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Host-guest interaction-induced selective oxidation of substrate inside aqueous Pd₆L₄ cage

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Chemical transformation inside artificial hosts like cages has been a booming field of research. However, the use of such artificial cages in carrying out selective transformation of one molecule from a mixture of different molecules has been underexplored. Herein, we report the oxidation of the benzylic $C(sp^3)$ -H of alkylarenes inside an aqueous Pd_6L_4 cage 1 without using any traditional oxidant. 1 was an efficient host in inducing complete oxidation of the alkyl arenes such as xanthene, thioxanthene, fluorene, and acridine derivatives inside its cavity, which other reported Pd_6 cages did not show under similar conditions. It was also observed that encapsulation within the cage was a necessary criterion for oxidation to occur in water. Using this criterion and the higher binding affinity of cage 1 to fluorene over other fluorene derivatives such as 2-bromofluorene and 2,7-dibromofluorene, 1 was able to selectively oxidize fluorene from a mixture of fluorene derivatives through selective encapsulation. This work provides insight into an alternate approach for the selective oxidation of active methylene-containing organic compounds using differences in host-guest affinity in an aqueous environment.

Introduction

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In nature, enzymes function as molecular containers, featuring pockets that enable substrates to bind through non-covalent interactions, facilitating numerous chemical reactions.¹ The interactions between such enzymes and substrate is highly specific owing to the presence of multiple non-covalent interactions between the substrate and the enzyme.² Such highly specific interaction enables enzymes to catalyse the reactions of only certain substrates from a milieu of different compounds.³ Over recent decades, chemists have been creating a diverse range of artificial hosts that mimic enzyme-like capabilities that have a variety of shapes, sizes, and functions.⁴⁻⁶ These artificial structures, containing well-defined internal cavities, are often referred to as host molecules, while the entities they encapsulate are called guest molecules. Hosts can be classified as either organic or metalorganic.7-11 Organic cages, which are neutral, self-assembled structures, dissolve in organic solvents but often exhibit weaker guest binding abilities. Consequently, organic cages and macrocycles have seen limited application in catalysing chemical transformations within their cavities in aqueous medium.¹²⁻¹⁴ Conversely, metalorganic cages provide notable advantages due to their charged nature, enhancing their solubility in polar solvents such as water.¹⁵⁻¹⁸ These water-soluble hosts are generally synthesized via coordination-driven self-assembly, where metal acceptors and donor ligands form thermodynamically stable three-dimensional (3D) structures in a single step.¹⁹ This metal-ligand self-assembly process

^aDepartment of Inorganic and Physical Chemistry, Indian Institute of Science, Bangalore- 560012, India. Email: psm@iisc.ac.in. is a highly efficient method for constructing intricate molecular architectures.²⁰⁻²² In aqueous environments, metal-organic cages exhibit strong binding to organic guest molecules, which typically have little to no solubility in water. The hydrophobic cavities within these cages promote tight binding through hydrophobic interactions. Additionally, host-guest complexes are stabilized by various non-covalent interactions, such as π - π interactions, hydrogen bonding, CH- π interactions, and van der Waals forces. These characteristics make metal-organic cages particularly promising for applications in light harvesting,²³⁻²⁵ sensing,^{26,27} separations,^{28,29} and stabilizing transient species.^{30,31}

Much like enzymes, cages are also capable of acting as hosts for carrying out chemical transformations inside their cavities. Different chemical reactions have been demonstrated inside cages ranging from Knoevenagel condensation,³² Diels-Alder reaction³³ to aza-Darzen reaction³⁴ and many more.³⁵⁻³⁹ Such chemical transformations differ from traditional reaction in one key aspect, in the case of the former, host-guest interactions play a crucial role in determining the outcome of the final product.^{40,41} In traditional chemical reactions, selectivity often arises from differences in reactivity, where the more reactive substrate reacts faster, and under limiting conditions, the less reactive ones can remain unreacted.^{42,43} The measure of reactivity often comes down to difference in bond dissociation energies and/or electrophilicity of the reacting groups and other non-covalent factors seldom play a significant role. However, when it comes to reactions inside cages, the non-covalent interactions between the encapsulated substrate and the cage and by extension their association constants play a crucial role.44-46 Thus, the question arises: can we take different substrates with different binding efficiency to the host molecule, and bring forth selective chemical transformation of one substrate over

⁺Electronic Supplementary Information (ESI) available: NMR Spectra, ESI-MS, optimized structures, experimental details (PDF). See DOI: 10.1039/x0xx00000x.

another? Interestingly, the ability of cages to selectively bind certain molecules has been used for separation of isomers^{29,30} but its utility for selective chemical transformation inside cages has been limited. Most examples of selective reactions have been demonstrated only in terms of Diels-Alder reactions^{47,48} and the utility of such cages in carrying out selective chemical transformation in terms of other chemical reactions such as oxidation reactions remains underexplored. Further to the best of our knowledge, selectivity between substrates which otherwise undergo facile oxidation inside a cage has not been demonstrated before.

Herein, we report the selective oxidation of fluorene derivatives inside a newly synthesised water-soluble cage 1. Cage 1 was synthesized through the metal-ligand-coordination-driven selfassembly of the pyrimidine-based tripyridyl ligand with 90° cisblocked Pd^{II} acceptor A (Scheme 1). The optimized structure of the 1 showed the presence of a large cavity capable of encapsulating various organic guest molecules. The capability of 1 to encapsulate a variety of planar and non-planar guest molecules in water was investigated. Inside the cavity of cage 1, xanthene (9H-Xanthene) and similar molecules underwent facile oxidation to form the oxidized products without using traditional oxidants. The same reaction was then performed inside different cages with the same stoichiometry (A₆L₄) and it was found that the reaction was fastest inside cage 1. It was also observed that formation of host-guest complex was a crucial criterion for the oxidation of guest molecule. The selective hostguest binding ability of the cage was then utilized for the selective oxidation of fluorene over 2,7-dibromo fluorene with a selectivity of >99% and over 2-bromo fluorene with a selectivity of 84%. To the best of our knowledge, this is the first example of host-guest interaction-based selective oxidation of substrates.



Scheme 1. Schematic representation of the cage synthesis and the selective oxidation reaction.

Results and discussion

Synthesis and characterization

The pyrimidine-based tripyridyl ligand **L** was synthesized as per previously reported procedure,⁴⁹ by the base-mediated condensation of 4-acetylpyridine and 4-pyridinecarbonitrile at 120 °C in an autoclave reactor (Scheme S1). The ligand was characterized by ESI-MS, ¹H, and ¹³C NMR in CDCl₃ (Fig. S1- S3). The ligand **L** exhibited a 2:1 splitting of the α - and β -hydrogens of the pyridine rings owing

1 was synthesized by the self-assembly of **L** with *cis*-[(en)Pd(NO₃)₂] (**A**) [en = ethylenediamine] in a 2:3 molar ratio in water at 60 °C for 2 hours (Scheme S2). The solution became transparent during the reaction as the ligand was consumed. After the reaction was completed, **1** was obtained by concentrating the solution under reduced pressure and triturating it with acetone.

The analysis of 1 was conducted using ¹H NMR (in D₂O), revealing three unique peaks in the aromatic region (Fig. 1 and S4). ¹H DOSY analysis indicated that all the three peaks correspond to the same assembly, with a shared diffusion coefficient of D = $1.62 \times 10^{-10} \text{ m}^2\text{s}^{-1}$ (logD = -9.79) and the hydrodynamic radius r_h is 12.17 Å. The peaks were additionally analysed using ¹H-¹H COSY and NOESY NMR in D₂O (Fig. S6, S7). From COSY and NOESY data we found that the α hydrogen peaks (a and a') of the pyridine rings (which were separate in ligand L) were merged in the ¹H NMR of the self-assembled cage. Additionally, one of the β -hydrogen peaks (designated as b) coincided with the pyrimidine peak (designated as c). This led to a smaller number of peaks in the ¹H NMR of the self-assembled cage compared to that of ligand L. The proton integration of 1 was subsequently verified (Fig. S4). Owing to the low symmetric nature of the ligand L, the self-assembled cage could have the ligands arranged in different ways such that the central pyrimidine core could orient itself in different positions, this led to an overall broadening of the ¹H NMR peaks of cage 1.



Fig. 1. Stacked ¹H NMR spectra of (a) cage 1 in D_2O , (b) ligand L in $CDCI_{3,}$ and (c) ¹H NMR DOSY spectrum of 1 in D_2O .

To check the composition of the cage, ESI-MS spectrum of the NTf₂⁻ analogue was recorded in acetonitrile. The spectrum showed peaks at m/z = 1121.4307 and 1588.5493, corresponding to the fragments $[A_6L_4(NTf_2)_9]^{3+}$ and $[A_6L_4(NTf_2)_8]^{4+}$ (Fig. 2 and S8). It displayed that 1 was a [6+4] self-assembly of the acceptor A with the tridentate ligand L. Such self-assembled products can either have a double-square⁵⁰ or an octahedral shape.⁵¹ In double-square structures ligand peaks split

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in a 1:2 ratio, as this splitting was not observed in the ¹H NMR of cage **1**, it could thus be concluded that **1** possessed an octahedral structure. However, after several attempts, single crystals of **1** suitable for X-ray diffraction could not be obtained. The structure of **1** was thus optimized using the DFT method and LanL2DZ basis set was used in the case of the palladium atom and the 6-31g(d) basis set for all other atoms in all calculations.



Fig. 2. ESI-MS spectrum of the NTf₂⁻ analogue of **1** in acetonitrile. The experimental isotopic distribution pattern of the $[A_6L_4(NTf_2)_9]^{3+}$ fragment (Inset).



Fig. 3. The DFT optimized structure of **1**. a) view of the inner-cavity with different Pd-Pd distances labelled, b) side view of the **1**, c) space-fill model of the **1** [color scheme: H, white; C, green; N, blue; Pd, purple], d) the PM6 optimized structure of the host-guest complex with the space-fill model of the guest inside the cavity of the **1**.

1 was optimized in the octahedral structure. This showed that an octahedral structure would have a distance between diagonally Pd to Pd metal as 18.7 Å and the adjacent Pd to Pd distance as 12.7 Å (Fig. 3). As such a large cavity would suggest that 1 could encapsulate

different smaller guests, the capability of **1** to encapsulate a variety of organic molecules like pyrene, xanthene, floorene) thioxanthene, and acridine derivatives was investigated.

Guest Encapsulation Studies

The host-guest chemistry of 1 was investigated with xanthene, thioxanthene, fluorene, acridine, and their derivatives. Excess solid xanthene (X) was introduced to an aqueous solution of 1 to evaluate the guest encapsulation capabilities, and the mixture was heated at 50 °C for 10 hours. A yellow turbid was formed, which was subsequently centrifuged, and the supernatant was utilized for further characterization. The ¹H NMR of this solution (termed as X⊂1) exhibited additional peaks in the upfield area of 7 ppm (Fig. 4 and S9). Correspondingly, the α -hydrogen peaks of the pyridine rings exhibited a downfield shift. The alteration in the ¹H NMR peaks of the host and guest molecules indicated the encapsulation of the guest within the cavity of a cage. The internal binding was additionally confirmed by the ¹H DOSY NMR of $X \subset 1$ in D₂O, which exhibited a single diffusion band $[D = 1.26 \times 10^{-10} \text{ m}^2\text{s}^{-1} (\log D = -9.9)]$ (Fig. S10). The host-guest interaction was corroborated by the ¹H-¹H NOESY NMR study of $X \subset 1$ in D₂O. This demonstrated a corelation between the α -hydrogens of the pyridine rings of **1** and the upfield-shifted aromatic protons of X (Fig. S11).

Oxidation of guests in aqueous medium through encapsulation inside cage 1

As cage **1** could encapsulate a variety of guests, its ability to act as a host for chemical reaction was investigated. The facile oxidation of xanthene, thioxanthene, fluorene, acridine, and their derivatives was checked under confinement inside cage **1**. The reaction was selected as these oxidized guest molecules hold significant importance due to their diverse biological activities and practical applications. Specifically, xanthones (the oxidized form of xanthene), have been utilized to treat various diseases, including convulsions, hypertension, thrombosis, tumours, and Alzheimer's disease.⁵²⁻⁵⁵ Similarly, thioxanthone derivatives find extensive use in microelectronics, coatings, photoresists, and photo-initiators.⁵⁶⁻⁵⁹



Fig. 4. ¹H NMR stack plot of a) **1** in D₂O, b) **X** \Box **1** (**X**: Xanthene) in D₂O. The guest peaks are highlighted in grey.

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Acridones also play a vital role in medicine, particularly for their substantial antitumor activity.60,61 It had been reported that the oxidation of such compounds can be performed under mild conditions in organic solvents like DMSO⁶² however, a report of the reaction in aqueous medium is not known.

The reaction was first performed with xanthene (X) as the model compound. To an aqueous solution of 1, solid X (5 mg, excess) was added and stirred at 50 °C for 10 h. The resultant solution was then centrifuged and a clear supernatant that contained the aqueous solution of the host-guest complex **X1** was taken. The solution was then stirred in the presence of white light [45 W LED (λ > 400 nm)] at 50 °C for 10 hours. The product obtained was then extracted with chloroform and analyzed by ¹H NMR and ESI-MS. The aqueous solution of the cage (after removal of the product) could then be further used for another set of reactions (Scheme S4). The ¹H NMR and ESI-MS of the product showed that under these conditions xanthene was oxidized to xanthone (XO) with >96% conversion.

The reaction of xanthene was optimized by performing the reaction under different conditions (Table 1). In the presence of TEMPO [2,2,6,6-Tetramethylpiperidin-1-yl)oxyl], a recognized radical scavenger, the reaction involving 1 yielded a reduced amount of XO (Table 1 and Fig. S33). This analysis verified that the reactions within 1 transpired through the generation of a radical species. In this regard, the adduct of TEMPO with the intermediate radical species was trapped and characterized by ESI-MS (Fig. S34).

It was further observed that the reaction inside cage 1 occurred even under an argon (Ar) inert atmosphere (Table 1 and Fig. S33). However, if the reaction was done in a non-aqueous solvent like acetonitrile, the product was not formed. This suggests that H₂O (solvent) could in the absence of oxygen act as an oxidizing agent for the formation of **XO**. Similar unusual oxidation of molecules inside cages by H₂O has been previously reported.⁶³ In the cage, the radical can react with molecular oxygen or, in its absence, with H_2O to produce the oxidized product.



Entry	Solvent	Atmo s- phere	Temp e- ratur e	Light	Time	Cage/ Acceptor/ Ligand	Convers ion
1	Water	Air	r. t.	Yes	10 h	Cage	70%
2	Water	Air	50 °C	Yes	10 h	Cage	>96%
3	Water	Air	50 °C	Yes	10 h	Ligand	No Reactio n
4	Water	Air	50 °C	Yes	10 h	Acceptor	No Reactio n
5	Water	Argon	50 °C	Yes	10 h	Cage	95%
6	Water	Air	50 °C	No	10 h	Cage	30%
7	CH₃CN	N ₂	50 °C	Yes	10 h	Cage	10%

8	Water	Air	50 °C	Yes	10 h DO	Blank _{View Ar} : 10.1039/D5	ticle Online CG261%F n
9	Water/ CH₃OH	Air	50 °C	Yes	10 h	Blank	No Reactio n
10	Water + TEMPO	Air	50 °C	Yes	10 h	Cage	42%

Table 1. Reaction conditions for the reaction performed with 1. The percent conversion was calculated using ¹H NMR, by the relative abundance of the product (XO) peaks in the CHCl₃ extract from the aqueous solution after the reaction versus that of the starting material (X) peaks, and % conversion was calculated by the ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Interestingly, the ligand and acceptor did not show any significant oxidation of xanthene (Fig. S33) which clearly showed that encapsulation was pivotal for oxidation to occur in aqueous medium. Similarly, in the absence of cage 1 only xanthene in aqueous medium remained unoxidized when subjected to similar conditions (Fig. S33). Based on these findings a mechanism could be envisioned (Fig. S31a) which followed previously known mechanisms for oxidation inside cages.^{64,65} After light irradiation, a radical was generated on the benzylic carbon of the guest molecule, subsequently this radical was rapidly trapped by oxygen or water (in the absence of O_2) to get the oxidized product. Inside the host 1 only one molecule of the xanthene was encapsulated (as shown by the ¹H NMR integration (Fig. S13) which ruled out any possibility of dimerization of the xanthene radical and only oxidized product was obtained.



Fig. 5. (a) Schematic representation for the formation of octahedral cage ${\bf 2}$ and double-square cage ${\bf 3},$ (b) partial ${}^1{\rm H}$ NMR plot of the product obtained from 1, (c) 2, (d) 3, and (e) partial ¹H NMR plot of the xanthene. Peaks for the internal standard (1,3,5-Trimethoxybenzene) are highlighted in green.

Next, we wanted to check the utility of cage 1 in oxidizing the substrate compared to other previously known cages. Thus, oxidation of xanthene inside cages 2 and 3 was explored under the same reaction conditions (Fig. 5). 2 has a similar octahedral structure

as that of 1, while 3 has a double-square structure. It was observed that within the same time frame, complete oxidation of xanthene was not possible inside cages 2 and 3 and the product formed contained a higher amount of un-reacted xanthene (45% and 35% for cages 2 and 3, respectively) along with oxidized product xanthone (XO). To understand the reason behind this, we monitored the product formation inside different cages by ¹H NMR. It could be seen that product formation inside cage 1 was faster than inside cages 2 and 3 (Fig. S31b), probably due to better binding of the guest and reactive intermediate species inside cage 1 compared to other cages (2 and 3) (Table S1.). The profile obtained for the % conversion vs time graph was complicated and further conclusion could not be drawn in part due to the experimental limitations and the complicated nature of the reaction mechanism which involves multiple reaction intermediates (Fig. S31b). However, the faster product formation inside cage 1 and the usefulness of this cage over other cages (2 and 3) could be clearly demonstrated.

Next the usefulness of this oxidation procedure to oxidize other substrates was investigated. Thioxanthene and acridine derivatives could also be oxidized in a similar fashion (Fig. 6). However, in case of fluorene and its derivatives, owing to a stronger C-H bond strength as compared to xanthene and acridine derivatives, greater activation energy was required. Thus, 390 nm 100W LED was required instead of white light for 10 hours at ambient temperature, to efficiently oxidize fluorene and its derivatives.



Fig. 6. Scope of the aqueous cage **1** catalyzed $C(sp^3)$ –H oxidation of the alkylarenes. The yield is calculated by the ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b: 390 nm 100W LED was used]. The % conversion was calculated by ¹H NMR using internal standard 1,3,5-trimethoxy benzene.

Selective oxidation using cage 1

In literature, most transition metal catalysts use the difference in reactivity of substrates to bring forth selectivity. In case of cage **1** such can be easily achieved with a mixture of xanthene and fluorene. As the C-H bond strength of fluorene is stronger than xanthene, if we take an equimolar mixture of xanthene and fluorene and treat it with aqueous solution of cage **1** and subject it to white light irradiation at 50 °C for 10 hours, (following the optimized procedure in Scheme S4), only xanthene could be oxidized selectively (Fig. 7c). The ¹H NMR of the product contained peaks for xanthone and un-oxidized fluorene. However, we wanted to investigate the possibility of

selective oxidation through host-guest chemistry using non-covalent interactions. DOI: 10.1039/D5SC02078F

To check this, we chose fluorene and its derivatives. First, a mixture of fluorene and 2,7-dibromofluorene was selected. An equimolar ratio of the two was added to an aqueous solution of **1** and then the mixture was stirred for 12 hours at 60 °C. The same reaction mixture was irradiated under 390 nm LED at room temperature for 10 hours. The mixture was then centrifuged, and the clear supernatant was taken. The product was then extracted in chloroform and characterized by ¹H NMR spectroscopy. It was found that from such a mixture only fluorene was extracted, further, the product contained exclusively only fluorenone and no 2,7-dibromofluorene or 2,7-dibromofluorene mixture. In this case as well the product obtained contained selectively only 2-bromofluorene and no 2,7-dibromofluorene or 2,7-dibromofluorene or 2,7-dibromofluorene or 2,7-dibromofluorene or 2,7-dibromofluorene mixture. In this case as well the product obtained contained selectively only 2-bromofluorene and no 2,7-dibromofluorene or 2,7-dibromofluorene or

To better understand the mechanism behind this selective oxidation through selective encapsulation first, selective encapsulation experiments were performed. It was found that from a mixture of fluorene and 2,7-dibromofluorene, cage 1 selectively encapsulated only fluorene (Fig. S42). Similarly, from a mixture of 2-bromofluorene and 2,7-dibromofluorene only 2-bromofluorene was encapsulated by 1 (Fig. S43). To better realize this, the Ka values for the formation of the host-guest complexes were then calculated using UV-Visible titration and BindFit software. It was found that the K_a value for the host-guest complex of 1 with fluorene was 3.97×10⁴ M⁻¹, K_a value for the complex with 2-bromofluorene was 2.78×10⁴ M⁻¹ and K_a value for the one with 2,7-dibromofluorene was 1.66×10⁴ M⁻¹ (Fig. S37-39). This clearly showed that by levering the difference in binding affinity of the substrate to the host, selective oxidation could be achieved. To further verify that the selective oxidation was due to difference in binding affinity, the mixture of fluorene and 2-bromofluorene was selected, as they have more similar binding affinity, it is expected that in such case both the molecules would be oxidized, but as the binding affinity for fluorene is more, still more of fluorenone must be present in the mixture. The experimental observations verified this, when a mixture of fluorene and 2-bromofluorene was taken the product contained both the oxidized products in a ratio of 84:16 for fluorenone and 2-bromofluorenone, respectively.



Fig. 7. Schematic diagram of the selective oxidation of a) xanthene and b) fluorene. ¹H NMR (in CDCl₃) stack plot of the c) extracted product (purple plot) from the above mentioned reaction **a**. d) Xanthone (green) in CDCl₃, and e) fluorenone (red) in CDCl₃, and f) fluorene (blue) in CDCl₃, at 298 K. ¹H NMR stack plot of the g) extracted product (fluorenone, green) from the above-mentioned reaction **b**. h) 2,7-Dibromofluorenone (red) in CDCl₃, and i) fluorenone (blue) in CDCl₃ at 298 K. Peaks for the internal standard (1,3,5-trimethoxybenzene) are highlighted in green.

Selective guest encapsulation experiments also showed similar results and from a mixture of fluorene and 2-bromofluorene, cage **1** encapsulated both the molecules in a ratio of ~ 84:16 which closely collaborated with the ratio of oxidized products. This clearly established that binding affinity played a major role in determining the relative selectivity in oxidation.

Conclusion

In summary, we have demonstrated a strategy for the selective oxidation of benzylic C(sp³)-H by leveraging the selective binding affinity of a water-soluble Pd₆L₄ octahedral cage **1.1** was synthesized in high-yield through the metal-ligand coordination-driven selfassembly of acceptor cis-[(en)Pd(NO₃)₂] (A) with donor L [2,4,6tri(pyridine-4-yl)pyrimidine] in a 3:2 molar ratio. The cage 1 had an octahedral structure with a large interior hydrophobic cavity. 1 encapsulated a variety of organic molecules like xanthene, fluorene, thioxanthene, and acridine derivatives. Further, it was found that xanthene (X) encapsulated inside 1 was oxidized to xanthone (XO) when stirred in white light for 10 hours at 50 °C in air. This transformation was investigated with previously synthesized Pd₆L₄ cages 2 (with octahedral structure) and cage 3 (with double-square structure). Under similar conditions, cages 2 and 3 gave incomplete oxidation of xanthene, and reaction rate monitoring showed that reaction inside cage 1 was much faster than reactions inside other known Pd₆L₄ cages (2 and 3). Further, it was found that host-guest complex formation was pivotal for the oxidation of the substrate to occur in aqueous medium. As encapsulation was pivotal for oxidation, the selective host-guest complex formation ability of cage 1 could be further utilized for selective oxidation through selective encapsulation. Utilizing this approach, from a mixture of 2,7dibromofluorene and fluorene, fluorene could be selectively oxidized. Similarly, from a mixture of 2,7-dibromofluorene and 2bromofluorene selectively only 2-bromofluorene could be oxidized. Selective host-guest binding ability of the cage could also be utilized for the selective oxidation of fluorene over 2-bromo fluorene with a selectivity of 84%. We envision that this strategy can be used further in other chemical transformations to bring forth selectivity in chemical transformations observed in confined cavities.

Author contributions

D.C. and S.A designed the project and the experiments. S.A and D.C. carried out the experimental work, analyzed the data, and optimized the structures. P.S.M. supervised the project. All the authors contributed to the writing of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

All data are provided in ESI⁺ and additional data can be available upon request.

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All data are provided in ESI[†] and additional data can be available upon request.