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Supramolecular Activation of Hydrogen Peroxide in the Selective Sulfoxidation of Thioethers by a Self-Assembled Hexameric Capsule

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Abstract: An efficient metal-free organocatalytic activation of hydrogen peroxide (H_2O_2) towards thioethers leading to the corresponding sulfoxides in high yields at room temperature within hours was promoted by the hexameric capsule formed by the self-assembly of resorcin[4]arene units. The capsule plays a dual role of activating the oxidant through hydrogen bonding and favouring the oxidation reaction inside the cavity. Inactivation of the supramolecular organocatalyst was observed by using competitive ammonium guests, mimicking the inactivation of enzymes by competitive inhibitors.

Keywords: hydrogen peroxide; metal-free conditons; organocatalysis; sulfoxidation; supramolecular catalysis

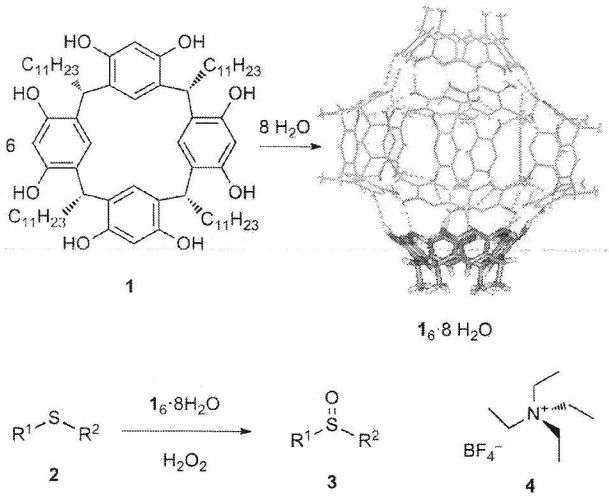
Introduction

Homogeneous catalysis is widening the way molecules are made taking inspiration from natural enzymes by exploring the use of organocatalysts,[1] the development of artificial enzyme mimetic catalysts[2] and supramolecular catalysis.[3] All these approaches are characterized by the implementation of weak intermolecular forces in substrate recognition and activation. These phenomena are favoured by a large contact surface between catalyst and substrates where weak intermolecular forces can deploy.[4] A wide range of catalytically active hosts have been developed in the recent years ranging from covalent unimolecular tubular,[5] to vase-shaped[6] to capsular structures and self-assemblies.[3] The self-assembly strategy has the intrinsic advantage of reducing the number of synthetic steps yielding a simple *in situ* formation of the supramolecular structure.

As far as self-assembled capsules are concerned, the size, shape and intrinsic features of the cavity play a crucial role in catalytic activity. Although the number of water-soluble self-assembled capsules is not so large, impressive examples exploiting the preferential binding of hydrophobic substrates with size and shape matching the dimensions of the cavity leading to unexpected selectivities and activities have already been reported.[7] Conversely, the development of self-assembled capsules operating in organic media and displaying catalytic activity is somehow a more challenging task since substrate binding and activation is strictly related to the specific interactions of the latter with the internal surface of the supramolecular catalyst and interferences with the self-assembling process may occur. After the seminal works of Rebek concerning the Diels–Alder cycloaddition reaction promoted by the hydrogen bonded softball dimeric capsule,[8] other examples of catalytically active capsules have indeed been rare.

The hexameric capsule obtained by the aggregation of six resorcin[4]arene **1** molecules with eight water molecules through a seam of sixty hydrogen bonds provides an assembly characterized by a large cavity of about 1375 Å^3 (Scheme 1)[9,10] that has been recently exploited for catalytic purposes.

The assembly efficiently complements cationic guests like organic ammonium and phosphonium ions[11] or metal species[12] stabilized through cation-π[13] interactions. Alternatively the capsule, thanks to its extended network of hydrogen bonds, proved to bind species like carboxylic acids, amino acids,[14] alcohols,[15] often used in large molar excess. The hexamer has been employed (i) as a nano-reactor where trapped transition metal catalysts showed modulation of catalytic activity[16] as well as steering of products[17] and substrate selectivity[18] or (ii) directly as a cata-



Scheme 1. Sulfoxidation of thioethers **2** with 30% H_2O_2 leading to the corresponding sulfoxides **3** mediated by the capsule $\mathbf{1}_6 \cdot 8\,H_2O$ and inhibited by competitive guest tetraethylammonium tetrafluoroborate **4**.

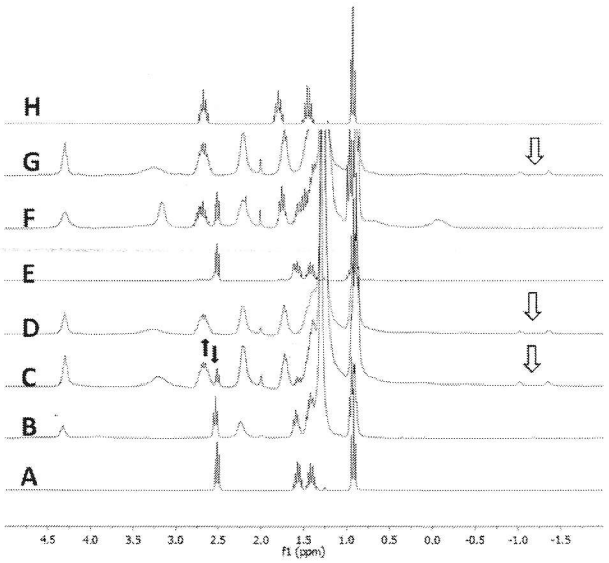


Figure 1. ^{1}H NMR spectra in water-saturated chloroform-*d*: A) dibutyl sulfide **2a** (60 mM); B) **2a** (60 mM) and $\mathbf{1}_6 \cdot 8\,H_2O$ (6 mM); C) **2a** (60 mM) with H_2O_2 (1.2 equiv.) and $\mathbf{1}_6 \cdot 8\,H_2O$ (6 mM) after 25 minutes; D) **2a** (60 mM) with H_2O_2 (1.2 equiv.) and $\mathbf{1}_6 \cdot 8\,H_2O$ (6 mM) after 65 minutes; E) **2a** (60 mM) with H_2O_2 (1.2 equiv.) after 90 minutes; F) **2a** (60 mM) with H_2O_2 (1.2 equiv.), $\mathbf{1}_6 \cdot 8\,H_2O$ (6 mM) and **4** (60 mM) after 90 minutes; G) dibutyl sulfoxide **3a** (60 mM) and $\mathbf{1}_6 \cdot 8\,H_2O$ (6 mM); H) dibutyl sulfoxide **3a** (60 mM); ↓ dibutyl sulfide, ↑ free dibutyl sulfoxide, ⇓ encapsulated dibutyl sulfoxide.

lyst.[19] Examples of the latter case are the Diels–Alder reaction in fluorinated solvents using a fluorinated analogue of resorcin[4]arene **1**,[20] the diethyl acetal hydrolysis within the hexameric $\mathbf{1}_6 \cdot 8\,H_2O$,[21] the hydration of isonitriles to the corresponding formamides,[22] the synthesis of tetrazoles from isonitriles,[23] the 1,3-dipolar cycloaddition between diazoacetate esters and electron-poor alkenes leading to 4,5-dihydro-1*H*-pyrazoles,[24] the intramolecular hydroalkoxylation of unactivated hydroxy olefins[25] and very recently the terpene cyclization.[26] In all cases, the encapsulation of reagents turned out to be pivotal to promote the reaction. It is worthy of note that, to the best of our knowledge, no examples of activation in oxidation reactions has ever been reported with hydrogen bonded self-assembled capsules.

Herein we present a very efficient metal-free supramolecular H_2O_2 activation by the hexameric capsule $\mathbf{1}_6 \cdot 8\,H_2O$ for the oxidation of thioethers efficiently leading to the corresponding sulfoxides under mild conditions within hours (Scheme 1). The reaction occurs within the cavity of the supramolecular capsule showing inhibition of the catalytic activity in the presence of competitive tetraethylammonium guests **4**, all features reminiscent of enzymatic catalysis.

Results and Discussion

The oxidation reaction of dibutyl sulfide **2a** as a model substrate was investigated in the presence of 1.2 equivalents of a 35% aqueous solution of H_2O_2 observing only 10% yield after 90 minutes for the spontaneous reaction (Figure 1E and Table 1, entry 1), while rapid formation of dibutyl sulfoxide **3a** (Table 1, entry 2) was observed in the presence of sub-stoichiometric amounts of capsule (10 mol%) with quantitative formation of the sulfoxide **3a** obtained within 65 minutes (Figure 1D).

Table 1. Catalytic tests for the sulfoxidation of **2a** with 30% H_2O_2.[a]

Entry	$\mathbf{1}_6 \cdot 8\,H_2O$	**4**	Time [min]	**3a** [%][b]
1	–	–	90	10
2	+	–	65	>98
3[c]	–	–	90	21
4[d]	–	–	90	28
5	+	+	65	46
6	–	+	90	15

[a] [**1**] = 36 mM, [**2a**] = 60 mM, 30% H_2O_2 1.2 equiv.; [tetraethylammonium tetrafluoroborate **4**] = 60 mM, water-saturated chloroform-*d* 1.5 mL, *T* = room temperature. +: presence; –: absence.

[b] Determined by ^{1}H NMR.

[c] [acetic acid] = 6 mM (1 equiv. with respect to $\mathbf{1}_6 \cdot 8\,H_2O$).

[d] [resorcinol] = 144 mM (24 equiv. with respect to $\mathbf{1}_6 \cdot 8\,H_2O$).

It was initially observed that no resonances for the encapsulated species were found in the ^{1}H NMR spec-

trum upon addition of ten equivalents of dibutyl sulfide **2a** to a solution of the hexamer $\mathbf{1}_6 \cdot 8H_2O$ in chloroform-*d* (Figure 1A). In the presence of capsule and H_2O_2, apart from the resonances at 2.7 ppm corresponding to free **3a**, the spectrum showed the appearance of new up-field shifted resonances in the range −0.75 to −1.5 ppm (Figure 1C and D). To confirm the nature of the encapsulated species, experiments were carried out adding increasing amounts of sulfoxide **3a** to a solution of $\mathbf{1}_6 \cdot 8H_2O$ observing the formation of exactly the same up-field shifted resonances (Figure 1G) recorded during the oxidation reaction, thus confirming that sulfoxide **3a** is a suitable guest for the capsule.

It is widely accepted that the electrophilic oxidation reaction of thioethers with H_2O_2 typically occurs *via* activation of the oxidant by means of metal catalysts[27] as well as protonation or hydrogen bond activation with organic molecules like alcohols, phenols, ureas, sulfoxides,[28] surfactants[29] and many others[30] also in the enantioselective form.[31] Recently Tiefenbacher and co-workers demonstrated that the hexamer behaves as a weak acid assembly with a pK_a of about 5.5,[21] while resorcinol alone has a pK_a of 9.15. In order to ascertain whether the activation of H_2O_2 was due to the Brønsted acidity of the hexamer, we performed the oxidation reaction with one equivalent of acetic acid (pK_a 4.7) with respect to the capsule observing only 21% of sulfoxide **2a** after 90 min (Table 1, entry 3). Moreover, since commercially available 35% H_2O_2 solution has an apparent pH <2, activation due to protonation by the capsule seems very unlikely. Activation of H_2O_2 by simple hydrogen bonding to the capsule could not justify the reactivity observed as confirmed by testing the reaction with 24 equivalents of disassembled resorcinol that led to only 28% yield of **3a** after 90 min (Table 1, entry 4). To investigate the effect of the capsule cavity in promoting this oxidation, we repeated the reaction adding ten equivalents of tetraethylammonium tetrafluoroborate **4** as a competitive cationic guest to a solution of **2a**, H_2O_2 and capsule.[32] The ammonium guests was rapidly encapsulated as demonstrated by the appearance of a broad resonance at −0.05 ppm (Figure 1F) and its effect was to reduce the catalytic activity (Table 1, entry 5), even if to a lower extent with respect to other catalytic reactions where the inhibition was complete. Compound **4** turned out to be intrinsically unable to promote the oxidation reaction (Table 1, entry 6) even though recent examples of ammonium salt catalysis for sulfoxidation have been reported in the case of some weakly acidic cations having H-bond donor and acceptors moieties in the ion pairs.[33]

The lack of macroscopic encapsulation of the sulfide, the absence of evidence of acidic activation of hydrogen peroxide, as well as the moderate inhibition effect by ammonium, seem to suggest that the reaction, rather than by substrate activation, is favoured by the capsule through a dual synergic effect: (i) the displacement of the bridging water molecules in the H-bond seam by H_2O_2 that becomes more electrophilic (oxidant activation) and (ii) the stabilization of the polar transition state typical of the electrophilic sulfoxidation inside the self-assembled capsule exerted by its electron-rich internal surface, even if conclusive experimental evidence in this respect is missing.

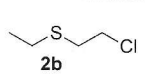
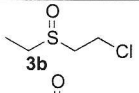
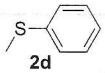
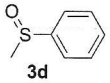
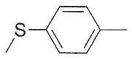
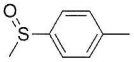
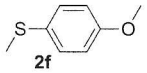
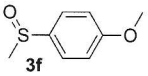
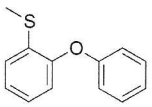
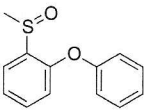
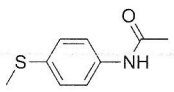
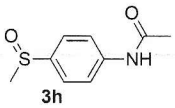
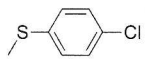
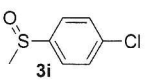
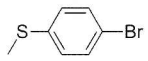
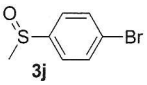
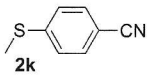
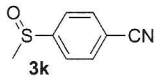
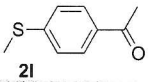
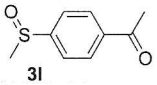
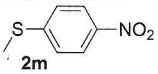
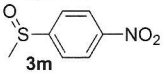
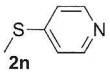
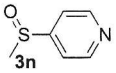
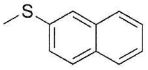
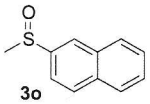
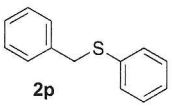
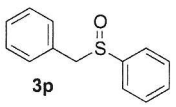
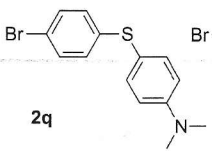
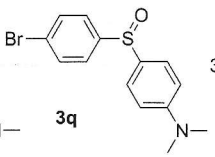
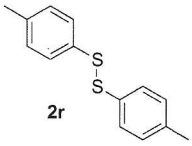
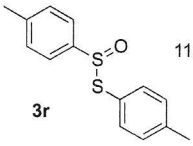
The chemoselectivity of the oxidation reaction was demonstrated by repeating the reaction under the same experimental conditions as in Table 1, entry 2 using the sulfoxide **3a** as substrate in place of the thioether **2a**. No conversion to sulfone was observed even after 24 hours at room temperature, in agreement with the electrophilic nature of the oxygen transfer step typical of the sulfoxidation reaction.

The scope of the reaction was investigated observing excellent yields in sulfoxides **3** within a few hours with bis-aliphatic thioethers such as the analogue of the warfare agent mustard gas **2b** and *tert*-butyl methyl sulfide **2c** (Table 2, entries 1 and 2). Alkyl aryl sulfides are intrinsically less reactive giving from good to excellent sulfoxide yields as a function of the electronic properties of the substrates (Table 2, entries 3–15). Substrates bearing electron-donating groups like methyl, methoxy, phenoxy and acetamido showed good reactivity in the presence of the supramolecular catalyst $\mathbf{1}_6 \cdot 8H_2O$, while substrates bearing electron-withdrawing groups like halogen atoms, acetyl, cyano and pyridyl moieties required longer reaction times to ensure good product formation. Even larger substrates like **2o** and **2p** reacted readily forming the corresponding sulfoxides under the usual conditions, showing the well-known importance of the electron density on the S atom for this reaction.

Diaryl sulfides turned out to be poorly reactive as observed in the oxidation of the substrate **2q** where the presence of the dimethylamino moiety increases the electron density of the S atom favouring its sulfoxidation (Table 2, entry 16). Finally, *p*-tolyl disulfide **2r** was used as substrate observing the chemoselective oxidation to the mono-sulfoxide in 51% yield after 18.5 h using a large amount of oxidant.

Comparable inhibition effects due to competitive occupation of cavity of the hexamer by **4** were observed in all the substrates investigated in Table 2. In particular, it is worth noting that larger differences in sulfoxide yield between free and occupied capsule were observed with less electron-rich substrates due to their intrinsic lower reactivity. In fact, substrates like **2c** and **2h** showed no or little difference between free and occupied cavity, while electron-poor substrates like the series **2i–2n** showed a marked decrease of the catalytic activity in the presence of the ammonium competitive guest **4**. Moreover, the same

Table 2. Sulfoxidation of thioethers **2b–2r** with H_2O_2 mediated by $\mathbf{1}_6{\cdot}8H_2O$ and inhibited by the presence of the competitive cationic guest **4**.

Entry	Substrate	Product	Time [min]	Conv. [%][b]
1	 **2b**	 **3b**	120	95 22[c]
2	 **2c**	 **3c**	35	>98 >98[c]
3	 **2d**	 **3d**	110	>98 23[c]
4	 **2e**	 **3e**	60	>98 50[c]
5	 **2f**	 **3f**	100	>98 40[c]
6	 **2g**	 **3g**	80	>98 19[c]
7	 **2h**	 **3h**	20	>98 75[c]
8	 **2i**	 **3i**	150	76 13[c]
9	 **2j**	 **3j**	80	90 28[c]
10	 **2k**	 **3k**	130	68 15[c]
11	 **2l**	 **3l**	180	70 6[c]
12	 **2m**	 **3m**	375	80 6[c]
13	 **2n**	 **3n**	380	70 10[c]
14	 **2o**	 **3o**	180	80 10[c]
15	 **2p**	 **3p**	20	94[e] 23[c,e]
16	 **2q**	 **3q**	340	67[e] 15[c,e]
17	 **2r**	 **3r**	1100	51[c,f] 21[c,e,f]

[a] *Experimental conditions:* [**2b–2r**] = 60 mM, 30% H_2O_2 1.2 equiv.; [**1**] = 36 mM, water-saturated chloroform-*d* 1.5 mL, *T* = room temperature.
[b] Determined by ^{1}H NMR.
[c] [**4**] = 60 mM.
[d] Sulfone oxidation product.
[e] Determined by GC.
[f] H_2O_2 (5.0 equiv.).

trend was observed moving from small substrates to larger ones like **2o** and **2p**, indicating that the residual space left in the cavity by the competitive ammonium guest allows oxidation of smaller substrates that can be more likely co-encapsulated along with the ammonium species still fitting the best packing coefficient of 0.45–0.55 typical of supramolecular encapsulation phenomena.[34]

With the aim of investigating the possible effect of the preferential encapsulation of the sulfoxides in the oxidation reaction we carried out a series of experiments at constant capsule concentration with increasing amounts of substrate *p*-chlorothioanisole **2i** chosen because of its moderate reactivity under the selected experimental conditions. The results observed showed that the capsule maintained its catalytic activity in the presence 10, 25 and 50 equivalents of **2i** observing almost superimposable plots of the yield of **3i** with time (Figure 2A). Only when the amount of substrate was drastically increased to 200 equivalents with respect to the capsule, did the reaction profile show a reduction in yield over time that after 400 min

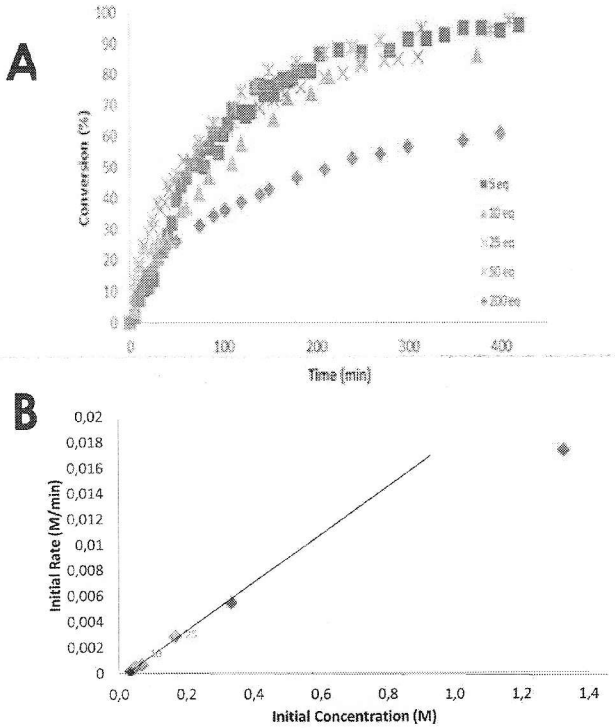


Figure 2. A) Conversion of different equivalents of **2i** to the corresponding sulfoxide **3i** over time. [**1**] = 36 mM, H_2O_2/**2i** = 1.2, water-saturated chloroform-*d* 1.5 mL, room temperature. B) Initial rate for the oxidation reaction of **2i** to the corresponding sulfoxide **3i** as a function of the initial concentration of **2i**. [**1**] = 36 mM, H_2O_2 = 1.2 equivalents, water-saturated chloroform-*d* 1.5 mL, room temperature.

is only slightly above 50%. Whether or not this is indicative of inhibition by product is doubtful in view of an analysis of the initial rates that can be extracted and plotted against the substrate concentration because the concentration of H_2O_2 in chloroform can be assumed as constant and corresponding to saturation, the system being two-phase. A first-order dependence is evident (Figure 2B) as is generally the case for this oxidation reaction[35] while at high substrate concentration a sharp departure from linearity appears. This kinetic effect is typical of enzymes and is a good indication of an association process, with the oxygen transfer step occurring inside the capsule.

Conclusions

In conclusion, have we reported an example of supramolecular activation of H_2O_2 by the hexameric capsule $\mathbf{1}_6 \cdot 8H_2O$ leading to the selective oxidation of thioethers **2** to the corresponding sulfoxides **3** where hydrogen peroxide likely displaces water molecules in the network of H-bonds in $\mathbf{1}_6 \cdot 8H_2O$ and this enhances the electrophilic character of the oxidant. At the same time, the large capsule stabilizes the polar transition state derived by the combination of the oxidant and the substrate that can be suitably hosted in the presence of competitors like ammonium cations or the sulfoxide product. Both effects proved fundamental to obtain an efficient, chemoselective metal-free catalytic system for sulfoxide production with a catalytic activity among the best known for organocatalytic systems using H_2O_2.[36] The results reported here compare well in terms of yields and versatility of the reaction with some of the best metal catalysts in this field and, albeit with some intrinsic limitations in terms of practicality, represent an important proof of concept demonstration of the potentialities of supramolecular organocatalysis.

Experimental Section

General Reagents and Materials

^{1}H NMR spectra were recorded at 298 K, unless otherwise stated, on a Bruker AVANCE 300 spectrometer operating at 300.15 MHz. δ values in ppm are relative to $SiMe_4$. GC analysis were performed on HP Series II 5890 equipped with a HP5 column (30 m, I. D. 0.25 m, film 0.25 μm) using He as gas carrier and FID. GC-MS analyses were performed on a GC Trace GC 2000 equipped with an HP5-MS column (30 m, I.D. 0.25 mm, film 0.25 μm) using He gas carrier and coupled with a quadrupole MS Thermo Finnigan Trace MS with the *Full Scan* method.

Solvents and reactants were used as received; otherwise they were purified as reported in the literature.[37] TLC analysis were performed on TLC Polygram ® Sil G/UV254 of 0.25 mm thickness and flash chromatography separations were performed on silica gel Merk 60, 230–400 mesh.[38]

Substrates and Capsule

Dibutyl sulfide, 2-chloroethyl ethyl sulfide, *tert*-butyl methyl sulfide, thioanisole, 4-methoxythioanisole, 4-chlorothioanisole, 4-bromothioanisole, 4-acetylthioanisole, 4-(methylthio)-benzonitrile, 4-nitrothioanisole, benzyl phenyl sulfide, 2-(methylthio)naphthalene, 4-mercaptopyridine, tetraethylammonium tetrafluoroborate, hydrogen peroxide, resorcinol, acetic acid are all commercially available products and were used as received without any further purification.

Resorcin[4]arene[39] was prepared as reported in the literature. All the sulfoxidation products were identified by GC-MS and ^{1}H NMR analysis.

The substrates 1-(methylsulfanyl)-2-phenoxybenzene, [40] *N*-[4-(methylsulfanyl)phenyl]acetamide, [41] 4-[(4-bromophenyl)sulfanyl]-*N*,*N*-dimethylaniline, [42] bis(4-methylphenyl) disulfide[43] were synthesized following reported procedures.

Catalytic Studies

Water-saturated solvent was prepared by shaking chloroform-*d* with bidistilled water at room temperature in a separation funnel. Resorcin[4]arene **1** (6 equivalents, 36 mM)

was placed in a screw-capped vial equipped with silicone septum and dissolved in the water-saturated chloroform-*d* (1.5 mL) by stirring for a few minutes. To this solution, the chosen thioether (10 equivalents, 60 mM), and 30% H_2O_2 (1.2 equivalents) were added. The reaction was left under vigorous stirring at room temperature and the reaction progress was monitored by periodically sampling directly 50 μL of solution and diluting it into 450 μL of chloroform-*d* and subsequent immediate ^{1}H-NMR ad GC analysis.

Conversion, product assignment and distribution were determined by direct GC, GC-MS and ^{1}H NMR analysis of the reaction mixture as the average of three experiments.

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