundamental Research, India (65). An oscillator output with a center wavelength of 810 nm, a bandwidth of ~100 nm, and a repetition rate of 80 MHz was amplified 10^6 times using a commercial regenerative amplifier. The output of the amplifier was 30 fs/4 mJ per pulse, with a repetition rate of 1 kHz and a bandwidth of ~65 nm. We generated a 400-nm pump by frequency doubling a portion of the 810-nm output from the amplifier from a beta barium borate (BBO) crystal. The amplifier output was directed to an optical parametric amplifier (Coherent OPerA Solo Ultrafast Optical Parametric Amplifier system) for generation of the 490-nm pump pulse. For measurements, a pump beam was attenuated to ~200 to 400 nJ per pulse. The white-light broadband probe continuum (440 to 1400 nm) was generated by focusing a portion of the amplified 810-nm output on a 2-mm-thick sapphire and then directing it to a multi-channel detector. The pump and probe pulses were focused and overlapped spatially and temporally within the sample cuvette. For measurements, we used a flow cuvette of 2-mm path length. Kinetic fitting of the raw data traces were performed using a mathematical program for deconvoluting the time constants from the recorded instrument response function (IRF) in IGOR Pro 5 software. Global and target analyses of the transient absorption data were carried out with the help of the Surface Xplorer and Glotaran software (66).

Photoreaction on host-guest complexes
We used commercial cheap LEDs (photon flux, ~80 to 100 mW) for all the photoreactions. Then, a green LED (λ = 530 nm) for 9-MA ⊂ Cage and a blue LED (λ = 460 nm) for 1-MeNap ⊂ Cage were illuminated for 1.5 and 7.5 hours, respectively, in a side illumination fashion (distance of the LED from the vial was kept at ~5 cm). For Tol ⊂ Cage, we used a round-bottom flask connected with a water condenser to avoid any loss of Tol because of its volatile nature, and an O$_2$ balloon (pressure is ~1.5 atm) was attached at the top of the condenser. Then, we illuminated with a blue LED (λ = 400 nm) for 8 to 40 hours depending on whether it is a stoichiometric photoreaction or a photocatalytic reaction. After completion of the reaction, the aqueous solution was extracted with an organic solvent, dichloromethane (CH$_2$Cl$_2$). The extracted photoproducts were either purified by column chromatography or analyzed by GC-MS, specifically for Tol and its derivatives.
Molecular modeling of Tol inside the Pd$_4$L$_4$$^{12+}$ cage to estimate distances between substrate methyl C–H bonds and cage Pd$^{2+}$ centers

The initial coordinates of the Pd$_4$L$_4$$^{12+}$ (Pd, ethylenediamine-palladium) cationic cage were obtained from the Cambridge Crystallographic Data Centre (CCDC number 277006) and optimized using density functional theory (DFT) at a B3LYP/Lanl2dz/6-31G* level of theory. Then, a single Tol molecule was placed close to one of the four triazine moieties of the optimized cationic cage using the distance constraints (see table S1) obtained from 2D ROESY NMR experiments (Fig. 5A). The Tol-cage complex was then minimized in water with the polarizable continuum model (PCM) (67), keeping the cage structure fixed and using the same level of theory mentioned above. For the resultant optimized Tol-cage complex, average distances between all hydrogen atom pairs of Tol and cage and between Tol H and Pd atoms were calculated and compared with NMR ROESY experimental data (see section S1.3).

Estimating the effect of E-fields on the ground-state alkyl C–H Raman stretch frequencies for Tol and 9-MA

We calculated Raman frequencies for Tol and 9-MA molecules in the presence of E-fields of varying strengths and directions to estimate E-field–induced prepolarization of methyl C–H bonds inside the charged cage. The E-field strengths were varied from 0.05 to 26 V/A, and the fields were applied along the methyl group symmetry axis, either parallel (↑↑) or antiparallel (↑↓) to the methyl-phenyl bond. For 9-MA, we carried out calculations only with the ↑↑ E-field. First, structures were optimized using the DFT method with the 6-31G* basis set on all atoms, and the B3LYP hybrid exchange-corrugational functional and vibrational Raman frequencies were calculated at the same level of theory in the presence of E-fields. All calculations were performed in the Gaussian 09 program (68). Further details of the calculations and analysis of calculated Raman modes as a function of E-field strength are provided in section S1.3.

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/5/2/eaav4806/DC1

Section 51. Materials and methods

Fig. 51. Calibration distance for 2D ROESY NMR.
Fig. 52. Octahedral nanocage.
Fig. 53. $^1$H NMR spectrum of a synthesized Pd$_4$L$_4$$^{12+}$ nanocage in D$_2$O.
Fig. 54. $^{13}$C NMR spectrum of a synthesized Pd$_4$L$_4$$^{12+}$ nanocage.
Fig. 55. Visible charge transfer complex of 9-MA.
Fig. 56. Host-guest complexation and NMR upfield shifts.
Fig. 57. Temperature dependence of population heterogeneity of caged 9-MA.
Fig. 58. Charge transfer complex with 1-MeNap.
Fig. 59. Host-guest complexation of 1-MeNap.
Fig. S10. Temperature-dependent $^1$H NMR of methyl protons.
Fig. S11. Complexation of Tol and nanocage.
Fig. S12. $^{13}$C NMR spectrum of Tol ⊂ Cage.
Fig. S13. Optimized structure of Tol inside a nanocage.
Fig. S14. Substituent-dependent steady-state absorption of host-guest CT complexes of Tol derivatives.
Fig. S15. Formation of ortho-xylene ⊂ Cage complex.
Fig. S16. 2D ROESY spectrum of ortho-xylene ⊂ Cage complex in D$_2$O in 800 MHz.
Fig. S17. Formation of para-xylene ⊂ Cage complex.
Fig. S18. ROESY spectrum of para-xylene ⊂ Cage complex in D$_2$O (800 MHz).
Fig. S19. Formation of meta-xylene ⊂ Cage complex.
Fig. S20. $^1$H 2D ROESY NMR spectrum of meta-xylene ⊂ Cage complex in D$_2$O in 800 MHz.
Fig. S21. Complexation of para-OMeTol with nanocage.
Fig. S22. 2D $^1$H ROESY NMR spectrum of para-OMeTol ⊂ Cage complex in D$_2$O.
Fig. S23. Complexation of para-FluoroTol with nanocage.
Fig. S24. 2D $^1$H ROESY NMR spectrum of para-FluoroTol ⊂ Cage complex in D$_2$O (800 MHz).

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