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Calix[8]arene Nanoreactor for Cu(I)-Catalysed C–S Coupling†

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The catalytic activity of Cu(I) confined within a phenanthroline-containing calix[8]arene derivative was tested in C–S cross-coupling reactions. The substrate selectivity, solvent dependence, and catalyst loading differ significantly from those reported for bimetallic molecular systems. The putative monomeric complex represents the first calix[8]arene functionalised for *endo*-oriented metal chelation used as a nanoreactor.

The small compartments in metalloenzymatic active sites are the prototypes of well-defined confined environments around metal ions and substrates that are chemically distinct from the environment in bulk solvent. In synthetic systems designed for metal confinement within a supramolecular container, dramatic alterations of catalytic performance relative to analogous molecular catalyst have been observed.[1] As a result, supramolecular catalysts with enhanced activity can be obtained, which may stabilise reactive intermediates and enable effective collisions by increasing the local concentration of reactants.[2] These reaction pockets may also give rise to enhanced or unusual selectivity by imposing steric restrictions, exclusion affinity for substrates, and promoting alternative reaction pathways. Additionally, the opening process on the container appears to be essential to control the outcome of chemical transformations by modulation of the encapsulation of precursors and the subsequent dissociation of products.[3] In the context of non-covalent interactions that control these processes, the rational design of supramolecular catalysts remains a challenging task. Nonetheless, greater insights on such factors will represent a significant advancement towards the development of superior catalysts with tuneable features. Customarily, self-assembled nanocages[4] and cavitands, like cyclodextrins[5] and cucurbiturils,[6] operate as nanoreactors in analogy to binding sites in enzymes. Although calix[n]arenes (n

= 4,6) have been also used as platforms for catalysis, most available systems result from *exo*-oriented metal-coordination with reactivity outside the cavity, and offer limited inner space for substrate-binding.[7,8] To date, only a few metallocalix[6]arenes exhibit adequate space for internal binding of small molecules for ligand-exchange and dioxygen-activation relevant to Cu-monooxygenases.[9] Conversely, the integration of the host and size attributes of the larger calix[8]arene should result in an effective tool in catalysis; however, little work has been reported on metallocalix[8]arene catalysts, and the sole reports are restricted to *exo*-coordinated systems via the phenolic units.[7,10] In contrast, the use of calix[8]arenes bearing *endo*-coordinative residues to enforce metal binding and catalytic activity to occur internally remains elusive, probably due to the difficulty to introduce functional groups in a regioselective manner.
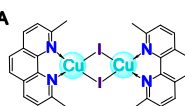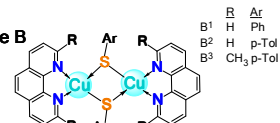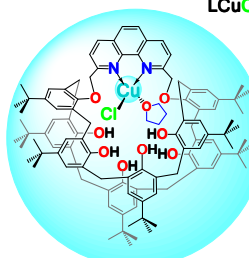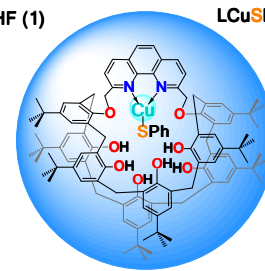
Chart 1 Molecular Cu(I) catalysts **A** and **B**, and supramolecular analogues **1** and **2**

Given the importance of aryl sulfides and related fine chemicals in the pharmaceutical and materials industries, several Cu(I)-based protocols have been developed for C–S

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coupling reactions.[11] Significant contributions to this area have been reported by the groups of Venkataraman[12] and Hartwig[13] regarding the thioetherification of haloarenes (Chart 1). Similar to these systems, our approach entails an *endo*-oriented phenanthroline motif appended to a calix[8]arene in the 1,5-phenolic positions as ligand **L** for Cu(I)-catalysed C–S coupling within the macrocyclic cavity as nanoreactor. To our knowledge, no prior examples of supramolecular approaches for this purpose have been informed. Recently, we reported the preparation and conformational aspects of **L**;[14] herein, we employ the complexes **LCuCl** (**1**) (isolated as the C_s-symmetric **LCuCl-THF**) and **LCuSPh** (**2**) (Chart 1) formulated as monomers based on VT-NMR, DOSY-NMR, and MS data (see ESI†) in Ullmann-type C–S coupling reactions. We chose this particular reaction as proof-of-concept to assess the suitability and repercussions of metal-confinement on catalytic performance; the reported molecular analogues serve as benchmarks for proper comparisons to discern the role of the calixarene cavitand. Covalent attachment of reactive sites to supramolecular scaffolds to generate robust frameworks may be difficult; compounds **1** and **2** represent rare examples of systems engineered to operate through the synergy of the recognition properties of the calix[8]arene, and the catalytic attributes of Cu(I)-phenanthroline complexes. Our observations highlight the advantages of metal confinement and may provide a general strategy to carry out diverse organic reactions within calix[8]arene nanoreactors.

Typically, the reaction was carried out in toluene at 110°C with equimolar amounts of sodium thiophenolate and an aryl halide. Additionally, 2.5% of **L** and 2.5% of CuCl were added (Table 1). The protocol is compatible with both electron-deficient and electron-rich aryl halides, resulting in good to excellent isolated yields of the substituted arylthioethers. Control experiments with CuCl or CuI (5% mol) were carried out; we did not detect significant amounts of coupled products after 24 h in refluxing toluene. As additional control experiments, the use of isolated **LCuCl-THF** (**1**) as catalyst afforded virtually identical results in terms of reaction time and yield of coupled products as those obtained when **L** and CuCl were added separately. This indicates that *in situ* formation of the pre-catalyst **LCuCl** must occur rapidly. To confirm the role of **1** as precursor of the active catalyst **2**, we isolated the corresponding thiophenolate **LCuSPh** (**2**) from the reaction of equimolar amounts of **1** and sodium thiophenolate. **2** reacts efficiently with one equivalent of haloarene to quantitatively form the corresponding aryl thioether in a few hours (Scheme 1). These results suggest that **2** may be an intermediate in the catalytic production of aryl sulfides. Further insight into the mechanism of thioetherification may be obtained from the reaction of **1** and **2** with *o*-(allyloxy)iodobenzene (entry 9, Table 1 and Scheme 1). The corresponding C–S coupling product was isolated in over 80% yield, without evidence of the cyclic product expected if a radical mechanism was involved. This outcome parallels the observations by Hartwig *et al.*, which indicate that the absence of cyclic products imply that C–S coupling occurs without intermediacy of aryl radicals, and confirms that Cu-

thiophenolates are competent catalysts in the thioetherification of haloarenes through Cu(III) intermediates.[13] Such mechanism also agrees with calculations predicting that neutral LCu(I)–SPh are the active catalysts in Ullmann *S*–arylations, especially in non-polar toluene.[15]

Table 1 Thioetherification of aryl halides catalysed by *in situ* formed **LCuCl**[a]
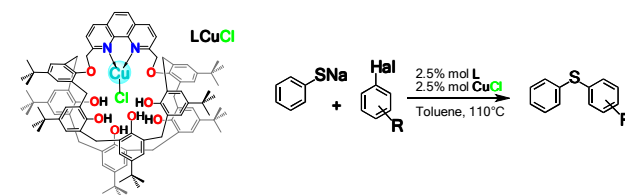
Entry	Aryl halide	Product	Time (h)	Yield(%)[b]
1			15	88
2			15	95
3			15	95
4			12	93
5			12	95
6			12	87
7			10	95
8			16	70
9			16	80
10			16	94
11			20	92
12			10	95
13			12	94

[a] This species should not contain THF, in contrast with **LCuCl-THF** (**1**) prepared in THF. [b] Isolated yields after column chromatography

Our results are intriguing since most reports on Cu(I)-mediated C–S coupling reactions usually suffer from limitations such as the requirement of high polarity solvents (HMPA, DMF, DMSO, dioxane, NMP), high temperatures, sub-stoichiometric catalyst loadings (10%–20%), and excess of aryl halides.[11] Moreover,

the efficiency of the reaction tends to be highly dependent on the functional groups on the aryl halide; for instance, products derived from electron-rich haloarenes are difficult to obtain in good yields (see entries 6–9, Table 1). Thus, the great performance of supramolecular catalyst **1** could be directly ascribed to the benefits of active-site confinement within the calix[8]arene hydrophobic cavity. Unlike the smaller calix[n]arene congeners (n = 4,6), calix[8]arene seems to provide a suitable hydrophobic pocket to encapsulate guests; in this scenario, the calixarene framework should experience conformational variations in order to correctly bind substrates and release products. As substrates are sequestered by **1** or **2** from bulk solvent, their encapsulation may be translated into increased likelihood of effective collisions and stabilisation of reactive intermediates (Fig. 1). Additionally, confinement of the catalytic Cu(I)-centre allows site-isolation for higher reactivity: dimer formation prevalent in related molecular systems is prevented by the calixarene framework. This also precludes degradation and deactivation of the active site; **1** and **2** maintain their integrity for extended periods of time even when exposed to air. These attributes are further evidenced by comparison of the catalytic performance of **1** and its molecular analogue **A** (Chart 1).[12] The use of **1** led to high conversions of haloarenes into the corresponding thioethers in less time and with lower catalyst loadings, decreasing from 10% of **A** to 2.5% mol of **1**. While catalyst **A** was only effective with iodoarenes, **1** was efficient with iodo-, bromo-, and some activated chloroarenes (Table 1). Notably, the protocol for **A** exhibits modest results with CuCl as precursor, and CuI was used instead; in contrast, our system works efficiently with the normally less active CuCl. Likewise, **2** is a more effective precursor when compared to type-**B** thiophenolates. Table S1 and Scheme S1 in the ESI† compare **1** and **2** versus their molecular counterparts **A** and **B**, clearly attesting to the advantages of the supramolecular platform.
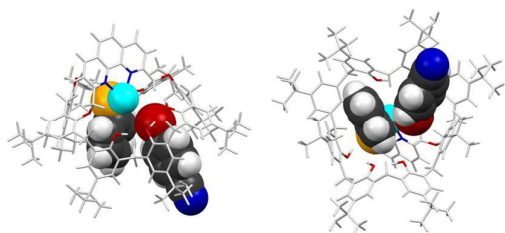

Fig. 1 Simulation of the inclusion of 4-Bromobenzonitrile within the calixarene pocket of **LCuSPh** (**2**) (Energy-minimised simulations; MMFF, Spartan)

Although the effect is subtle, the calixarene pocket apparently affects the selectivity for the halogen substrate. The reactivity of arylbromides was generally superior to that of aryliodides, as evidenced by the slightly higher yields and shorter reaction times (Table 1); the latter observation is also interesting since the analogous **A** is only efficient for C–S coupling of aryliodides. Thus, the calixarene enables a higher reactivity for the smaller arylbromides, overruling the usual trend of superior reactivity for iodides.[11] Further insight into size- and shape-selectivity may be obtained from competition

reactions of one equivalent of **2** with a mixture of haloarenes (one equivalent of each halide, Scheme 1). These results suggest that the calixarene imposes steric restrictions around the catalytic centre, and the less congested aryl halides access more easily the Cu(I) ion. In this sense, the calix[8]arene pocket kinetically discriminates between substrates and induces selectivity effects, which may not be easily attained through modifications on molecular catalysts **A** and **B**.
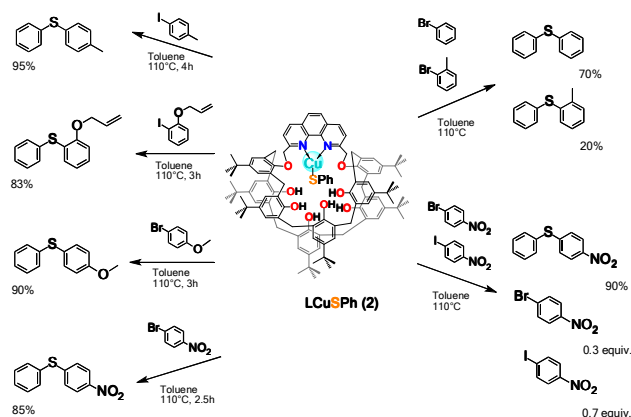
Scheme 1 Selected C–S coupling reactions of **LCuSPh** (**2**) (*left*) and substrate-selectivity experiments (*right*)

Various solvents were screened to test the catalytic activity of **1** under the conditions in Table 1. Methanol and THF promoted low yields of the target products (around 50%), and formation of disulfide. The use of more polar solvent mixtures such as water:MeOH (2:1), DMF, and DMSO led to even lower yields of the target thioethers (ca. 30%), together with starting materials, and undesired phenyl disulfide. Hence, the less polar toluene was confirmed to be the most effective medium for this reaction. Interestingly, this outcome differs from the polar and high-boiling point solvents generally used for C–S coupling reactions.[11] On the basis of the aforementioned observations, we reasoned that the solvent-dependent catalytic behaviour of supramolecular compounds **1** and **2** could be associated to an opening-closing mechanism of the *t*-Bu-rich calixarene upper rim that modulates the traffic of substrates and products in and out of the cavity. Considering that access to the catalytic centre and release of products must occur through the gate defined by the eight *t*-Bu groups, our hypothesis is that the polar solvents may enforce grouping of *t*-Bu moieties by hydrophobic interactions. This effectively shuts access to the macrocyclic cavity by creating a *t*-Bu "seam", thus compromising the host properties of **1** and **2**. Since efficient catalysis requires that the product readily dissociates from the calixarene structure, easy access and release from the cavity by opening the hydrophobic *t*-Bu seam may be favoured by the non-polar environment in toluene. Further support of this idea was obtained in our previous studies on the dynamic nature of calixarene **L**, which revealed that cone conformers predominate at high temperature (393 K) in the low polarity $C_2D_2Cl_4$. Accordingly, the stable cone conformation of **L** is constructed by two ¾-cone clefts whose

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eight *t*-Bu groups are oriented *syn*,[14] with an open conformation as observed in related 1,5-functionalised calix[8]arenes.[16] Interestingly, the corresponding open cone conformation in **1** and **2** appears to be rigid due to the reduced conformational mobility imposed by the CuCl-THF and CuSPh moieties inside the cavity; this is evident from the presence of an AB system for the methylene linkers of the phenanthroline group. VT-NMR showed no coalescence for any of the signals up to 390 K in $C_2D_2Cl_4$ (see Fig. S3 in ESI†); this array is foreseen to meet the nanoreactor conditions for **1** and **2**.

In summary, we have presented the first case of a calix[8]arene cavitand employed as nanoreactor for metal confinement in C–S catalytic coupling. Calixarene **L** served as a suitable platform for supramolecular complexes **1** and **2** that efficiently promoted the formation of aryl sulfides in toluene. Catalysts **1** and **2** present experimental advantages that can be translated into an improved catalytic performance when compared to their molecular analogues. The calixarene pocket also imposes steric restrictions that affect the selectivity for substrates: it appears that the less hindered bromoarenes react faster than iodoarenes, in contrast with their usually observed reactivity. Furthermore, the calixarene conformations seem to be affected by the nature of the solvents, leading to differing activities likely due to hydrophobic effects. Our observations clearly prove the supramolecular effects of calix[8]arene on the catalytic activity of confined Cu(I) centres, substrate selectivity, and solvent-induced reactivity. This supramolecular strategy represents a novel approach for transition metal catalysed transformations within calix[8]arene derivatives, which may pave the road for their further development, along with analogous supramolecular scaffolds. Investigation of this new class of supramolecular catalysts will provide insights into catalysis in confined space, and shed light on cavitand features relevant to fine tuning for the rational design of advanced catalysts.

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