## COMMUNICATION

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Cavity-promotion by pillar[5]arenes expedites organic photoredox-catalysed reductive dehalogenations†

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The efficiency of the photo-induced electron transfer in photo-redox catalysis is limited by the diffusional collision of the excited catalyst and the substrate. We herein present cavity-bound photo-redox catalysts, which preassociate the substrates, leading to significantly shortened reaction times. A pillar[5]arene serves as the cavity and phenothiazine as a catalyst in the reductive dehalogenation of aliphatic bromides as a proof of concept reaction.

Photoredox catalysts (PRCs) allow the conversion of light into chemical energy.[1,2] They are considered a more sustainable alternative to traditional catalyst systems, using light as a non-hazardous and environmentally friendly energy source instead of high temperatures or harsh reaction conditions. Significant advances have been achieved in recent years using PRCs in synthetic organic chemistry.[3–5] Both transition metal complexes[6,7] as well as organic dyes[8–10] have successfully been employed in a variety of synthetic transformations. One of the critical steps in photoredox catalysis is the photo-induced electron transfer (PET) from the catalyst in its excited state to the substrate, which usually is the first step of the catalytic cycle. The efficiency of the PET is limited by the diffusional collision of the catalyst and substrate during the lifetime of the excited state of the catalyst.[11] This leads to photoredox reactions often suffering from long reaction times, thereby consuming high amounts of light energy, or high catalyst loadings being necessary.[1] We herein present a catalyst system, where

the PRC is covalently bound to a cavity. This cavity can preassociate the substrate to make the PET more efficient by holding the substrate and catalyst in close proximity (Fig. 1A).[12] After completion of the PR catalytic cycle, the catalyst cavity is free to associate with a new substrate. Our catalyst design uses a pillar[5]arene (PA) as the cavity and phenothiazine (PT) as the PRC (Fig. 1B). Pillarenes have become versatile supramolecular hosts due to their facile synthesis, unique pillar shape, the possibility for further functionalization and their host–guest properties.[13,14] They have been used in supramolecular catalysis on several occasions[15] as well as in photocatalysis.[16] While
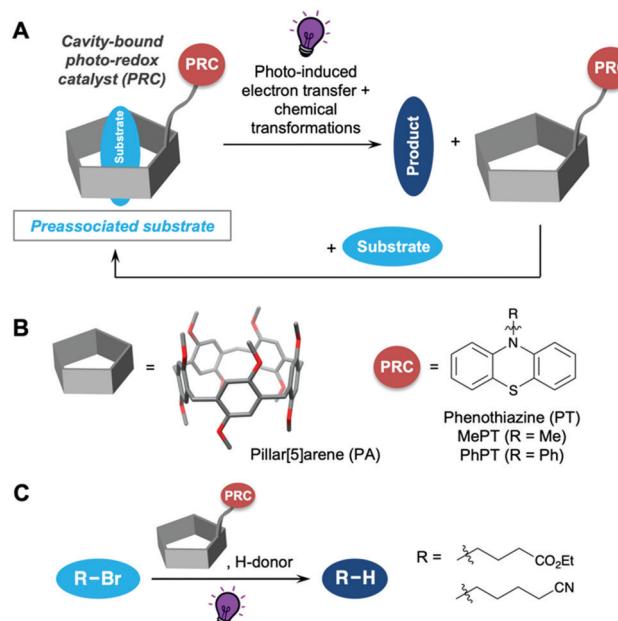
Fig. 1 (A) Concept of cavity-promotion in photoredox catalysis, investigated herein; (B) structure of pillar[5]arene (PA), used as a cavity, and phenothiazine (PT) as a photoredox catalyst; (C) photoredox-catalyzed reductive dehalogenation of aliphatic bromides used as a proof-of-concept reaction in this study.

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PET to substrates bound by a cage has been reported on a few occasions before,[17–20] no application of a pillarene in photoredox catalysis has yet appeared to the best of our knowledge.

As a proof of concept reaction we chose the reductive dehalogenation of aliphatic bromides (Fig. 1C). This reaction, developed by Hawker and Read de Alaniz in 2015,[21] allows for a mild photocatalytic dehalogenation using *N*-phenyl-PT (PhPT) as the PRC instead of the traditional protocols involving metal–halogen exchange,[22,23] tin hydrides[24] or other highly toxic reagents.[25–27] We used a UV nail dryer lamp as a widely available and cheap light source in this reaction. In spite of its lower light intensity compared to typically used LED setups, we were able to obtain good yields for the reductive dehalogenations, since cavity promotion increased the efficiency of the PET. This is an advantage in comparison to many PRC studies, which use specialized equipment and radiation sources not available to a standard synthetic laboratory. PT derivatives have also been employed in metal-free atom-transfer radical polymerizations[28–30] as well as many other reaction types.[31,32] Due to their reversible redox chemistry, phenothiazine derivatives have also found use as organic battery materials[33–35] and in other supramolecular applications.[36]

We designed three cavity-linked catalysts **PA-PhPT**, **PA-C4-PhPT** and **PA-C4-PT** (Scheme 1), which differ in the choice of linker between the pillar[5]arene and phenothiazine. The synthesis of all three started from decamethoxy-pillar[5]arene (**1**),[37] which we

transformed into mono-hydroxy-PA **2** following literature procedures.[38,39] Transformation of the hydroxy to a triflate group followed by Suzuki–Miyaura coupling with PT-based boronic ester **3** led to **PA-PhPT** in a high yield of 90% over these two steps. For butyl-linked **PA-C4-PhPT** we reacted **2** with PT-functionalized bromide **4**, and nucleophilic substitution furnished the catalyst in excellent yield of 93%. The same procedure using bromide **5** afforded catalyst **PA-C4-PT** in a high yield of 84%. For the syntheses of PT precursors **3**–**5**, see the ESI.† The PA-linked PRCs were characterized using 1- and 2D ^{1}H- and ^{13}C NMR spectroscopy and HRMS. We determined their excited state reduction potentials using cyclic voltammetry, UV/Vis absorption and emission spectroscopy (for data see the ESI†).[8] With $E_{1/2}^* = -2.84$ V (**PA-PhPT**), -2.85 V (**PA-C4-PhPT**) and -2.80 V (**PA-C4-PT**), the cavity-linked phenothiazines have slightly stronger reducing abilities compared to PhPT ($E_{1/2}^* = -2.56$ V) and MePT ($E_{1/2}^* = -2.69$ V, all *vs.* SCE). Pillarene **1** has no significant absorption at the wavelength used in the reaction (emission maximum of the nail dryer lamp at 365 nm), and hence no excited state of **1** is formed that could interfere with the mechanism.

We next employed the cavity-bound PRCs **PA-PhPT**, **PA-C4-PhPT** and **PA-C4-PT** in the reductive dehalogenation of ethyl 4-bromobutanoate (**6**) and 5-bromopentanenitrile (**7**) and compared the results to PhPT and MePT (see Fig. 1B) under identical conditions. We used 5 mol% of the PRC and five equivalents each of diisopropylethylamine and formic acid in acetonitrile (Table 1).[21] As a light source we used a cheap and widely available nail dryer lamp with an emission maximum of the bulb at 365 nm (for experimental setup see the ESI†). This lamp has a lower photon flux compared to typical LED setups used in the literature, which we determined using ferrioxalate actinometry[40] as a simple yet accurate method (see the ESI† for details and comparative values). Hence for the debromination of **6** and **7** using PhPT as PRC, the yield within 48 h amounted to 29% and 28% (entry 1), respectively, while 81% was obtained after 24 h for **6** in the literature using the higher flux LED setup. Using MePT we obtained 17% and 16%
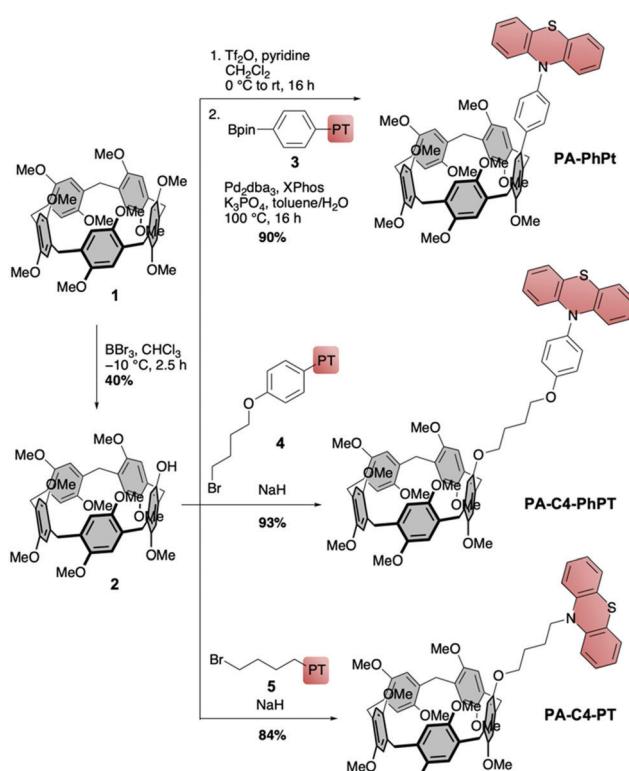
Scheme 1 Synthesis of cavity-linked catalysts with pillar[5]arene as the cavity and phenothiazine as a photoredox catalyst (with excited state reduction potentials *vs.* SCE).

Table 1 Comparison of cavity- and non-cavity-bound phenothiazine photoredox catalysts (PRCs) in the reductive dehalogenation of alkyl bromides **6** and **7**
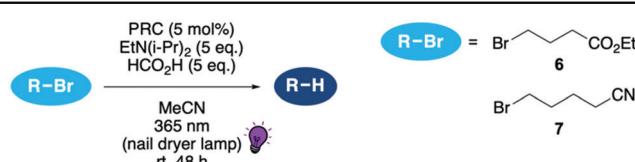
Entry	Catalyst (PRC)	Yield (R–Br = **6**)[a]	Yield (R–Br = **7**)[a]
1	PhPT	29%	28%
2	MePT	17%	16%
3	MePT + **1**	17%	14%
4	**1**	0%	0%
5	**PA-PhPT**	55%	61%
6	**PA-C4-PhPT**	61%	63%
7	**PA-C4-PT**	49%	60%

[a] Conversions after 48 h as the mean of three reactions, determined by ^{1}H NMR spectroscopy.

yield, respectively, using our setup due to the lower stability of its excited and/or oxidized state compared to PhPT[28] (entry 2). Simply adding decamethoxypillar[5]arene (1) to the reaction with MePT did not expedite its course (entry 3), and the presence of sole pillarene 1 did not lead to any transformation (entry 4). Using the cavity-bound PRCs **PA-PhPT**, **PA-C4-PhPT** and **PA-C4-PT**, on the other hand, led to significant increases in yield by factors of 1.6–3.8 compared to PhPT and MePT (entries 5–7). A particularly large improvement is observed for **PA-C4-PT** with 2.9 and 3.8 times higher yields, respectively, compared to MePT (entry 6); however, this catalyst was slightly less stable towards decomposition compared to the other catalysts due to the alkyl substitution on the phenothiazine nitrogen atom. The best overall performance was observed for **PA-C4-PhPT** and **PA-PhPT** with aryl substituents on the phenothiazine nitrogen atoms. Of these two, **PA-PhPT** is easier to synthesize in a gram scale, since no column chromatography is necessary in the purification of the PT-precursor, and this catalyst could also be recovered quantitatively after each photoredox-catalysed transformation. The increase in reaction rate can also be seen from the kinetic profiles comparing the rates of the dehalogenation of bromopentanenitrile (7) with **PA-PhPT** and PhPT (see the ESI†).

The results of the photoredox-catalysed experiments demonstrate that the pillarene cavity efficiently expedites the reductive dehalogenation reaction by keeping the substrate in close proximity to the catalyst. This is supported by the known ability of pillar[5]arenes to bind electron-poor alkyl halides.[14] The association constant for the complexation of 5-bromopentanenitrile (7) by 1 amounts to 1.7×10^4 M^{-1}.[41] This is 30 times higher than that for the debrominated product of the dehalogenation reaction, pentanenitrile, which has an association constant of 5.7×10^2 M^{-1}.[41] Hence the reduced product will leave the cavity, thereby releasing the catalyst and making room for a new substrate to enter and undergo the reductive dehalogenation. The calculated structure of the complex between **PA-PhPT** and 5-bromopentanenitrile (7) in Fig. 2 shows its perfect fit into the cavity and the proximity of the bromide to the PT catalyst. This orientation with the bromide of 7 facing toward the PT catalyst is 5.3 kcal mol^{-1} more stable than the other orientation where the bromide points downward (see the ESI†).
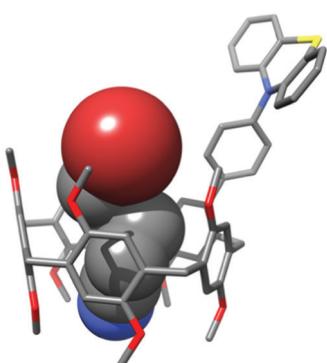

Fig. 2 Calculated structure (PBEh-3c) of the complex between **PA-PhPT** and 5-bromopentanenitrile (7).

Table 2 Reductive dehalogenations of sterically hindered substrates **8–11** (for reaction conditions see reaction scheme in Table 1) that cannot bind inside the pillar[5]arene cavity using cavity- and non-cavity-bound phenothiazine photoredox catalysts

Entry	Catalyst	8[a] (%)	9[a] (%)	10[a] (%)	11[a] (%)
		Substrate			
1	PhPT	65	12	51	81
2	**PA-PhPT**	61	11	50	75
3	**PA-C4-PhPT**	64	14	50	82

[a] Conversions after 48 h as the mean of three reactions, determined by ^{1}H NMR spectroscopy.

Stern–Volmer fluorescence quenching experiments showed that the excited states of the new catalysts **PA-PhPT** and **PA-C4-PhPT** are efficiently quenched by the substrates **6** and **7** (see the ESI†). Comparison with non-cavity-bound PhPT revealed a more efficient quenching for **PA-PhPT** and **PA-C4-PhPT** than for PhPT due to the substrates binding inside the cavities. Pillarene **1**, on the other hand, did not quench the fluorescence of PhPT, demonstrating its innocent nature.

To further prove the postulated concept we performed reactions using four substrates that are sterically hindered and cannot bind inside the pillar[5]arene cavity, namely 4-bromo-2,2-diphenylbutanenitrile (**8**), (bromomethyl)cyclohexane (**9**), 4-bromoanisole (**10**) and 4-bromobenzonitrile (**11**). We used both the pillarene-bound phenothiazine catalysts **PA-PhPT** and **PA-C4-PhPT** as well as PhPT as a cavity-free catalyst (Table 2). In each of these cases we obtained a similar yield for the reductive dehalogenation between the three catalysts (compare entries 1–3 for each substrate in Table 2). The slightly lower yields for **PA-PhPT** can be rationalized by the lower conformational flexibility of the phenothiazine unit due to the rigid phenylene linker to the pillar[5]arene. These comparative experiments demonstrate that when the substrate is unable to bind inside the cavity, the reaction rate remains similar between cavity- and non-cavity bound photoredox catalysts.

In conclusion, we introduced a concept in photoredox catalysis where preassociation of the substrate in close proximity to the catalyst makes the reaction significantly more efficient. We synthesized three pillar[5]arene-functionalized phenothiazines **PA-PhPT**, **PA-C4-PhPT** and **PA-C4-PT** as cavity-bound photoredox catalysts and used these in the reductive debromination of ethyl 4-bromobutanoate and 5-bromopentanenitrile. The reactions proceeded with up to 3.8 times higher yield compared with regular phenothiazine catalysts. This concept for photoredox catalysis can be applied to different types and sizes of cavities as well as different catalysts and transformations and will pave the way to making photoredox catalysis more energy- and time-efficient. Furthermore, using

cavities that selectively bind one substrate over another would allow realizing substrate selectivity.

Conflicts of interest

There are no conflicts to declare.

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