

## Orthogonal Stimuli Trigger Self-Assembly and Phase Transfer of FeL Cages and Cargoes

Anna J. McConnell, Cally Jo Elizabeth Haynes, Angela Beth Grommet,  
Catherine M. Aitchison, Julia Guilleme, Sigitas Mikutis, and Jonathan R. Nitschke

*J. Am. Chem. Soc.*, **Just Accepted Manuscript** • DOI: 10.1021/jacs.8b11324 • Publication Date (Web): 22 Nov 2018

Downloaded from <http://pubs.acs.org> on November 22, 2018

### Just Accepted

“Just Accepted” manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides “Just Accepted” as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. “Just Accepted” manuscripts appear in full in PDF format accompanied by an HTML abstract. “Just Accepted” manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). “Just Accepted” is an optional service offered to authors. Therefore, the “Just Accepted” Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the “Just Accepted” Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these “Just Accepted” manuscripts.



# Orthogonal Stimuli Trigger Self-Assembly and Phase Transfer of $\text{Fe}^{\text{II}}_4\text{L}_4$ Cages and Cargoes

Anna J. McConnell,<sup>‡,†,§</sup> Cally J. E. Haynes,<sup>‡,†</sup> Angela B. Grommet,<sup>†</sup> Catherine M. Aitchison,<sup>†</sup> Julia Guilleme,<sup>†</sup> Sigita Mikutis<sup>†</sup> and Jonathan R. Nitschke<sup>\*,†</sup>

<sup>†</sup> Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, U.K.

<sup>§</sup> Otto Diels Institute of Organic Chemistry, Kiel University, Otto-Hahn-Platz 4, Kiel D-24098, Germany.

## Supporting Information Placeholder

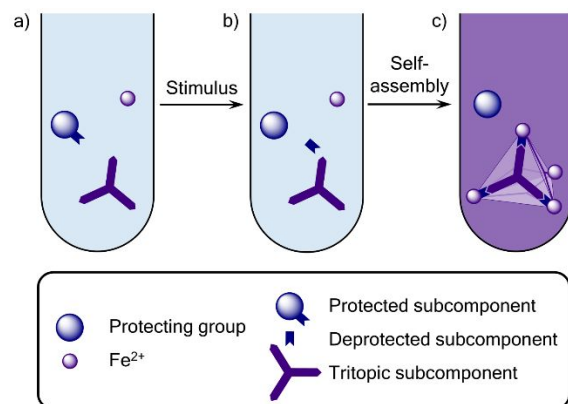
**ABSTRACT:** Two differently protected aldehydes, **A** and **B**, were demonstrated to deprotect selectively through the application of light and heat, respectively. In the presence of iron(II) and a triamine, two distinct  $\text{Fe}^{\text{II}}_4\text{L}_4$  cages, **1** and **2** were thus observed to form from the deprotected **A** and **B**, respectively. The alkyl tails of **B** and **2** render them preferentially soluble in cyclopentane, whereas **A** and **1** remain in acetonitrile. The stimulus applied (either light or heat) thus determines the outcome of self-assembly and dictates whether the cage and its ferrocene cargo remain in acetonitrile, or transport into cyclopentane. Cage self-assembly and cargo transport between phases can in this fashion be programmed using orthogonal stimuli.

The ability to control the spatial and temporal uptake, movement and release of substrates is an essential feature of the functioning of biological systems. In synthetic molecular networks,<sup>1</sup> stimuli-responsive<sup>2</sup> metal-organic structures<sup>3</sup> and container molecules<sup>4</sup> provide means for controlling the transport of guest molecules through the application of external signals.<sup>2d, 3a, 5</sup> For example, the phase transfer of coordination cages together with their guests has been triggered by chemical signals, such as anions.<sup>6</sup> The order of signal application has also been employed in molecular networks constructed from stimuli-responsive cages to release different guests depending on signal timing.<sup>5d, 7</sup>

We envisaged a new approach, where cage assembly and the attendant functions of phase transfer and guest binding, would be controlled by orthogonal signals. Others<sup>8</sup> and our group<sup>9</sup> have used subcomponent self-assembly to prepare cages, metallogels and helicates from amine and aldehyde subcomponents that combine dynamically around metal templates. We hypothesized that cage self-assembly could be rendered stimuli-responsive by masking the reactivity of one of the subcomponents using a protecting group. Deprotection of the subcomponent using a stimulus (Figure 1) would thus trigger cage self-assembly, allowing for different functional outcomes to be programmed.<sup>10</sup>

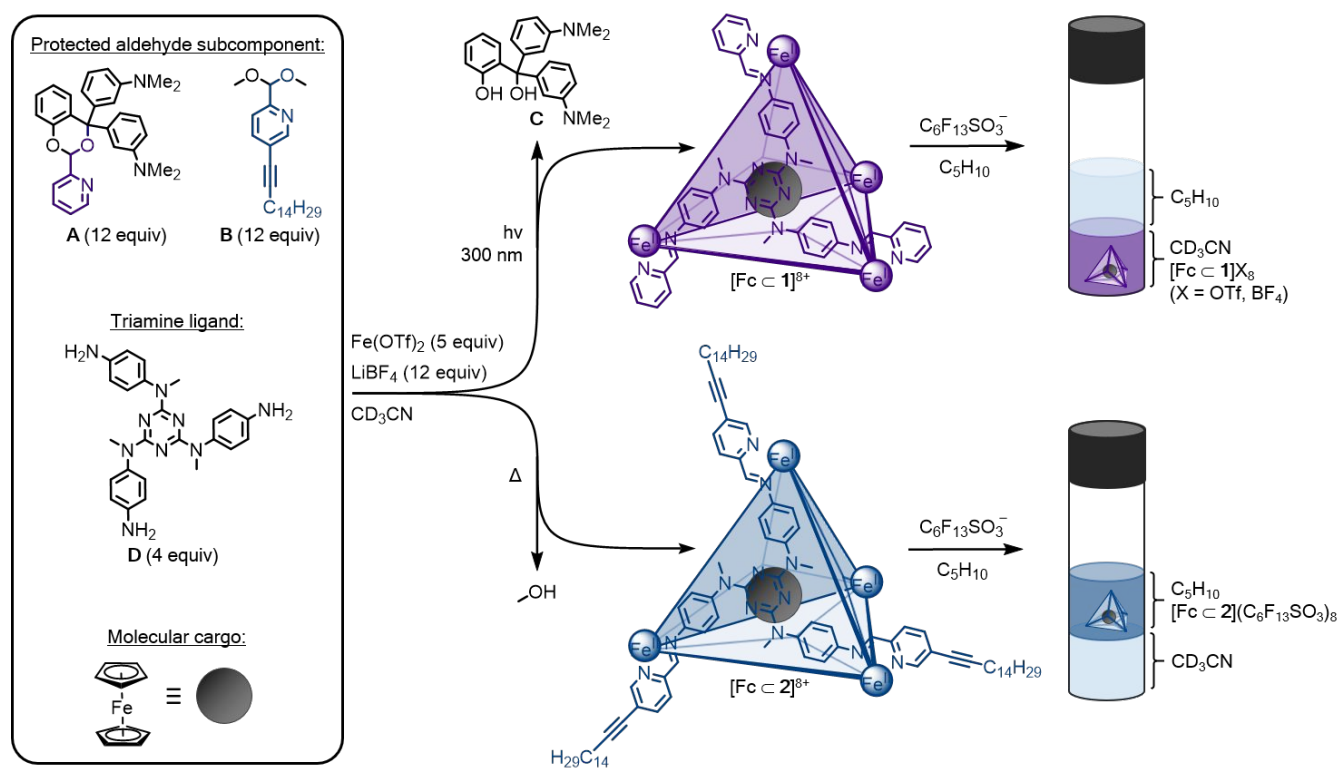
The development of two different masked subcomponents (**A** and **B**, Figure 2) with different solubility properties and orthogonal deprotection methods permitted the selective formation of either cage **1**<sup>11</sup> or **2**, depending on the stimulus. Light triggered the self-assembly of cage **1** through the specific deprotection of masked subcomponent **A**, whereas heat selectively deprotected masked subcomponent **B**, forming cage **2** that contains lipophilic chains

(Figure 2). Upon addition of a second hydrocarbon phase and a fluorosulfonate anion, phase transfer of alkylated cage **2** with its cargo became favorable, whereas cage **1** remained in the acetonitrile layer.



**Figure 1.** Stimuli-responsive deprotection of a masked aldehyde and subsequent  $\text{Fe}^{\text{II}}_4\text{L}_4$  cage formation.

Orthogonal subcomponent deprotection is a key feature of the system under study, requiring careful choice of stimuli. Light is attractive as a stimulus because no external reagents are required to trigger the response. The difficulty in engineering a change to cage structure as a consequence of photoswitching,<sup>12</sup> however, has rendered light-responsive cage systems<sup>3a, 5a, 5b, 13</sup> challenging to study. The integration of a photolabile<sup>14</sup> protecting group<sup>15</sup> thus enabled the preparation of a new type of photo-responsive cage system. For cage **1** we designed masked subcomponent **A** (Scheme 1a), consisting of 2-formylpyridine protected with photolabile protecting group **C** as a cyclic acetal.<sup>15b-d</sup> Aldehydes masked with **C** are known to undergo efficient photo-deprotection, and are stable in the dark to heat and acid. We chose dimethyl acetal as an orthogonal protecting group for masked subcomponent **B**, as acyclic acetals are reported to deprotect when treated with  $\text{LiBF}_4$  under mild conditions, whereas cyclic acetals such as **A** are much less reactive towards hydrolysis.<sup>16</sup>



**Figure 2.** Orthogonal deprotection of masked subcomponents **A** and **B** in the presence of triamine **D**, iron(II) trifluoromethanesulfonate (triflate, OTf), LiBF<sub>4</sub> and ferrocene (Fc) yields either [Fc < 1><sup>8+</sup> or [Fc < 2><sup>8+</sup> depending on the stimulus applied; [Fc < 2><sup>8+</sup> (but not [Fc < 1><sup>8+</sup>) then underwent phase transfer into cyclopentane in the presence of C<sub>6</sub>F<sub>13</sub>SO<sub>3</sub><sup>-</sup>.

The photo-responsive masked subcomponent **A** was prepared in two steps from **C** (Scheme S1). Deprotection was carried out using 300 nm light and the progress of photo-deprotection was monitored using UV-vis (Figure S43) and <sup>1</sup>H NMR spectroscopies (Figure S53). Control experiments probed the photostability of the side product **C** (Figure S46), 2-formylpyridine (Figure S47) and cage **1** to irradiation at 300 nm (Figure S48). Importantly, masked subcomponent **A** was stable in the presence and absence of the other constituents of cage **1** (triamine **D** and iron(II) triflate) in the dark (Figure S50), under lab lighting conditions (Figures S49, S51) and also to the heat generated during irradiation at 300 nm when protected by an aluminum foil sheath (Figures S49, S51).

Time-course <sup>1</sup>H NMR experiments revealed clean photo-deprotection of masked subcomponent **A** to generate 2-formylpyridine (Figure S53). Release of 2-formylpyridine was also observed upon photo-deprotection in the presence of either iron(II) triflate (Figure S58) or triamine **D** (Figure S59), although small amounts of side products were detected in the presence of triamine **D**. As the proposed deprotection mechanism<sup>15b-d</sup> involves the reaction of a protecting group residue with water, we infer **D** to have reacted with the intermediate derivative of protecting group **C** instead of water, resulting in side-product formation.

Light-triggered self-assembly of cage **1** was then investigated. Masked subcomponent **A**, triamine **D** and iron(II) triflate in CD<sub>3</sub>CN were irradiated for 40 min, and self-assembly of cage **1** was observed following equilibration at room temperature over 24 h (Figure S60). A small amount of 2-formylpyridine was still present after equilibration (Figure S61), which we infer to be a consequence of side-reactions with triamine **D** or iron(II) triflate, as discussed above. The photo-deprotection conditions were thus optimized to maximize the yield and purity of cage **1** in three ways: first, by using a slight excess of iron(II) triflate (5 equiv instead of 4 per cage) in order to rebalance the reaction stoichiometry away

from excess 2-formylpyridine; second, by carrying out the reaction in 98:2 CD<sub>3</sub>CN:D<sub>2</sub>O to help ensure that the released **C** anhydride residue reacted with water and not **D**; and third, by increasing the irradiation time to 55 min (Figure S63).

Following the successful light triggered self-assembly of cage **1**, guest uptake within the newly created cavity was investigated. Cage **1** binds a variety of guests, such as adamantane,<sup>11</sup> ferrocene (Figures S20-S25) and benzene (Figures S15-S19), in acetonitrile; these guests were observed to bind in cage **1** following irradiation and equilibration at room temperature (Figures S65-S66, S74). The difference in binding affinity of **1** towards these guests was exploited to selectively encapsulate adamantane from a solution also containing benzene (Figures S67-S69).

The protected subcomponent **B** was prepared in two steps (Scheme S2). Dimethyl-acetal-protected aldehydes are reported to undergo deprotection following the addition of LiBF<sub>4</sub> in wet acetonitrile.<sup>16</sup> We could not follow the deprotection of **B** in acetonitrile, as both **B** and the resulting aldehyde are insoluble in this solvent at room temperature. However, when **B** was mixed with triamine **D**, iron(II) triflate and LiBF<sub>4</sub> in 98:2 CD<sub>3</sub>CN:D<sub>2</sub>O (under conditions optimized for the formation of cage **1**), cage **2** was the only product observed following equilibration (Figures S26-S32). Brief heating (30 min at 90 °C) was found to be necessary for the deprotection of **B** and subsequent formation of cage **2**, but heating in the absence of LiBF<sub>4</sub> gave no cage formation (Figures S72).

We anticipated that the binding properties of cages **1** and **2** would be similar, as their only differences are in the presence or absence of peripheral substituents. As with **1**, deprotection and assembly in the presence of ferrocene (Fc) led to the formation of [Fc < 2>] (Figures S34-S41).

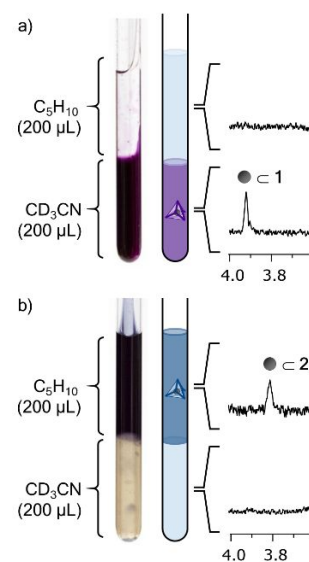
We hypothesized that the photolabile protecting group of masked subcomponent **A** would not cleave during the orthogonal deprotection of masked subcomponent **B** with  $\text{LiBF}_4$ , and that **A** would selectively photo-deprotect in the presence of **B**. Indeed, heating a solution of **A** and  $\text{LiBF}_4$  for 30 min at  $90^\circ\text{C}$  did not result in the removal of the photolabile protecting group (Figure S70). Likewise, irradiation of **B** in the presence of triamine **D**, iron(II) triflate and  $\text{LiBF}_4$  did not lead to the formation of any cage (Figure S71).

These observations set the stage for selective deprotection and cage formation within a mixture (Figure 2). When masked subcomponents **A** and **B** were mixed with triamine **D**, iron(II) triflate and  $\text{LiBF}_4$ , irradiation at 300 nm for 3 hours produced only cage **1** (Figure S73). Heating an identical sample to  $90^\circ\text{C}$  for 30 min, in contrast, resulted in the selective formation of cage **2** (Figure S73).

We hypothesized that the differences in the peripheral functionalization between cages **1** and **2** would result in differential affinities for immiscible solvent phases. We thus investigated the partitioning of the cages between a biphasic system of acetonitrile and cyclopentane (Figure 3). The phase localization of **1** and **2** at each stage could be gauged by eye and was confirmed using slice-selective  $^1\text{H}$  NMR spectroscopy (Figures S76-S80).<sup>6c</sup> This technique allowed the collection of distinct  $^1\text{H}$  NMR spectra from each phase within the sample (see details in SI). Initially, cages **1** and **2** were indistinguishable in that they both partitioned entirely into the acetonitrile phase (Figures S77a, S78a). However, following the application of a second triggering stimulus – 24 equivalents of potassium tridecafluorohexanesulfonate – cage **2** underwent spontaneous phase transfer from acetonitrile to cyclopentane (Figure 2, Figure S78b). Cage **1** remained localized in the acetonitrile phase under the same conditions (Figure S77b).

Slice-selective  $^1\text{H}$  NMR spectroscopy also allowed us to follow the phase transfer of an encapsulated cargo within cage **2**. We chose Fc as the cargo for three reasons. First, it bound within **1** and **2** in slow exchange on the NMR timescale, allowing for its clear identification. Second, Fc bound strongly enough not to be displaced by excess cyclopentane, which is also a competent guest for this cage (Figure S33). Third, both free and encapsulated Fc resonances appear in regions of the  $^1\text{H}$  NMR spectrum that are not obscured by other species in the system.

We thus prepared two identical acetonitrile solutions containing masked subcomponents **A** and **B**, triamine **D**, iron(II) triflate,  $\text{LiBF}_4$  and Fc. Each sample was subjected to either irradiation or heating, forming either  $[\text{Fc} \subset \mathbf{1}]$  or  $[\text{Fc} \subset \mathbf{2}]$  after equilibration (Figure 2, Figure S74). When cyclopentane was added to both samples, both host-guest complexes initially remained in the acetonitrile phase (Figures S79a, S80a). Upon the addition of  $\text{KO}_3\text{SC}_6\text{F}_{13}$  (24 equiv), however, the phase transport of cage **2** and its cargo into the upper cyclopentane phase was observed (Figure S80b), while cage **1** and its cargo remained in the acetonitrile layer (Figures S79b). This behavior was confirmed using slice-selective  $^1\text{H}$  NMR spectroscopy, which showed signals corresponding to the cage and, crucially, the encapsulated Fc in the corresponding phase (Figure 3). Hence, the information programmed into the system on application of the initial signal (light or heat) resulted in different functional outcomes after application of the second, triggering stimulus.



**Figure 3.** Photographs, cartoon representation and slice selective  $^1\text{H}$  NMR data from a)  $[\text{Fc} \subset \mathbf{1}]$  and b)  $[\text{Fc} \subset \mathbf{2}]$  partitioned between cyclopentane and acetonitrile in the presence of  $\text{KO}_3\text{SC}_6\text{F}_{13}$ . Slice-selective  $^1\text{H}$  NMR showed the location of the encapsulated Fc cargo in each case.

This study thus demonstrates how subcomponent self-assembly can follow different pathways in response to distinct stimuli, either light or heat. Stimulus application brings about cage assembly and guest uptake, and can direct the cage and cargo into either an acetonitrile or cyclopentane phase upon the addition of a trigger anion. Our strategy thus offers a new means by which information (in the form of stimuli) can be processed by a chemical system and read out (through  $\text{KO}_3\text{SC}_6\text{F}_{13}$  addition) at a later time, and a new complex mode of control for stimuli-responsive cage systems.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Complete experimental procedures including full characterization, NMR data and ESI mass spectra (PDF).

## AUTHOR INFORMATION

### Corresponding Author

jrn34@cam.ac.uk.

### Author Contributions

‡These authors contributed equally.

### Notes

The authors declare no competing financial interests.

## ACKNOWLEDGMENT

This work has been funded by European Research Council (695009), EPSRC (EP/P027067/1) and the Marie Curie Research Grants Scheme, project 701825 (J.G.). We thank Marion Kieffer for collecting ESI-MS data.

## REFERENCES

- (a) Miljanić, O. Š., Small-Molecule Systems Chemistry. *Chem* **2017**, *2* (4), 502-524; (b) Hai, Y.; Zou, H.; Ye, H.; You, L., Three Switchable

Orthogonal Dynamic Covalent Reactions and Complex Networks Based on the Control of Dual Reactivity. *J. Org. Chem.* **2018**, *83* (17), 9858-9869.

2. (a) Isaacs, L., Stimuli Responsive Systems Constructed Using Cucurbit[n]uril-Type Molecular Containers. *Acc. Chem. Res.* **2014**, *47* (7), 2052-2062; (b) Niess, F.; Duplan, V.; Diercks, C. S.; Sauvage, J.-P., Contractile and Extensible Molecular Figures-of-Eight. *Chem. Eur. J.* **2015**, *21* (41), 14393-14400; (c) Lascano, S.; Zhang, K.-D.; Wehlauch, R.; Gademann, K.; Sakai, N.; Matile, S., The Third Orthogonal Dynamic Covalent Bond. *Chem. Sci.* **2016**, *7* (7), 4720-4724; (d) McConnell, A. J.; Wood, C. S.; Neelakandan, P. P.; Nitschke, J. R., Stimuli-Responsive Metal-Ligand Assemblies. *Chem. Rev.* **2015**, *115* (15), 7729-7793; (e) Xiao, W.; Hu, C.; Ward, M. D., Guest Exchange through Single Crystal-Single Crystal Transformations in a Flexible Hydrogen-Bonded Framework. *J. Am. Chem. Soc.* **2014**, *136* (40), 14200-14206; (f) Miller, R. G.; Brooker, S., Reversible Quantitative Guest Sensing via Spin Crossover of an Iron(II) Triazole. *Chem. Sci.* **2016**, *7* (4), 2501-2505; (g) Su, X.; Arahamian, I., Hydrazone-Based Switches, Metallo-Assemblies and Sensors. *Chem. Soc. Rev.* **2014**, *43* (6), 1963-1981; (h) Balgley, R.; de Ruiter, G.; Evmenenko, G.; Bendikov, T.; Lahav, M.; van der Boom, M. E., Light-Induced Conversion of Chemical Permeability to Enhance Electron and Molecular Transfer in Nanoscale Assemblies. *J. Am. Chem. Soc.* **2016**, *138* (50), 16398-16406; (i) Hsu, C.-W.; Miljanic, O. S., Kinetically Controlled Simplification of a Multiresponsive [10 x 10] Dynamic Imine Library. *Chem. Commun.* **2016**, *52* (83), 12357-12359; (j) Chen, Q.; Sun, J.; Li, P.; Hod, I.; Moghadam, P. Z.; Kean, Z. S.; Snurr, R. Q.; Hupp, J. T.; Farha, O. K.; Stoddart, J. F., A Redox-Active Bistable Molecular Switch Mounted inside a Metal-Organic Framework. *J. Am. Chem. Soc.* **2016**, *138* (43), 14242-14245; (k) Howe, E. N. W.; Busschaert, N.; Wu, X.; Berry, S. N.; Ho, J.; Light, M. E.; Czech, D.; Klein, H. A.; Kitchen, J. A.; Gale, P. A., pH-Regulated Nonelectrogenic Anion Transport by Phenylthiosemicarbazones. *J. Am. Chem. Soc.* **2016**, *138* (26), 8301-8308; (l) Fan, L.; Jupp, A. R.; Stephan, D. W., Remote Stereochemistry of a Frustrated Lewis Pair Provides Thermal and Photochemical Control of Reactivity. *J. Am. Chem. Soc.* **2018**, *140* (26), 8119-8123; (m) Maity, C.; Trausel, F.; Eelkema, R., Selective Activation of Organocatalysts by Specific Signals. *Chem. Sci.* **2018**, *9*, 5999-6005; (n) Galli, M.; Lewis, J. E. M.; Goldup, S. M., A Stimuli-Responsive Rotaxane-Gold Catalyst: Regulation of Activity and Diastereoselectivity. *Angew. Chem. Int. Ed.* **2015**, *54* (46), 13545-13549; (o) Albertazzi, L.; van der Veeken, N.; Baker, M. B.; Palmans, A. R. A.; Meijer, E. W., Supramolecular Copolymers with Stimuli-Responsive Sequence Control. *Chem. Commun.* **2015**, *51* (90), 16166-16168; (p) Komáromy, D.; Teczan, M.; Schaeffer, G.; Marić, I.; Otto, S., Effector-Triggered Self-Replication in Coupled Subsystems. *Angew. Chem. Int. Ed.* **2017**, *56* (46), 14658-14662; (q) Park, J. S.; Park, J.; Yang, Y. J.; Tran, T. T.; Kim, I. S.; Sessler, J. L., Disparate Downstream Reactions Mediated by an Ionically Controlled Supramolecular Tristate Switch. *J. Am. Chem. Soc.* **2018**, *140* (24), 7598-7604; (r) Chen, L.-J.; Yang, H.-B., Construction of Stimuli-Responsive Functional Materials via Hierarchical Self-Assembly Involving Coordination Interactions. *Acc. Chem. Res.* **2018**, DOI: 10.1021/acs.accounts.8b00317; (s) Kakuta, T.; Yamagishi, T.-a.; Ogoshi, T., Stimuli-Responsive Supramolecular Assemblies Constructed from Pillar[n]arenes. *Acc. Chem. Res.* **2018**, *51* (7), 1656-1666; (t) Jansze, S. M.; Cecot, G.; Severin, K., Reversible Disassembly of Metallasupramolecular Structures Mediated by a Metastable-State Photoacid. *Chem. Sci.* **2018**, *9* (18), 4253-4257; (u) Neri, S.; Garcia Martin, S.; Pezzato, C.; Prins, L. J., Photoswitchable Catalysis by a Nanozyme Mediated by a Light-Sensitive Cofactor. *J. Am. Chem. Soc.* **2017**, *139* (5), 1794-1797.

3. (a) Kishi, N.; Akita, M.; Kamiya, M.; Hayashi, S.; Hsu, H.-F.; Yoshizawa, M., Facile Catch and Release of Fullerenes Using a Photoresponsive Molecular Tube. *J. Am. Chem. Soc.* **2013**, *135* (35), 12976-12979; (b) Sahoo, J.; Arunachalam, R.; Subramanian, P. S.; Suresh, E.; Valkonen, A.; Rissanen, K.; Albrecht, M., Coordinatively Unsaturated Lanthanide(III) Helicates: Luminescence Sensors for Adenosine Monophosphate in Aqueous Media. *Angew. Chem. Int. Ed.* **2016**, *55* (33), 9625-9629; (c) Aliprandi, A.; Mauro, M.; De Cola, L., Controlling and Imaging Biomimetic Self-Assembly. *Nat. Chem.* **2016**, *8* (1), 10-15; (d) Cook, T. R.; Stang, P. J., Recent Developments in the Preparation and Chemistry of Metallacycles and Metallacages via Coordination. *Chem. Rev.* **2015**, *115* (15), 7001-7045; (e) Cook, T. R.; Zheng, Y.-R.; Stang, P. J., Metal-Organic Frameworks and Self-Assembled Supramolecular Coordination Complexes: Comparing and Contrasting the Design, Synthesis, and Functionality of Metal-Organic Materials. *Chem. Rev.* **2013**, *113* (1), 734-777; (f) Akine, S.; Miyashita, M.; Nabeshima, T., A Metallo-

molecular Cage That Can Close the Apertures with Coordination Bonds. *J. Am. Chem. Soc.* **2017**, *139* (13), 4631-4634.

4. (a) Hong, S.; Rohman, M. R.; Jia, J.; Kim, Y.; Moon, D.; Kim, Y.; Ko, Y. H.; Lee, E.; Kim, K., Porphyrin Boxes: Rationally Designed Porous Organic Cages. *Angew. Chem. Int. Ed.* **2015**, *54* (45), 13241-13244; (b) Beaudoin, D.; Rominger, F.; Mastalerz, M., Chirality-Assisted Synthesis of a Very Large Octameric Hydrogen-Bonded Capsule. *Angew. Chem. Int. Ed.* **2016**, *55* (50), 15599-15603; (c) Shyshov, O.; Brachvogel, R.-C.; Bachmann, T.; Srikantharajah, R.; Segets, D.; Hampel, F.; Puchta, R.; von Delius, M., Adaptive Behavior of Dynamic Orthoester Cryptands. *Angew. Chem. Int. Ed.* **2017**, *56* (3), 776-781; (d) Catti, L.; Tiefenbacher, K., Brønsted Acid-Catalyzed Carbonyl-Olefin Metathesis inside a Self-Assembled Supramolecular Host. *Angew. Chem. Int. Ed.* **2018**, DOI: 10.1002/anie.201712141; (e) Ozores, H. L.; Amorin, M.; Granja, J. R., Self-Assembling Molecular Capsules Based on  $\alpha,\gamma$ -Cyclic Peptides. *J. Am. Chem. Soc.* **2017**, *139* (2), 776-784; (f) Zhang, P.; Wang, X.; Xuan, W.; Peng, P.; Li, Z.; Lu, R.; Wu, S.; Tian, Z.; Cao, X., Chiral Separation and Characterization of Triazatruxene-Based Face-Rotating Polyhedra: the Role of Non-Covalent Facial Interactions. *Chem. Commun.* **2018**, *54* (37), 4685-4688.

5. (a) Han, M.; Michel, R.; He, B.; Chen, Y.-S.; Stalke, D.; John, M.; Clever, G. H., Light-Triggered Guest Uptake and Release by a Photochromic Coordination Cage. *Angew. Chem. Int. Ed.* **2013**, *52* (4), 1319-1323; (b) Murase, T.; Sato, S.; Fujita, M., Switching the Interior Hydrophobicity of a Self-Assembled Spherical Complex through the Photoisomerization of Confined Azobenzene Chromophores. *Angew. Chem. Int. Ed.* **2007**, *46* (27), 5133-5136; (c) Lewis, J. E. M.; Gavey, E. L.; Cameron, S. A.; Crowley, J. D., Stimuli-Responsive Pd<sub>4</sub>L<sub>4</sub> Metallosupramolecular Cages: Towards Targeted Cisplatin Drug Delivery. *Chem. Sci.* **2012**, *3* (3), 778-784; (d) Castilla, A. M.; Ronson, T. K.; Nitschke, J. R., Sequence-Dependent Guest Release Triggered by Orthogonal Chemical Signals. *J. Am. Chem. Soc.* **2016**, *138* (7), 2342-2351; (e) Wood, C. S.; Browne, C.; Wood, D. M.; Nitschke, J. R., Fuel-Controlled Reassembly of Metal-Organic Architectures. *ACS Cent. Sci.* **2015**, *1* (9), 504-509.

6. (a) Grommet, A. B.; Nitschke, J. R., Directed Phase Transfer of an Fe<sup>II</sup><sub>4</sub>L<sub>4</sub> Cage and Encapsulated Cargo. *J. Am. Chem. Soc.* **2017**, *139* (6), 2176-2179; (b) Pilgrim, B. S.; Roberts, D. A.; Lohr, T. G.; Ronson, T. K.; Nitschke, J. R., Signal Transduction in a Covalent Post-Assembly Modification Cascade. *Nat. Chem.* **2017**, *9*, 1276-1281; (c) Grommet, A. B.; Hoffman, J. B.; Percástegui, E. G.; Mosquera, J.; Howe, D. J.; Bolliger, J. L.; Nitschke, J. R., Anion Exchange Drives Reversible Phase Transfer of Coordination Cages and Their Cargo. *J. Am. Chem. Soc.* **2018**, *10.1021/jacs.8b07900*.

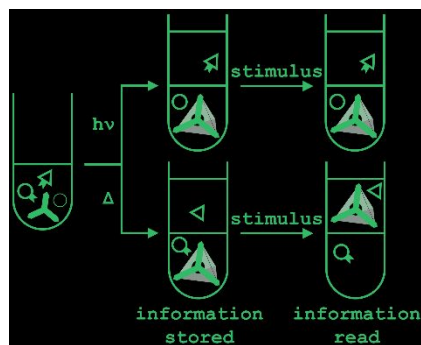
7. (a) McConnell, A. J.; Aitchison, C. M.; Grommet, A. B.; Nitschke, J. R., Subcomponent Exchange Transforms an Fe<sup>II</sup><sub>4</sub>L<sub>4</sub> Cage from High- to Low-Spin, Switching Guest Release in a Two-Cage System. *J. Am. Chem. Soc.* **2017**, *139* (18), 6294-6297; (b) Bravin, C.; Badetti, E.; Scaramuzzo, F. A.; Licini, G.; Zonta, C., Triggering Assembly and Disassembly of a Supramolecular Cage. *J. Am. Chem. Soc.* **2017**, *139* (18), 6456-6460.

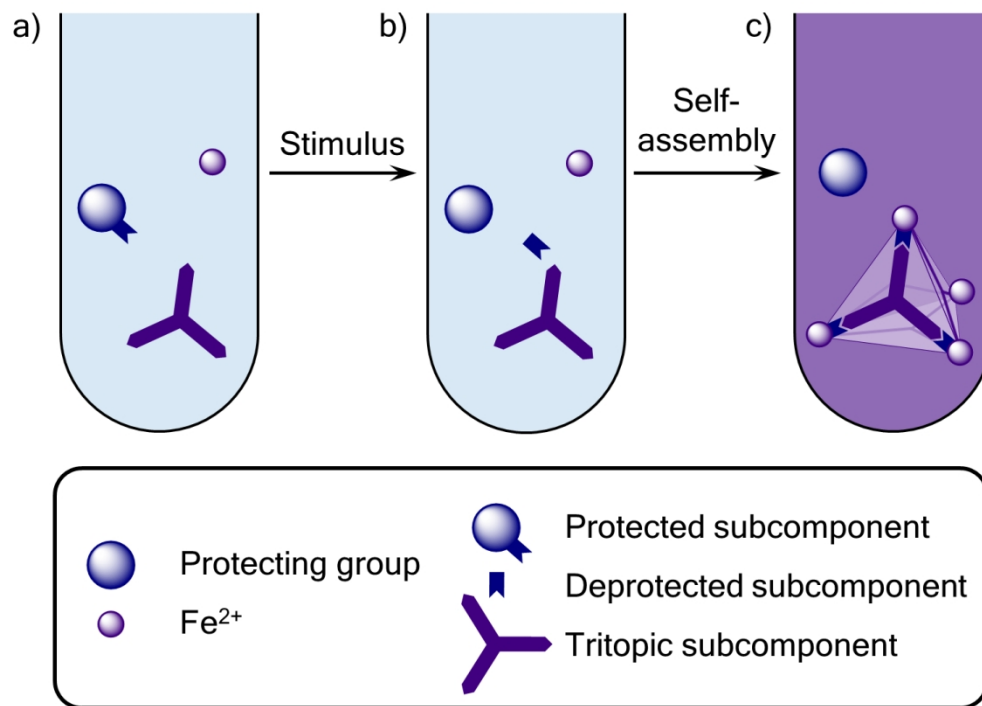
8. (a) Bunzen, H.; Nonappa; Kalenius, E.; Hietala, S.; Kolehmainen, E., Subcomponent Self-Assembly: A Quick Way to New Metallogels. *Chem. Eur. J.* **2013**, *19* (39), 12978-12981; (b) Dömer, J.; Slootweg, J. C.; Hupka, F.; Lammertsma, K.; Hahn, F. E., Subcomponent Assembly and Transmetalation of Dinuclear Helicates. *Angew. Chem. Int. Ed.* **2010**, *49* (36), 6430-6433; (c) Frischmann, P. D.; Kunz, V.; Würthner, F., Bright Fluorescence and Host-Guest Sensing with a Nanoscale M<sub>4</sub>L<sub>6</sub> Tetrahedron Accessed by Self-Assembly of Zinc-Imine Chelate Vertices and Perylene Bisimide Edges. *Angew. Chem. Int. Ed.* **2015**, *54* (25), 7285-7289; (d) Saha, M. L.; Zhou, Z.; Stang, P. J., A Four-Component Heterometallic Cu-Pt Quadrilateral via Self-Sorting. *Chem. Asian J.* **2016**, *11* (19), 2662-2666; (e) Luo, D.; Zhou, X.-P.; Li, D., Solvothermal Subcomponent Self-Assembly of Cubic Metal-Imidazolate Cages and Their Coordination Polymers. *Inorg. Chem.* **2015**, *54* (22), 10822-10828; (f) Li, X.; Wu, J.; He, C.; Zhang, R.; Duan, C., Multicomponent Self-Assembly of a Pentanuclear Ir-Zn Heterometal-Organic Polyhedron for Carbon Dioxide Fixation and Sulfite Sequestration. *Chem. Commun.* **2016**, *52* (29), 5104-5107.

9. Ronson, T. K.; Zarra, S.; Black, S. P.; Nitschke, J. R., Metal-Organic Container Molecules through Subcomponent Self-Assembly. *Chem. Commun.* **2013**, *49* (25), 2476-2490.

10. (a) Ji, X.; Wu, R.-T.; Long, L.; Ke, X.-S.; Guo, C.; Ghang, Y.-J.; Lynch, V. M.; Huang, F.; Sessler, J. L., Encoding, Reading, and Transforming Information Using Multifluorescent Supramolecular Polymeric Hydrogels. *Adv. Mater.* **2018**, *30* (11), 1705480; (b) Manna, D.; Udayabhaskararao, T.; Zhao, H.; Klajn, R., Orthogonal Light-Induced Self-Assembly of Nanoparticles using Differently Substituted Azobenzenes. *Angew. Chem. Int. Ed.* **2015**, *54* (42), 12394-12397.

11. Bolliger, J. L.; Ronson, T. K.; Ogawa, M.; Nitschke, J. R., Solvent Effects upon Guest Binding and Dynamics of a  $\text{Fe}^{\text{II}}\text{L}_4$  Cage. *J. Am. Chem. Soc.* **2014**, *136* (41), 14545-14553.
12. (a) Han, M.; Luo, Y.; Damaschke, B.; Gómez, L.; Ribas, X.; Jose, A.; Peretzki, P.; Seibt, M.; Clever, G. H., Light-Controlled Interconversion between a Self-Assembled Triangle and a Rhombicuboctahedral Sphere. *Angew. Chem. Int. Ed.* **2016**, *55* (1), 445-449; (b) Chen, S.; Chen, L.-J.; Yang, H.-B.; Tian, H.; Zhu, W., Light-Triggered Reversible Supramolecular Transformations of Multi-Bisthiénylene Hexagons. *J. Am. Chem. Soc.* **2012**, *134* (33), 13596-13599.
13. (a) Piper, J. R.; Cletheroe, L.; Taylor, C. G. P.; Metherell, A. J.; Weinstein, J. A.; Sazanovich, I. V.; Ward, M. D., Photoinduced Energy- and Electron-Transfer from a Photoactive Coordination Cage to Bound Guests. *Chem. Commun.* **2017**, *53* (2), 408-411; (b) Burke, M. J.; Nichol, G. S.; Lusby, P. J., Orthogonal Selection and Fixing of Coordination Self-Assembly Pathways for Robust Metallo-Organic Ensemble Construction. *J. Am. Chem. Soc.* **2016**, *138* (29), 9308-9315; (c) Park, J.; Sun, L.-B.; Chen, Y.-P.; Perry, Z.; Zhou, H.-C., Azobenzene-Functionalized Metal-Organic Polyhedra for the Optically Responsive Capture and Release of Guest Molecules. *Angew. Chem. Int. Ed.* **2014**, *53* (23), 5842-5846; (d) Samanta, D.; Galaktionova, D.; Gemen, J.; Shimon, L. J. W.; Diskin-Posner, Y.; Avram, L.; Král, P.; Klajn, R., Reversible Chromism of Spiropyran in the Cavity of a Flexible Coordination Cage. *Nat. Commun.* **2018**, *9* (1), 641; (e) Oldknow, S.; Martir, D. R.; Pritchard, V. E.; Blitz, M. A.; Fishwick, Colin W. G.; Zysman-Colman, E.; Hardie, M. J., Structure-Switching  $\text{M}_3\text{L}_2$  Ir(III) Coordination Cages with Photo-Isomerising Azo-Aromatic Linkers. *Chem. Sci.* **2018**, *9* (42), 8150-8159.
14. (a) Yamashita, K.-i.; Sato, K.-i.; Kawano, M.; Fujita, M., Photo-Induced Self-Assembly of Pt(II)-Linked Rings and Cages via the Photolabilization of a Pt(II)-Py Bond. *New J. Chem.* **2009**, *33* (2), 264-270; (b) Laramée-Milette, B.; Nastasi, F.; Puntoriero, F.; Campagna, S.; Hanan, G. S., Photo-Induced Assembly of a Luminescent Tetraruthenium Square. *Chem. Eur. J.* **2017**, *23* (65), 16497-16504.
15. (a) Zimmermann, M.; Cal, R.; Janett, E.; Hoffmann, V.; Bochet, C. G.; Constable, E.; Beaufils, F.; Wymann, M. P., Cell-Permeant and Photocleavable Chemical Inducer of Dimerization. *Angew. Chem. Int. Ed.* **2014**, *53* (18), 4717-4720; (b) Wang, P.; Hu, H.; Wang, Y., Application of the Excited State Meta Effect in Photolabile Protecting Group Design. *Org. Lett.* **2007**, *9* (15), 2831-2833; (c) Yang, H.; Zhang, X.; Zhou, L.; Wang, P., Development of a Photolabile Carbonyl-Protecting Group Toolbox. *J. Org. Chem.* **2011**, *76* (7), 2040-2048; (d) Wang, P.; Hu, H.; Wang, Y., Novel Photolabile Protecting Group for Carbonyl Compounds. *Org. Lett.* **2007**, *9* (8), 1533-1535.
16. Lipshutz, B. H.; Harvey, D. F., Hydrolysis of Acetals and Ketals Using  $\text{LiBF}_4$ . *Synth. Commun.* **1982**, *12* (4), 267-277.





30 Figure 1. Stimuli-responsive deprotection of a masked aldehyde and subsequent  $\text{Fe}^{\text{II}}_4\text{L}_4$  cage formation.

31 129x92mm (300 x 300 DPI)



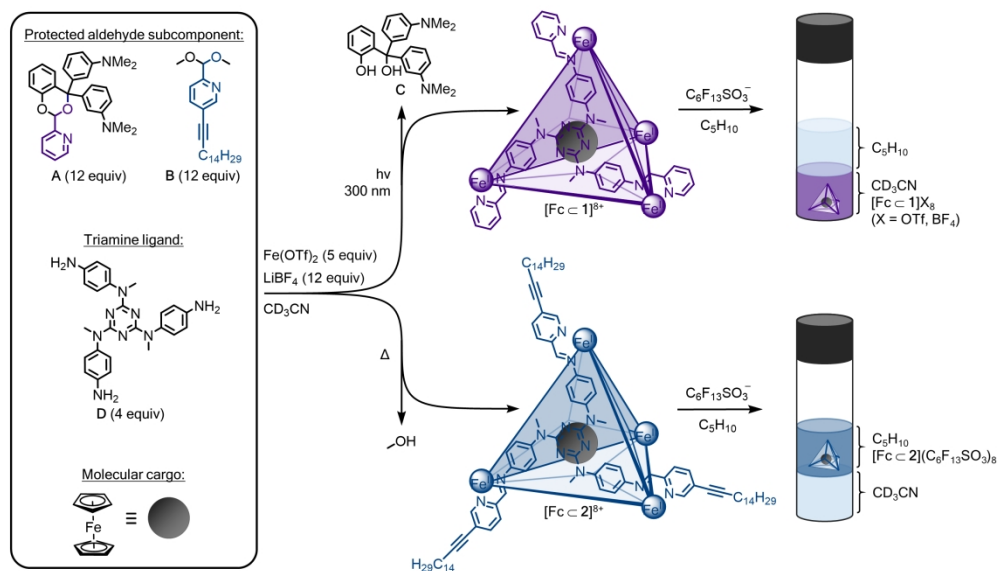
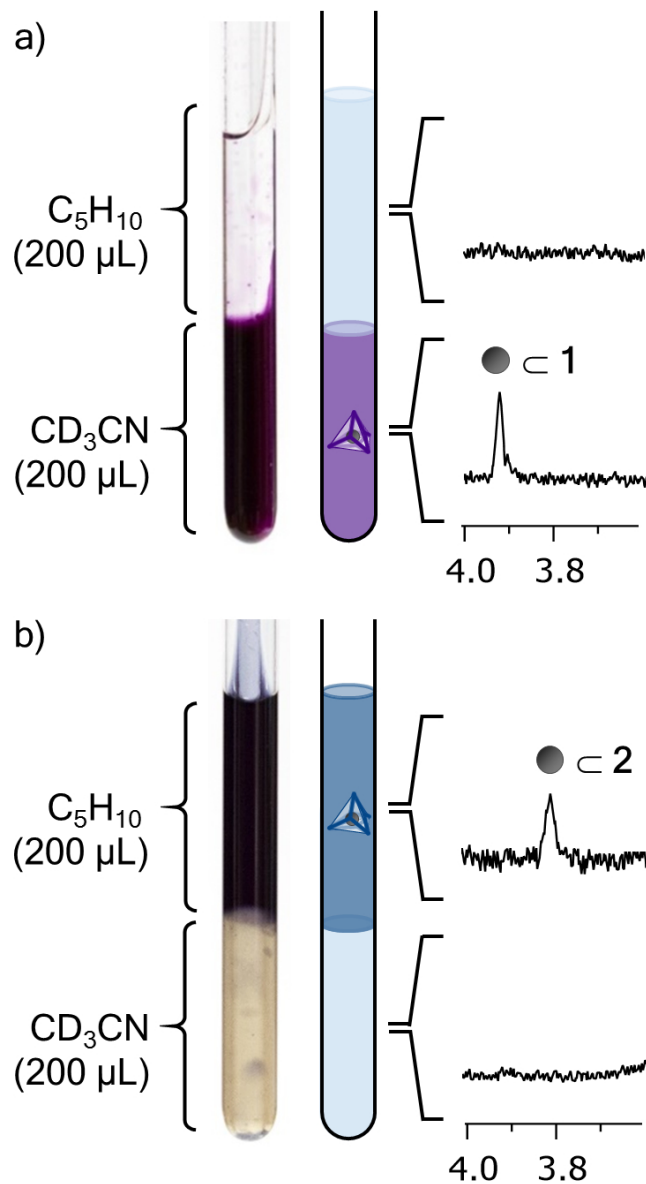


Figure 2. Orthogonal deprotection of masked subcomponents **A** and **B** in the presence of triamine **D**, iron(II) trifluoromethanesulfonate (triflate, OTf),  $\text{LiBF}_4$  and ferrocene (Fc) yields either  $[\text{Fc} \square 1]^{8+}$  or  $[\text{Fc} \square 2]^{8+}$  depending on the stimulus applied;  $[\text{Fc} \square 2]^{8+}$  (but not  $[\text{Fc} \square 1]^{8+}$ ) then underwent phase transfer into cyclopentane in the presence of  $\text{C}_6\text{F}_{13}\text{SO}_3^-$ .

251x143mm (300 x 300 DPI)



45 Figure 3. Photographs, cartoon representation and slice selective  $^1H$  NMR data from a) [Fc  $\square$  1] and b) [Fc  
46  $\square$  2] partitioned between cyclopentane and acetonitrile in the presence of  $KO_3SC_6F_{13}$ . Slice-selective  $^1H$   
47 NMR showed the location of the encapsulated Fc cargo in each case.

49 66x115mm (300 x 300 DPI)