Photoswitchable catalysis by a self-assembled molecular cage

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ABSTRACT: A heteroleptic $[Pd_2L_2L'_2]^{4+}$ coordination cage containing a photoswitchable azobenzene-derived ligand catalyzes the Michael addition reaction between methyl vinyl ketone and benzoyl nitromethane within its cavity. The corresponding homoleptic cages are catalytically inactive. The heteroleptic cage can be reversibly disassembled and reassembled using 530 nm light and 405 nm light, respectively, allowing catalysis within the cage to be switched *ON* and *OFF* at will.

Over the past three decades, supramolecular cages have evolved from simple hosts to systems with impressive catalytic functions.[1-8] Inspired by how enzymes accelerate reactions, catalytic cages can leverage their activity in multiple ways. These include methods that rely on reducing the entropy of activation, for example using binding to limit conformational freedom,[9-10] or by encapsulating more than one substrate to increase effective concentration.[11-13] Cages can also use electrostatic forces to drive catalysis, for example leading to either enhanced basicity[14] or acidity[15] of the substrate compared to the non-bound species, and/or stabilizing any subsequent higher energy species.[16-18] Other methods of accelerating reactions include binding substrates in higher energy conformational states,[19] or using the local high concentration of ions around the cage portals.[20-21] When more than one of these mechanisms is used simultaneously, very high activity can be observed.[22] Molecular cages have also been used to control regioselectivity, although these reactions are not typically catalytic.[23-24]

A key feature of enzyme catalysis is regulated activity. This area of cage catalysis remains significantly underdeveloped and invariably relies on either the endo or exo binding of a guest that is not a substrate.[25] One way to mediate cage catalysis would be using light irradiation. Light-responsive molecular cages have been prepared using photoswitchable ligands and metal ions. These include those based on diarylethene photoswitches that form cages with different geometries and cavity sizes, allowing selective guest binding.[26-30] Diazocine-based cages are unique as they can be switched from a thermodynamically stable *Z*-isomer to the *E*-isomer using visible light, forming metastable cages that encapsulate guests.[31] A related example uses two diazocine ligands that allow light to selectively disassemble one cage and assemble another.[32] We have recently reported an azobenzene-based molecular cage that reversibly responds to visible light to change its composition from a $[Pd_2L_4]^{4+}$ lantern-like structure to a $[PdL_2]^{2+}$ monomeric product.[33] However, guest molecules do not readily bind within the cavity of the lantern-like cage,[33] instead preferentially binding on the exterior. Molecular cages can also act as photosensitizers,[34] and have been used to drive photochemical reactions away from equilibrium.[35]

Photoswitchable catalysis[36-41] has progressed significantly since the earliest reports,[42] with examples of enantioselective catalysis,[43-44] polymerization[45] and cooperative catalysis.[46] In these examples, the catalysis is switched by changing the electronic properties of a donor atom,[47] blocking an active site with steric bulk,[42] bringing together cooperative organocatalytic groups,[43] or forming a more reactive functional group.[48] While there are reports of switchable catalysis within macrocycles,[49-50] on surfaces of nanoparticles,[51-54] and using rotaxanes,[55] to the best of our knowledge, there are no reports of photoswitchable catalysis using discrete self-assembled species. Herein we report light-regulated catalysis using a heteroleptic $[Pd_2L_2L'_2]^{4+}$ cage system (Figure 1).

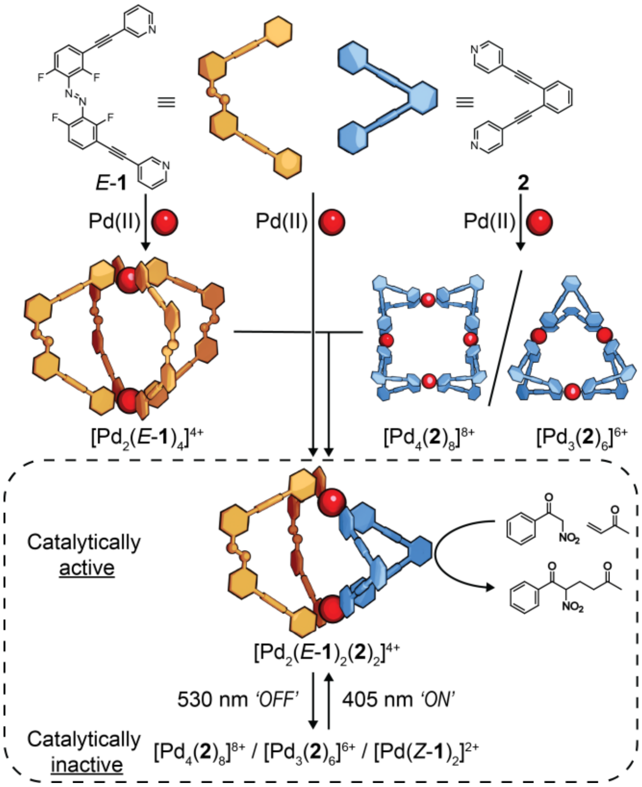

Figure 1. Self-assembly of homoleptic cages $[Pd_2(E\text{-}\mathbf{1})_4]^{4+}$, $[Pd_4(\mathbf{2})_8]^{8+}$, $[Pd_3(\mathbf{2})_6]^{6+}$ and photoswitchable heteroleptic cage catalyst $[Pd_2(E\text{-}\mathbf{1})_2(\mathbf{2})_2]^{4+}$.

Photoswitchable ligand **1** was synthesized via Sonogashira cross-coupling (see SI-S2) of 3–bromo–2,6–difluoroaniline and 3-ethynylpyridine to give 2,6-difluoro-3-(pyridin-3-

ylethynyl)aniline in 80% yield. The reaction of two equivalents of this aniline with *N*-chlorosuccinimide (NCS) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[56] gave photoswitchable ligand **1** in 33% yield. A single-crystal X-ray structure of *E*-**1** (CCDC: 2343887, see SI-S2.4) confirmed the rings are almost coplanar, similar to related ligands we have reported.[33, 57]

The photoswitching properties of ligand **1** were investigated using NMR and UV-vis absorption spectroscopies (see SI S3). Photostationary states (PSS) were generated by irradiating a sample of *E*-**1** in DMSO-d_6 with a 530 nm LED for 10 minutes (PSS_{530} = 88% *Z*-**1**) or 405 nm LED for 20 minutes (PSS_{405} = 86% *E*-**1**). The metastable isomer, *Z*-**1**, has a thermal half-life of around a month at room temperature in DMSO (see SI S3.3), in line with that of related switches.[33]

Reaction of ligand *E*-**1** (4.6 mM, 1 equiv.) and $[Pd(MeCN)_4](BF_4)_2$ (2.3 mM, 0.5 equiv.) in DMSO-d_6 gives the homoleptic lantern-like complex $[Pd_2(E\text{-}\mathbf{1})_4](BF_4)_4$, as shown by the combination of NMR spectroscopy (Figure 2) and electrospray ionization mass spectrometry (ESI-MS) (see SI S6). When $[Pd_2(E\text{-}\mathbf{1})_4](BF_4)_4$ in DMSO-d_6 is irradiated with 530 nm light, the monomeric complex $[Pd(Z\text{-}\mathbf{1})_2](BF_4)_2$ is formed, as confirmed by NMR and ESI-MS experiments (see SI S7). This behavior is analogous to that of a related $[Pd_2L_4](BF_4)_4$ cage.[33] With this favorable photochemical switching, the host-guest chemistry of $[Pd_2(E\text{-}\mathbf{1})_4]^{4+}$ was then explored using the analogous tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BAr_F) salt.[58] The use of these large, "greasy" counteranions facilities both host-guest chemistry[58] and catalysis[5] with simple Pd_2L_4 cages. This is because they maximize polar (and electrostatically activating) interactions in less polar solvents by removing competitive counteranion binding.

To prepare the BAr_F salt, *E*-**1** was reacted with $[Pd(Py^*)_4](BAr_F)_2$ (where Py* = 3-chloropyridine, see SI S4)[59] in acetonitrile to give $[Pd_2(E\text{-}\mathbf{1})_4](BAr_F)_4$, which was characterized by NMR and ESI-MS data (see SI S6.4, S6.5). Disappointingly, $[Pd_2(E\text{-}\mathbf{1})_4](BAr_F)_4$ showed little evidence of guest binding, nor was it able to catalyze the representative Michael addition reaction of methyl vinyl ketone and benzoyl nitromethane in the presence of 18-crown-6, similar to the behavior of a related cage[33] (SI-S5.2, S5.3 S15.4.3).

There are several possible reasons for this lack of host-guest chemistry and reactivity. Empirical observations have suggested that the co-binding of both substrates is necessary for catalysis.[15] Therefore, it could be that the relative size and shape of the cavity of $[Pd_2(E\text{-}\mathbf{1})_4](BAr_F)_4$ is unsuitable for dual binding. A molecular model of the homoleptic cage also reveals another potential problem; $[Pd_2(E\text{-}\mathbf{1})_4]^{4+}$ has a pronounced twisted conformation (Figure 2b), a consequence of the non-parallel coordination vectors of *E*-**1**, similar to a related cage.[33] In turn, this twisting distorts the pocket of four inward-facing *ortho*-pyridyl hydrogen atoms. This distortion prevents the CH···O hydrogen bonds between the cage and substrate, which are thought to be crucial for catalysis.

Looking at an alternative cage design, and to address the twisted conformation that could hinder catalysis, we targeted a heteroleptic system combining rigid ligand **2** with *E*-**1**. This combination of ligands was selected for their shape complementarity.[60-64]

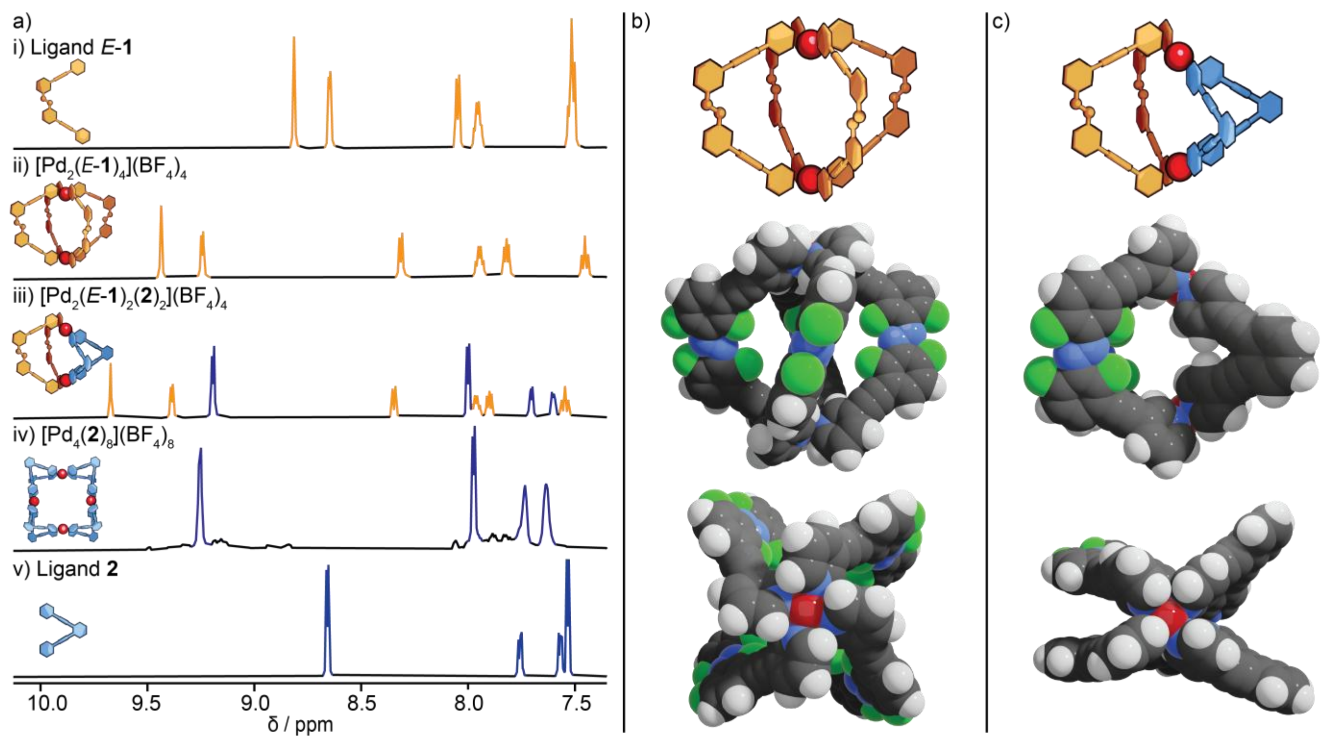

Figure 2. Characterization of homoleptic and heteroleptic cages. a) ^{1}H NMR spectra (600 MHz, DMSO-d_6) of i) photoswitchable ligand **1**; ii) homoleptic $[Pd_2(E\text{-}\mathbf{1})_4](BF_4)_2$; iii) heteroleptic $[Pd_2(E\text{-}\mathbf{1})_2(\mathbf{2})_2](BF_4)_4$; iv) homoleptic $[Pd_3(\mathbf{2})_6](BF_4)_6$ and $[Pd_4(\mathbf{2})_8](BF_4)_8$, as reported[65]; v) ligand **2**. b) Molecular mechanics model of homoleptic $[Pd_2(E\text{-}\mathbf{1})_4](BF_4)_4$. c) Single crystal X-ray structure of heteroleptic $[Pd_2(E\text{-}\mathbf{1})_2(\mathbf{2})_2](BF_4)_4$, CCDC: 2343886. Color codes: grey: carbon; white: hydrogen; blue: nitrogen; green: fluorine; red: palladium. Anions and solvent molecules are omitted for clarity.

On its own, ligand **2** is known[65] to react with palladium(II) ions to form a $[Pd_3(\mathbf{2})_6]^{6+}$ double-walled triangle in acetonitrile and a $[Pd_4(\mathbf{2})_8]^{8+}$ double-walled square in DMSO,[65] which we also observe (Figure 2aiv, SI S8 and S9).

When one equivalent of each of ligand *E*-**1**, ligand **2**, and $[Pd(MeCN)_4](BF_4)_2$ are combined in DMSO-d_6 a single new species is formed within 10 min at room temperature (Figure 2aiii, SI S10). An identical result is obtained if the homoleptic cages $[Pd_2(E\text{-}\mathbf{1})_4](BF_4)_4$ and $[Pd_4(\mathbf{2})_8](BF_4)_8$ are combined in DMSO-d_6 and heated with a heat gun for 5 min (see SI S10.1), indicating that the heteroleptic cage is the thermodynamic product.Multinuclear NMR experiments (SI-S10.2) confirm the heteroleptic cage is symmetrical with a single environment for each of the ligands, *E*-**1** and **2**. Inter-ligand ROESY interactions indicate that both ligands are coordinated to the same metal ion (SI-S10.2). ESI-MS confirmed the composition as $[Pd_2(\mathbf{1})_2(\mathbf{2})_2]^{4+}$ with a series of ions with isotope patterns corresponding to sequential loss of BF_4 anions (SI S10.3). Finally, a single crystal suitable for X-ray diffraction unambiguously confirmed the heteroleptic species as *cis*-$[Pd_2(E\text{-}\mathbf{1})_2(\mathbf{2})_2](BF_4)_4$ (Figure 2c, CCDC: 2343887, SI S10.4), in line with expectations from shape complementarity prediction.[60-64] The cage has a Pd···Pd separation of 9.92 Å. The pyridyl units are not significantly twisted (angles between the *trans* pyridyl rings range from 16 to 22 °), and therefore the *ortho*-pyridyl hydrogen-bond donors project into the cavity for optimal guest binding and catalysis.

When the heteroleptic cage $[Pd_2(E\text{-}\mathbf{1})_2(\mathbf{2})_2](BF_4)_4$ in DMSO-d_6 is irradiated with 530 nm light it is disassembled, and the ^{1}H NMR spectrum (Figure 3ii) shows a mixture of products is formed. The mixture includes $[Pd(Z\text{-}\mathbf{1})_2]^{2+}$ and $[Pd_4(\mathbf{2})_8]^{8+}$, and possibly $[Pd_2(Z\text{-}\mathbf{1})_2(\mathbf{2})_2]^{4+}$ (SI S11). Upon irradiating with 405 nm light the heteroleptic cage

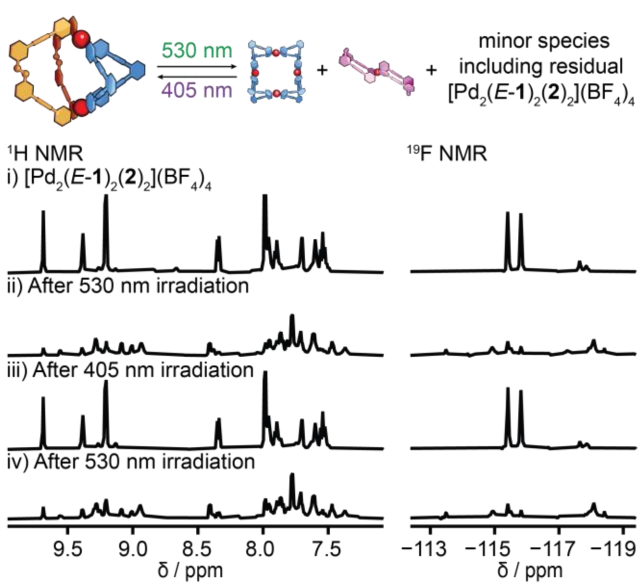

Figure 3. Partial ^{1}H (600 MHz) and ^{19}F (565 MHz) NMR spectra in DMSO-d_6 showing photoswitching of heteroleptic cage $[Pd_2(E\text{-}1)_2(2)_2](BF_4)_4$ i) before irradiation; ii) after 530 nm 10 min; iii) 405 nm 5 min; iv) 530 nm light 10 min irradiation. The PSS composition (PSS_{530} = 88% *Z*-**1**, the same as for the free ligand **1**) was confirmed by adding *N*,*N*-dimethyl-4-aminopyridine (DMAP) to displace the ligands. See SI S11.3 for details.

$[Pd_2(E\text{-}\mathbf{1})_2(\mathbf{2})_2](BF_4)_4$ is reformed near quantitatively (Figure 3iii, SI-S11.3). This data confirms heteroleptic cage $[Pd_2(E\text{-}\mathbf{1})_2(\mathbf{2})_2](BF_4)_4$ can be reversibly assembled and disassembled using visible light.

Turning to the equivalent BAr_F salt, we then tested whether the heteroleptic cage $[Pd_2(E\text{-}\mathbf{1})_2(\mathbf{2})_2](BAr_F)_4$ could be formed, and in particular, whether it could be generated from the rearrangement of the two homoleptic structures. Homoleptic structures $[Pd_2(E\text{-}\mathbf{1})_4](BAr_F)_4$ and $[Pd_3(\mathbf{2})_6](BAr_F)_6/[Pd_4(\mathbf{2})_8](BAr_F)_8$ can be assembled with $[Pd(Py^*)_4](BAr_F)_2$ in CD_3CN, and were characterized by NMR (SI-S6.4, S9.4) and ESI-MS data (SI-S6.5, S9.5). When a 1:1 mixture of these two homoleptic cages was combined in CD_3CN and heated at 50 degrees for 30 min, the heteroleptic cage was also formed quantitatively (SI S10.5). This indicates that swapping from BF_4 to BAr_F counteranions does not lead to problems of kinetic trapping.

A $[Pd_2L_4](BAr_F)_4$ cage has been shown to catalyze Michael addition reactions in the presence of 18-crown-6.[15] However, the solvent that is optimal for this catalysis—dichloromethane—is poorly coordinating and therefore does not promote the rapid ligand exchange required for cage switching. We found a solvent mixture of 11:1 CD_2Cl_2/CD_3CN, was a good compromise to maximize the host-guest chemistry while providing some coordinating properties to facilitate cage rearrangement (see SI S12, S13).

Using these mixed solvent conditions, we investigated whether $[Pd_2(E\text{-}\mathbf{1})_4](BAr_F)_4$, $[Pd_3(\mathbf{2})_6](BAr_F)_6/[Pd_4(\mathbf{2})_8](BAr_F)_8$ and $[Pd_2(E\text{-}\mathbf{1})_2(\mathbf{2})_2](BAr_F)_4$ could catalyze the reaction between methyl vinyl ketone and benzoyl nitromethane (Figure 4, SI-S15).[66] The consumption of benzoyl nitromethane and the generation of the Michael addition product were monitored using ^{1}H NMR spectroscopy (Figure 4, SI-S15.4).

The homoleptic species $[Pd_3(\mathbf{2})_6](BAr_F)_6/[Pd_4(\mathbf{2})_8](BAr_F)_8$ converted trace amounts (<1%) of benzoyl nitromethane to the

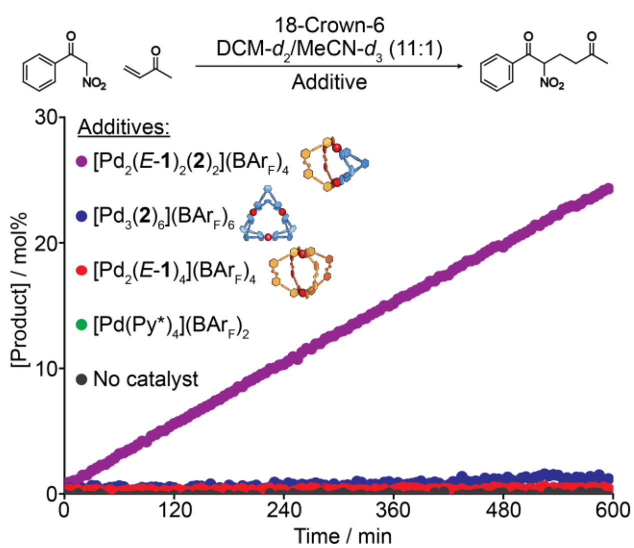

Figure 4. Catalysis of a Michael addition reaction by self-assembled cages. Reaction conditions: CD_2Cl_2/CD_3CN (11:1), benzoyl nitromethane (14 mM), methyl vinyl ketone (27 mM), and 18-crown-6 (11 mM). All cases with palladium [Pd] = 1.6 mM. Product formation measured by ^{1}H NMR spectroscopy. See SI-S15.4.

product over 10 hours, and $[Pd_2(E\text{-}\mathbf{1})_4](BAr_F)_4$ did not catalyze the reaction at all. However, the heteroleptic species $[Pd_2(E\text{-}\mathbf{1})_2(\mathbf{2})_2](BAr_F)_4$ converted 24% of the benzoyl nitromethane to the Michael addition product in 10 hours. To ensure $[Pd_2(E\text{-}\mathbf{1})_2(\mathbf{2})_2](BAr_F)_4$ was responsible for the catalysis, control experiments were performed using no catalyst and with $[Pd(Py^*)_4](BAr_F)_2$. For both control experiments, no product formation was observed.

Having shown that we can reversibly switch the heteroleptic cage with light and that it is also an active catalyst, it was time for photoswitchable catalysis! The $[Pd_2(E\text{-}\mathbf{1})_2(\mathbf{2})_2](BAr_F)_4$ cage was successfully disassembled (530 nm light for 10 min) and reassembled (405 nm light for 5 min) in 11:1 CD_2Cl_2/CD_3CN (see SI-S16), showing similar behavior to the BF_4 salt in DMSO-d_6 (Figure 3).[31] Benzoyl nitromethane, methyl vinyl ketone and 18-crown-6 were added to the sample and the reaction was monitored using ^{1}H NMR spectroscopy (Figure 5a), showing the cage was catalytically active. Next, the sample was irradiated with a 530 nm LED for 10 min, which resulted in a 10-fold decrease in the rate of product formation as the cage was disassembled. The reaction was then reactivated by irradiating with a 405 nm LED for 5 min. Following this reactivation, the rate of product formation was almost identical to that prior to 530 nm irradiation, showing that the photoswitching is completely reversible.

The system can also be kept dormant by first irradiating $[Pd_2(E\text{-}\mathbf{1})_2(\mathbf{2})_2](BAr_F)_4$ with a 530 nm LED before the substrates are added (Figure 5b, SI-S16.3). The reaction can then be activated at will by irradiating the sample with a 405 nm LED. The long thermal half-life of the photoswitch ensures the cage remains in the state it is programmed after the irradiation is stopped. The responsiveness of the system to visible light demonstrates that using a molecular photoswitch to control self-assembly can lead to excellent control of chemical reactivity.

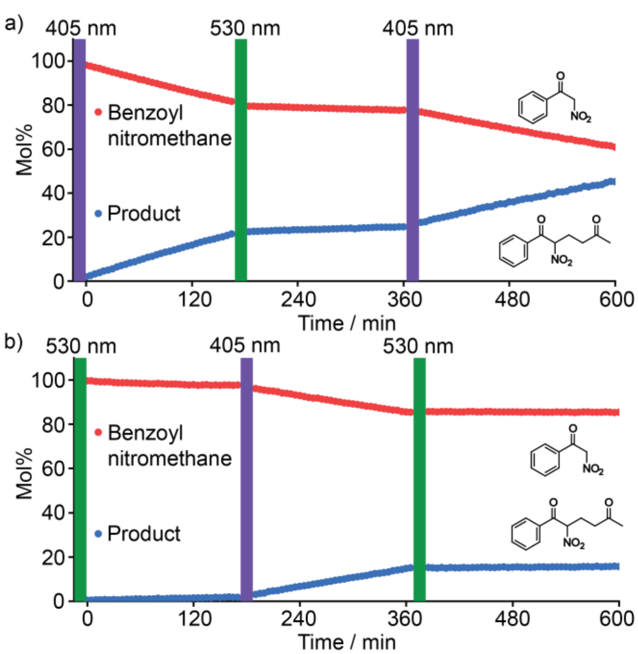

Figure 5. Photoswitchable catalysis by the heteroleptic cage $[Pd_2(E\text{-}\mathbf{1})_2(\mathbf{2})_2](BAr_F)_4$ in CD_2Cl_2:CD_3CN 11:1 monitored by ^{1}H NMR spectroscopy. Reaction conditions: benzoyl nitromethane (17 mM), methyl vinyl ketone (33 mM), and 18-crown-6 (12 mM), [Pd] 2.0 mM. Irradiation by 405 nm (5 min) and 530 (10 min) outside of the NMR instrument, with colored bars representing the time between NMR measurements, see SI-S16 for details.

In conclusion, we have shown the first example of photoswitchable catalysis within a self-assembled molecular cage. The mechanism of catalysis relies on electrostatic interactions within the cavity, which is only possible in the heteroleptic cage with a cavity preorganized for guest binding. The catalysis can be switched on and off with visible light (405 nm and 530 nm) and is entirely reversible. Controlling the catalytic activity of self-assembled cavities with non-destructive visible light is a new method for directing chemical reactions. Combining photoswitchable ligands with facile ligand-exchange reactions allows a system to be driven towards assemblies comprised of different components, with programmable stoichiometries, shapes, affinities and now catalytic functions. We anticipate future examples could include different self-assembled cages each capable of catalyzing different reactions, allowing more complex multi-step reactions to be performed simply by using visible light.

ASSOCIATED CONTENT

SUPPORTING INFORMATION

Experimental data, spectra and other data are supplied as SI.

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Author Contributions

The manuscript was written through contributions of all authors.

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66. The sample containing free Py* (arising from the displacement from [Pd(Py*)4](BArF)2). We explored the role of Py* in the rearrangement process and found it plays no significant role when there is a significant proportion of acetonitrile in the sample (see SI-14). In nitromethane (or nitromethane/DCM mixtures) the rate of ligand exchange was still slow.