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Copper (II) Serves as an Efficient Additive for Metal-Directed Self-Assembly of Over 20 Thiacyclophanes

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Cu^{2+} salts are presented as an alternative to previously reported pnictogen additives in the self-assembly of 23 different thiacyclophanes. This process allows for further tuning of library equilibrium mixtures: for instance, by altering additive types and concentrations, trimeric macrocycles are amplified. These trimeric disulfides can then be covalently trapped to form 2 novel thioethers, highlighting the facile route to access these new naphthalene-bridged cyclophanes.

Metal-directed self-assembly has allowed synthetic chemists to access a variety of elegant thermodynamic products over kinetic side products,[1–4] in part due to the lability of metal-ligand bonds allowing for "kinetic mistakes"[5,6] to be corrected. Metal-ligand bonds are also highly directional, thus the stereochemical preference and symmetry of metal coordination may be imposed onto the self-assembling system of interest.[7] For these reasons, metal-directed self-assembled structures have been employed in many applications, such as supramolecular catalysis,[8,9] guest transport across phase boundaries,[10] or in the stabilization of reactive species.[11] A complementary supramolecular approach to the assembly of complex structures makes use of dynamic covalent chemistry (DCC), which relates to chemical reactions carried out reversibly under conditions of equilibrium control.[12] One great advantage of DCC is its ability to control the product distribution by changes in the chemical environment, such as temperature, concentration or additives.[13,14]

Recently, our laboratory reported a system in which we coupled the use of metalloid-directed self-assembly and DCC to form two-fold symmetric dimeric through hexameric macrocyclic disulfides and three-dimensional tetrahedral cages (**Scheme 1**).[15,16] These discrete cyclophane structures have often been elusive due to lengthy stepwise reactions and a

tendency for self-assembly approaches to favor kinetic products, such as insoluble polymers (**Scheme 1**).[17–20] For instance, the thioether form of tetrahedral cage **L^3$_4$** was synthesized by our group through a two-step self-assembly and covalent capture approach,[16] in contrast to a traditional step-wise synthesis comprising seven individual steps.[21] Since then, we have focused on using pnictogen (Pn) additives (Group 15 elements) to maximize the yield of these complex discrete disulfides.

Mercaptomethyl (i.e. benzylic thiol) substituents accommodate the Pn's trigonal pyramidal geometry and thiophilicity. Addition of a mild oxidant (I$_2$) and a Pn salt to dithiols affords selective synthesis of disulfide dimers to
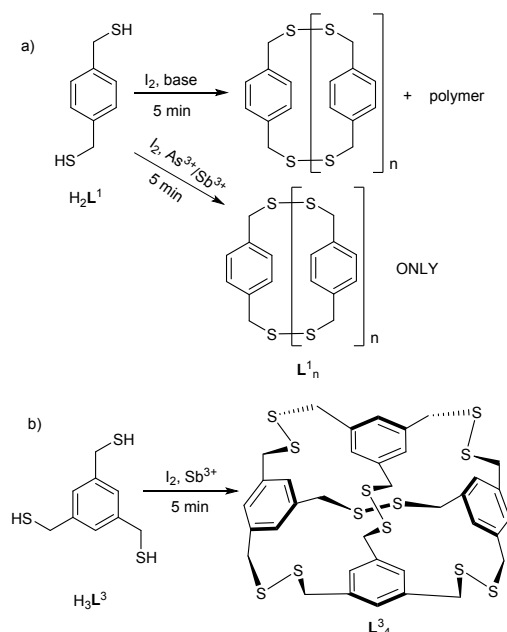
hexamers (**Scheme 2**) over competing polymers. These

Scheme 1. a) Iodine oxidation of a dithiol to macrocyclic disulfides with or without pnictogen additives. b) Iodine oxidation of a trithiol to a three-dimensional tetrahedral cage.

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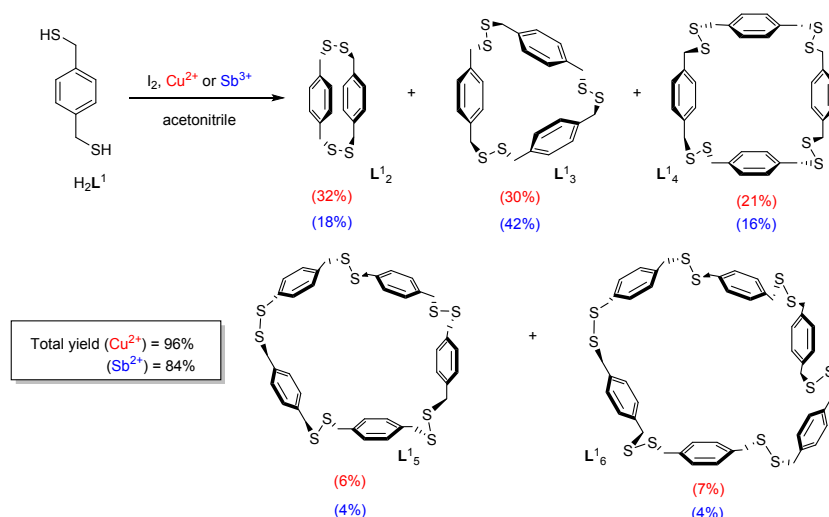
Scheme 2. Comparison of pnictogen trichloride and copper(II) additives in the oxidation of H_2L^1 to produce a series of discrete disulfide macrocycles (3 mM solution, 1 equiv. H_2L^1, 2 equiv. I_2, 2 equiv. additive).

disulfides can then be kinetically captured *via* sulfur extrusion with hexamethylphosphorous triamide (HMPT), providing a direct route to stable thioethers in high yields.[16] The final sulfur atom of thioethers can be extruded to yield hydrocarbon cyclophanes,[17,22] which show potential to be excellent precursors for ring-opening polymerizations to form, for example, commercially relevant parylene derivatives.[23]

Herein we report this process of "metalloid"-assisted disulfide self-assembly is not only the domain of the Group 15 elements: Cu^{2+} also serves as an effective additive for the self-assembly and ultimate covalent capture of a variety of known and new disulfides and thioether (thia)cyclophanes. Cu^{2+} has been used as a benign catalyst or as a mediating reagent in many important transformations,[24,25] and since metal complexes of Cu^{2+} with thiolate ligands are known,[26] such complexes were expected to promote our self-assembly process. To our delight, the clean formation of disulfides was observed upon the addition of 2.0 equivalents of Cu^{2+} to a reaction mixture of 1.0 equivalent of the dithiol H_2L^1 and 2.0 equivalents of I_2 in acetone-d_6. The counter anions do not appear to play a significant role in dictating the formation of the disulfides. Use of either $CuCl_2$ and $Cu(BF_4)_2$ in this system yielded virtually the same products. We use this method to report the syntheses of 13 previously known thiacyclophanes (L^1_2-L^1_6, L^2_2-L^2_6, L^3_2, L^3_4, $L^{1,5nap}_3$) and then use the method to synthesize what we believe to be the first reported naphthalene-bridged cyclophanes, synthesizing nine new disulfides ($L^{1,4nap}_2$–$L^{1,4nap}_6$ and $L^{2,6nap}_2$– $L^{2,6nap}_5$), isolating seven of them ($L^{1,4nap}_2$–$L^{1,4nap}_5$ and $L^{2,6nap}_2$– $L^{2,6nap}_4$), and converting two to thioethers (**1**, **2**).

Preliminary studies in acetone showed that while this method could prepare the desired disulfide assemblies, poor yields arose from the low solubility of the presumed Cu-thiolate intermediate. The yield was optimized by switching solvent to acetonitrile, which could allow an increase in the scalability of the thiol-to-disulfide transformation compared to traditional cyclophane synthesis, in which the concentration of starting material must be kept dilute to prevent oligomerization.[16]

Previous studies using an As^{3+} additive revealed that selectivity at low concentrations gave preferential assembly of the dimer (L^1_2), whereas at higher concentrations ([As^{3+}] > 0.25 mM), the trimer (L^1_3) was the dominant species.[15] In contrast, when Cu^{2+} was used as the additive, the dimer L^1_2 was found to be the dominant species even at a relatively high [Cu^{2+}] (3.0 mM compared to 0.25 mM). One exciting feature of using Cu^{2+} as the additive for the oxidation reaction of thiol ligand was that disulfide oxidation occurred rapidly in air, indicating I_2 was not strictly required as the oxidant. Disulfide structures and some Cu-thiolate intermediates were observed immediately after Cu^{2+} was added to H_2L^1 open to air. After about four days, intermediate thiol-metal complexes disappeared, giving rise to a clean ^{1}H NMR spectrum featuring only resonances attributed to disulfide macrocycles (although the reaction is much faster with stoichiometric iodine; **Figure S3**).

To better understand whether Cu^{2+} is acting catalytically or stoichiometrically, we conducted a quantitative study of Cu-assisted iodine oxidation by varying the amount of $CuCl_2$. Reaction with 1.0 equivalent of H_2L^1, 2.0 equivalent of I_2, and 2.0 equivalents of Cu^{2+} (in acetonitrile-d_3) went to completion almost immediately, as the ^{1}H NMR spectrum showed no sign of starting materials or any Cu-thiolate intermediates. We observed similar results in reactions with excess Cu^{2+}, whereas sub-stoichiometric amounts of Cu^{2+} decreased product yields almost linearly (**Table S1**). These experiments suggested that Cu^{2+} is not a catalyst (or at least not a highly active catalyst), but likely a stoichiometric reagent as reactions using sub-stoichiometric amounts of Cu^{2+} appeared to reach an equilibrium of disulfides and Cu-thiolate intermediates that remained almost unchanged after 4 hours.

Our previously reported Pn-directed self-assembly method also exhibited modest tolerance to substitution on the aryl ring.[16] The Cu-directed self-assembly also showed this same tolerance (the scope of which we are currently exploring). Methoxy-substituted disulfide macrocycles were again isolated from the reaction with either additive (**Figure S4**), indicating

that Cu^{2+} is an effective alternative for Sb^{3+} in these self-assembly reactions in general.

To demonstrate that Cu^{2+} is a more benign alternative for the oxidation reaction more broadly, the reactivity of Cu^{2+} and Sb^{3+} additives were compared in another more complex system. Previously, Pn-assisted iodine oxidation[16] was used to synthesize strained compounds like L^3_2 or tetrahedral cages like L^3_4 by oxidizing H_3L^3 (**Figure 1**). We now show that these two compounds can also be efficiently prepared with $CuCl_2$. Using tetrachloroethane as the internal standard, we quantify the ratio of L^3_2 to L^3_4 as 3:1 in the system with Sb^{3+} and 1.8:1 in the system with Cu^{2+}. We have shown in the H_2L^1 system that this method is sensitive to solvent effects that can vary the product distribution of disulfide macrocycles.[27] Concentration effects are also well-known for these types of macrocycles, in which smaller species tend to dominate at lower concentration.[27] We were thus surprised to find that the identity of the additives could also contribute to a change in product distribution. With all variables kept constant, switching out one additive to another could amplify a product within the dynamic mixture relative to its equilibrium distribution based on apparently subtle supramolecular interactions during self-assembly.[13,14]
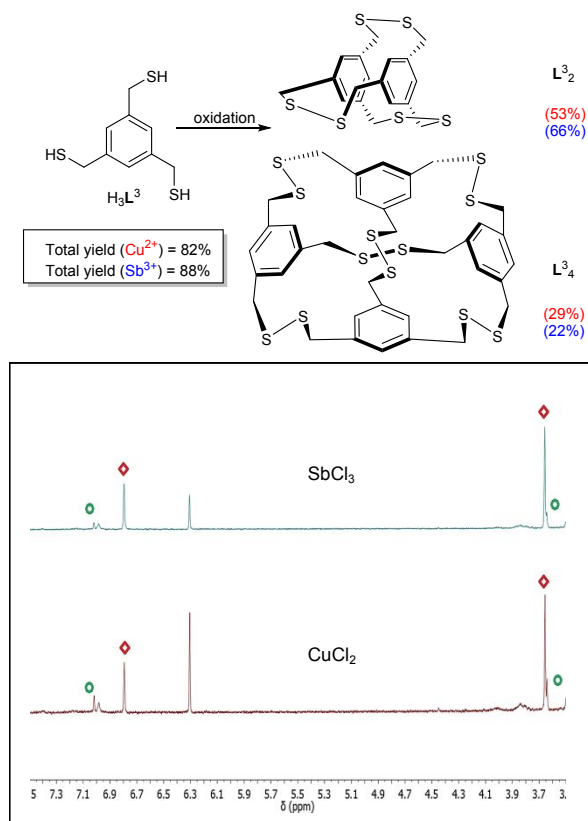
Figure 1. ^{1}H NMR of the oxidation of H_3L^3 to form L^3_2 and L^3_4. Top: Sb^{3+} additive. Bottom: Cu^{2+} additive. Green circle denotes the dimer L^3_2, red diamond denotes the tetrahedron L^3_4.

Having this new additive to access a variety of discrete disulfides, we also attempted to synthesize $L^{1,5nap}_3$ using Cu^{2+} as an additive. Previously, the crystal structure of $L^{1,5nap}_3$ was isolated over a slow-evaporation process, but a directed synthesis was not yet reported.[15] In this work, the synthesis of

$L^{1,5nap}_3$ was possible using 1,5-bismercaptomethylnapthalene, I_2 and $CuCl_2$ in acetonitrile-d_3. $L^{1,5nap}_3$ formed as a dominant product in 79% yield (**Scheme 3**).

Inspired by the observation that the Cu^{2+} additive selectively favors $L^{1,5nap}_3$ over other naphthyl disulfide structures (such as $L^{1,5nap}_2$, $L^{1,5nap}_4$, etc.) we were curious to see if these reaction conditions could be used to form previously unknown cyclophanes from other naphthalene isomers: 1,4- and 2,6-bismercaptomethylnaphthalene (**Scheme 3**). We observed the formation of disulfides of all sizes ranging from dimer to pentamer ($L^{2,6nap}$) or hexamer ($L^{1,4nap}$) in the circulating gel permeation chromatograms (GPC) (**Figure S15**, **S16**). In each system the trimer was again the dominant species: $L^{1,4nap}_3$ formed in 43% yield and $L^{2,6nap}_3$ in 45% with the collection of discrete macrocycles forming in 90+% yield in each case (see ESI). We were able to grow single crystals suitable for X-ray diffraction for the dimeric disulfides in each system (**Scheme 3**, right) confirming the success of our method.

To the best of our knowledge, these are the first examples of naphthalene-bridged cyclophanes to be reported. Therefore, we sought to carry these species on to the more stable, covalently trapped thioether cyclophanes. For each ligand system, the trimer disulfides were chosen to carry on to the corresponding thioether species since non-dimeric cyclophane structures are harder to synthesize than two-fold symmetric species in traditional stepwise approaches. Circulating GPC allowed for clean separation of each disulfide trimer from the crude mixture and sulfur extrusion using HMPT was utilized to give rise to two new thioethers **1** and **2** (**Scheme 3**). These studies once again stressed the utility of this method to self-assemble complex macrocycles from extended dithiol ligands.

In this work we discussed a new approach for the clean and rapid formation of libraries of disulfides through a self-assembly method. By switching out the toxic metalloids As^{3+}/Sb^{3+} for more benign Cu^{2+} salts, a great diversity of known and new discrete disulfides was reported, which can be kinetically trapped through a variety of pathways, such as sulfur extrusion.[11] This study also highlights the internal handles (reagent equivalents, concentration) for regulating disulfide distribution; further work will explore the external handles (temperature, guests, etc.) that might also affect the product distribution. We are optimistic this approach might provide a parallel avenue toward the generation of self-assembling libraries in which one element of the system is amplified and isolated by altering the identity of the additive in a dynamic system. While As^{3+} and Sb^{3+} are effective additives for these self-assembly reactions, we feel the use of Cu^{2+} salts is a more approachable, and perhaps "greener", synthetic alternative. With this greener tool, we synthesized three previously unknown cyclophane systems, and this method could prove scalable to enable further applications of this approach.
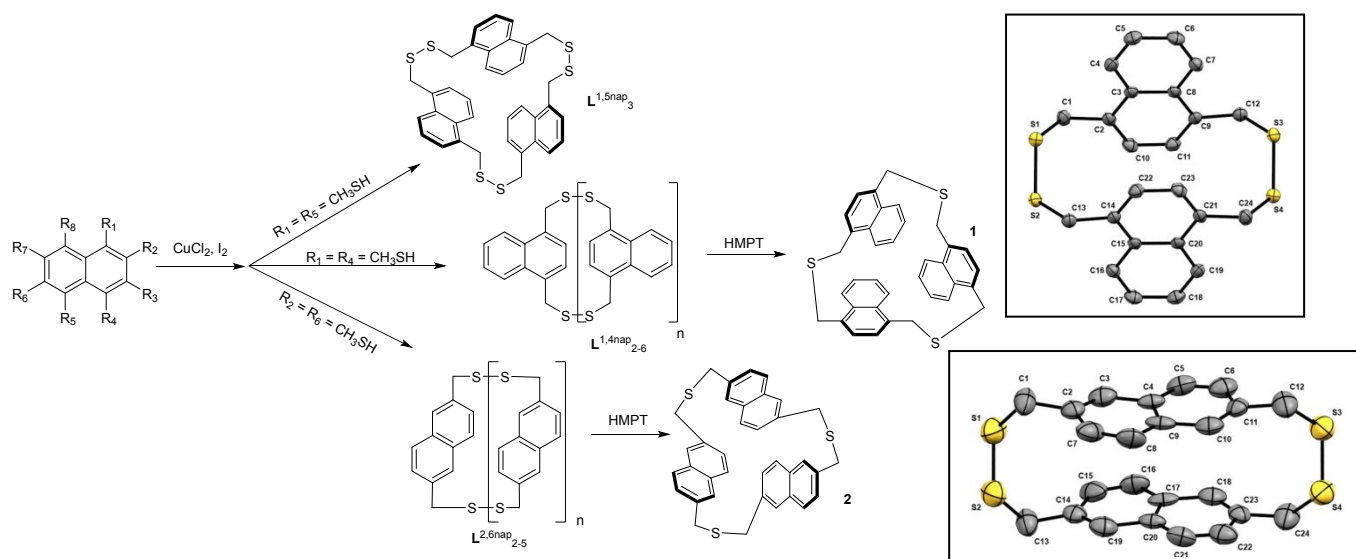
Scheme 3. Cu-assisted iodine oxidation and sulfur extrusion of naphthalene-bridged cyclophanes. (right) ORTEP diagrams of $L^{1,4nap}_2$ and $L^{2,6nap}_2$.

Conflicts of interest

There are no conflicts to declare.

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