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Disulfides, Imines, and Metal Coordination within a Single System: Interplay between Three Dynamic Equilibria

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Abstract: We report a system in which three distinct dynamic linkages, disulfide (S−S), imine (C=N), and coordinative (N→metal) bonds were shown to be capable of simultaneous reversible exchange. The "disulfide layer" of the system under study consists of two homo-disulfides, bis(4-aminophenyl) disulfide **1** and bis(4-methoxyphenyl) disulfide **2** that equilibrate in the presence of catalytic amount of triethylamine to favor the formation of a hetero-disulfide product, 4-aminophenyl-4′-methoxyphenyl disulfide **3**. The addition of 2-formylpyridine and a metal salt strongly perturbed this $\mathbf{1}+\mathbf{2}\rightleftarrows\mathbf{3}$ equilibrium through the formation of metal complexes incorporating disulfide **1** as a subcomponent. Cu^{I} perturbed the equilibrium by a factor of 3.3, and Fe^{II} by a factor of 179, in both cases in favor of the homo-disulfides. The disulfide equilibrium could be further modified, following metal-complex formation, by coordinative (transmetallation: substitution of Fe^{II} for Cu^{I}) or covalent (imine exchange: the substitution of one amine residue for another) exchange. Thus, although the three kinds of dynamic linkages were demonstrated to be mutually compatible, changes at one kind of linkage could be used to predictably perturb an equilibrium involving another.

Keywords: coordination chemistry · disulfides · dynamic combinatorial chemistry · self-assembly · systems chemistry

Introduction

Dynamic combinatorial chemistry is a powerful tool for identifying thermodynamic minima in complex mixtures.[1] This technique has found application in the development of receptors for guest molecules,[2] in which strong interactions with an added template create a driving force for the amplification of the template's receptors within the system. It has also been demonstrated that dynamic libraries can be driven in specific directions through efficient intramolecular interactions within some of the library members, enabling folding-driven synthesis.[3]

Metallo-organic self-assembly has proven very useful for the preparation of complex structures from metal ions and polyvalent ligands.[4,5] A new branch of this discipline is subcomponent self-assembly,[6,7] involving the simultaneous formation of dynamic covalent[8] imine and coordinative bonds. The reversibility of these two kinds of linkages permits the application of the concepts and tools of dynamic combinatorial chemistry[1] to systems of structures formed by subcomponent self-assembly. Specific structures may thus be selected out of dynamic libraries of subcomponents, with selectivities applied by steric, electronic, and entropic effects.[7,9]

Herein we report a system in which three distinct kinds of linkages, disulfide (S−S), imine (C=N) and coordinative (N→metal) were shown to be capable of simultaneous dynamic exchange.[10] Equilibria between the homo- and hetero-disulfide subcomponents of this system could be perturbed by more than two orders of magnitude by changes at the coordinative and imine linkages. None of these dynamic exchange processes interfered chemically with the others, marking the three as mutually compatible and "orthogonal", in similar fashion to systems investigated in the groups of Miller,[11] Lehn,[12] and Meijer.[13] This study thus represents the first report on the interplay between three separate reversible chemistries, allowing a novel entry into the emerging area of systems chemistry.[10,14]

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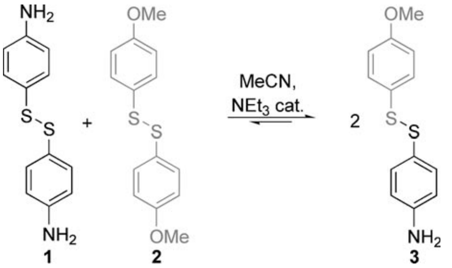
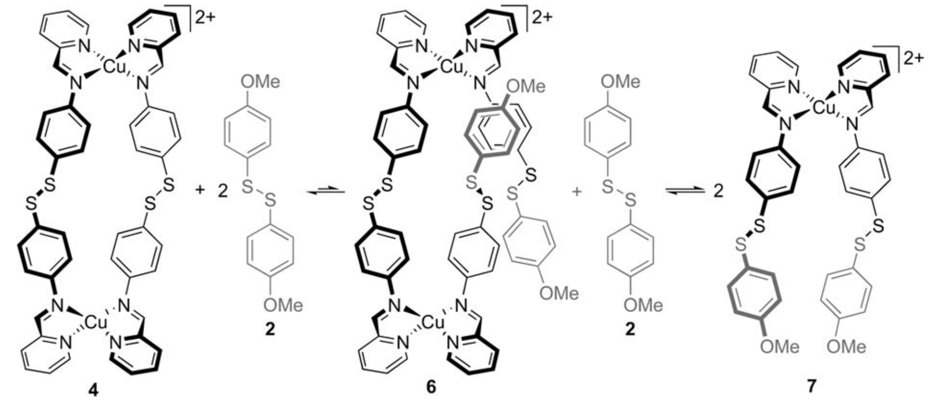
Results and Discussion

The “disulfide layer” of the system under study consists of the base-catalyzed equilibration of the two homo-disulfides **1** and **2** with hetero-disulfide **3** (Scheme 1). In all cases discussed herein where **1** and **2** are present simultaneously, they were added in equimolar amounts. Since the only equilibrium involving disulfides here is $\mathbf{1}+\mathbf{2}\rightleftarrows\mathbf{3}$, the concentrations of **1** and **2** should thus always be equivalent.



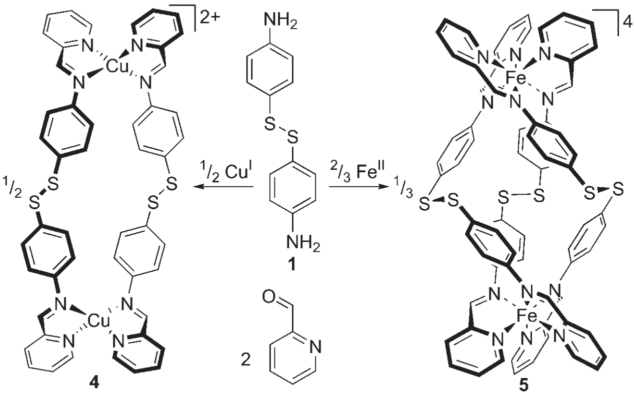
Scheme 1. Equilibration of disulfides **1** and **2** in acetonitrile favoring the formation of **3**.

Statistically, a mixture starting with equimolar amounts of **1** and **2** should contain a 1:2 mixture of **2** and **3** at equilibrium.[15] As measured by ^{1}H integration, the deviation of the observed ratio of 1:2.3 (0.43) from the statistical ratio is small, indicating only a small preference for hetero-disulfide formation.



Scheme 3. Dynamic combinatorial library formed via equilibration between **4** and **2**.

The “imine layer” and the “metal-coordination layer” of this system may be built up by taking advantage of the amino groups of **1** to build it as a subcomponent[7] into metal-containing assemblies **4** and **5** (Scheme 2). These structures did not undergo any decomposition in acetonitrile over two weeks at room temperature, underlining the mutual compatibility of the metal-based and disulfide chemistries.

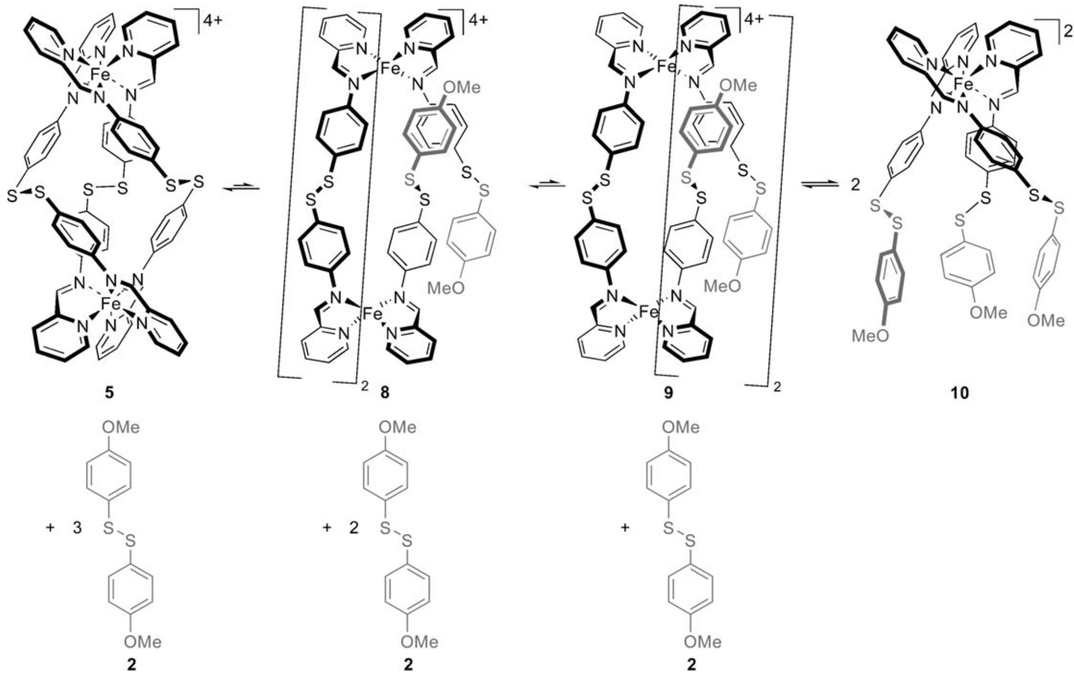


Scheme 2. Preparation of assemblies **4** and **5**.

The reaction of **1** (1 equiv), **2** (1 equiv), 2-formylpyridine (2 equiv) and copper(I) tetrafluoroborate (1 equiv) in acetonitrile produced the dynamic combinatorial library (DCL)[1] shown in Scheme 3. In this system the preference for hetero-disulfide formation observed in Scheme 1 was reversed: As measured by ^{1}H NMR integration, the ratio between free **2** and residues of **3** (incorporated into **6** and **7**) was 1.4. The disulfide equilibrium was thus shifted by a factor of 3.3.

Of the three product mixtures shown in Scheme 3, the one on the left was thus strongly preferred, even though the same number of covalent and coordinative bonds are present in each of the different mixtures. We suspect that this selectivity is primarily entropic in nature: the number of particles in the system is maximized when the subcomponents combine to form one equivalent of **4** and two equivalents of **2**. Each of the other states shown in Scheme 3 involves the formation of only two particles; these two states should thus be of similar translational entropy. Thus, the system may be said to produce complex structure **4** by expelling a bystander compound **2** that is not able to participate in metal–ligand interactions. This process resembles the way biology converts simple nutrients into complex structures, which is in part driven by dissipating energy through liberating small bystander molecules such as carbon dioxide.

Within the corresponding DCL incorporating hexacoordinate Fe^{II} in place of tetracoordinate Cu^{I} (Scheme 4), the homo-disulfide library members were favored even more strongly. In this case the ratio between free **2** and residues of **3** (incorporated into **8**, **9**, and **10**) was 77, shifted by a factor of 179 relative to the metal-free system of Scheme 1. This selectivity also appeared to be entropic in nature: once again the system preferred to form the largest number of independent species by forming **5**, accompanied by three molecules of **2**. The tight packing of three ligands around the

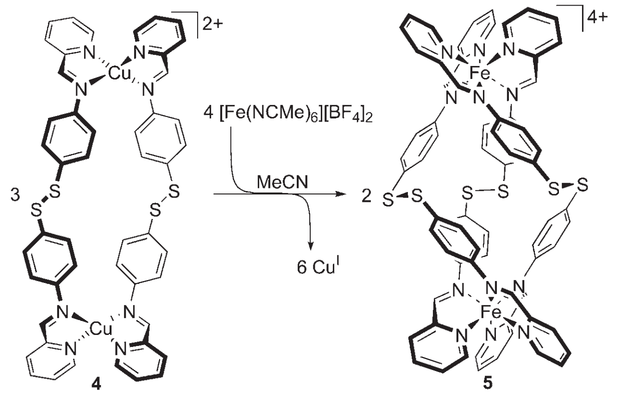


Scheme 4. Dynamic combinatorial library formed via equilibration between **5** and **2**.

two metal centers of **5** could also favor its formation: models suggest that the inclusion of residues of **3** (as in structure **8**) could result in a steric clash between -S-C_6H_4-OMe groups, enthalpically disfavoring such structures.

The reversible nature of the imine and coordinative bonds of **4** and **5** allowed the equilibria of these systems to be readily manipulated. We were able to address both coordinative (N→metal) and covalent (C=N) linkages independently, as described below.

First, transmetallation was used to alter the equilibrium between homo- and hetero-disulfides. The addition of iron(II) tetrafluoroborate to copper-containing **4** resulted in the quantitative transformation of **4** into **5** (Scheme 5) within 1 h at RT, as has been observed in other systems.[16,17]



Scheme 5. Reaction of Fe^{II} with **4** to produce **5**. When carried out in the presence of disulfide **2** this transmetallation allowed the observed ratio of **2**:**3** to be reduced from one imposed by Cu^{I} (1.4) to a value associated with Fe^{II} (83).

This reaction appears to be driven by a slight gain in entropy (7 particles of reactants become 8 particles of products) and a more substantially favorable enthalpy change (N→Fe^{II} bonds are stronger than N→Cu^{I} bonds[18]). When this transformation was carried out in the presence of disulfide **2**, the system's ratio of **2** to residues of **3** could thus be altered from a value associated with **4** (measured **2**:**3** = 1.4) to one imposed by **5** (measured **2**:**3** = 83). The ^{1}H NMR spectra for the metal-free library, the perturbation of the library upon addition of Cu^{I} and the subsequent transmetallation reaction with Fe^{II} in the presence of the triethylamine catalyst are shown in Figure 1.

Second, covalent imine exchange could also be used to perturb the equilibrium between disulfides. The addition of chelating amine **11** to complex **5** resulted in the quantitative formation of mononuclear complex **12**[18] and the liberation of dianiline **1** (Scheme 6). This reaction seems likely to be favorable both entropically (three particles of reactants become five particles of products) and enthalpically (alkylimines have a greater metal-ion affinity than arylimines).[19]

Following its liberation from **5**, diamine **1** became free to re-establish its equilibrium with **2**, settling upon an equilibrium ratio of **2**:**3** = 0.43, identical to the value observed in Scheme 1.

Conclusion

We have thus demonstrated the possibility of strongly biasing a small dynamic library, allowing control over the degree of self-sorting,[10,16,20] through the manipulation of two additional layers of dynamic linkages. Imine and metal

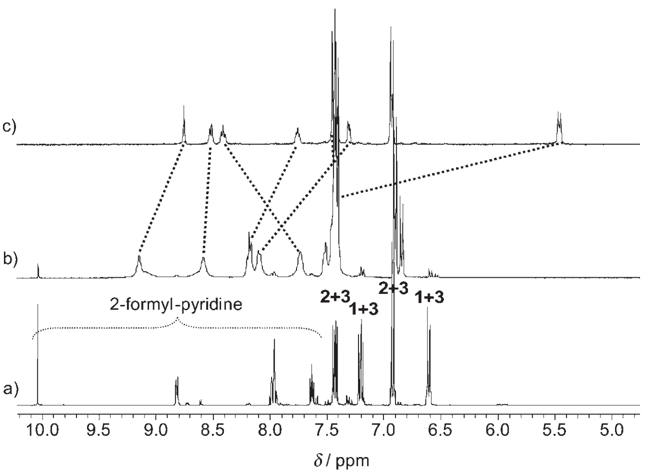
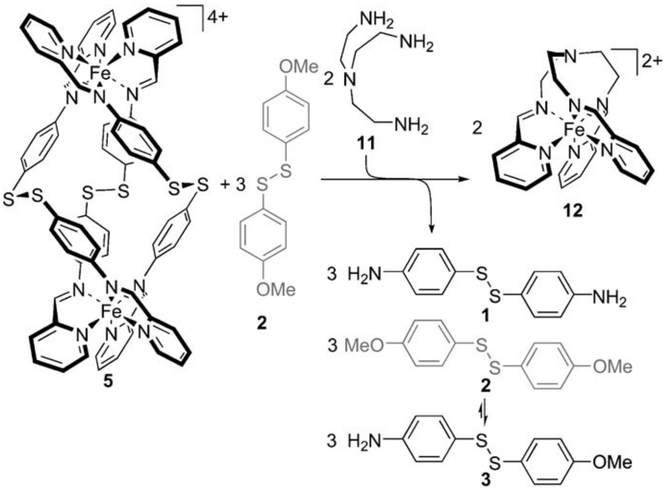


Figure 1. ^{1}H NMR spectra corresponding to a) the mixture of 2-formylpyridine (2 equiv), **1** (1 equiv) and **2** (1 equiv); b) the above mixture to which Cu^{I} (1 equiv) has been added; c) mixture in b to which Fe^{II} (0.67 equiv) has been added; all spectra were taken following thermodynamic equilibration.



Scheme 6. The reaction of tetraamine **11** with the DCL of Scheme 3 (which consists almost entirely of **5** and **2**) to yield **12** and reestablish the disulfide equilibrium of Scheme 1.

complex formation shifted the disulfide equilibrium of Scheme 1 by a factor of up to 179. An important driving force favoring the formation of complexes **4** and **5** within DCLs appears thus to have been the entropy increase associated with the liberation of bystander disulfide **2**, much in the way the complexity of life is in part facilitated through the expulsion of small molecule metabolites.

These complex systems of equilibria are reminiscent of biological signaling mechanisms: the presence of copper or iron in the system results in the liberation of **2**, with the amount liberated being linked to the identity and quantity of the metal ion present. Such systems might thus be harnessed as metal-ion sensors.[5,21] Similar dynamic systems may develop into useful tools in systems chemistry[14] and may lead to an improved understanding of the organizational principles of chemical and biological networks, and of self-sorting systems in general.

Experimental Section

General: All manipulations were carried out in degassed solvents by using reagents of the highest commercially available purity. $[Cu(NCMe)_4][BF_4]$ and $[Fe(NCMe)_6][BF_4]_2$ were prepared following literature procedures.[22] NMR spectra were assigned with the help of COSY, HSQC, NOESY, ROESY, and HMBC measurements. All chemical shifts were referenced to the residual proton (^{1}H) or carbon (^{13}C) signal of the solvent. All experiments were carried out at room temperature (RT) = 298(±2) K.

Equilibration of 1 and 2 with 3 (Scheme 1): 4,4′-Diaminophenyl disulfide **1** (0.6 mg, 2.5 μmol), 4,4′-dimethoxyphenyl disulfide **2** (0.7 mg, 2.5 μmol), triethylamine (0.015 mg, 0.15 μmol), and [D$_3$]acetonitrile (0.4 mL) were placed in an NMR tube with a Teflon screw-cap. All materials dissolved giving a homogeneous solution. The tube's atmosphere was replaced with argon. The reaction was followed using ^{1}H NMR, and signals attributed to **3** were observed to grow-in, reaching equilibrium over a period of 120 h. The ratio of **3**:**2** of 2.3 was determined by ^{1}H NMR integration of the peaks corresponding to the methoxy groups of **2** and **3** through Gaussian deconvolution.

Compounds **1** and **2** (before equilibration): ^{1}H NMR (400 MHz, 298 K, CD_3CN): $\delta = 7.43$ (d, $J = 8.8$ Hz, 4H; phenylene of **2**), 7.19 (d, $J = 8.8$ Hz, 4H; phenylene of **1**), 6.92 (d, $J = 8.8$ Hz, 4H; phenylene of **2**), 6.60 (d, $J = 8.8$ Hz, 4H; phenylene of **1**), 4.44 (br s, 4H; amino group of **1**), 3.80 ppm (s, 6H; methoxy of **2**); ^{13}C NMR (100 MHz, 298 K, CD_3CN): $\delta = 162.2$, 150.3, 135.2, 133.4, 128.7, 124.3, 115.8, 115.7, 56.2 ppm.

Compounds **1**, **2** and **3** (after equilibration): ^{1}H NMR (400 MHz, 298 K, CD_3CN): $\delta = 7.43$ (m, phenylene of **2** and **3**), 7.17 (m, phenylene of **1** and **3**), 6.90 (d, $J = 8.4$ Hz; phenylene of **2** and **3**), 6.58 (d, $J = 8.4$ Hz; phenylene of **1** and **3**), 4.42 (br s, 4H; amino group of **1**), 3.78 (s, methoxy group of **3**), 3.77 (s, methoxy group of **2**), 2.49 (q, $J = 7.2$ Hz; methylene of triethylamine), 0.99 ppm (t, $J = 7.2$ Hz; methyl of triethylamine); ^{13}C NMR (100 MHz, 298 K, CD_3CN): $\delta = 161.3$, 161.2, 150.5, 150.3, 135.2, 135.0, 133.7, 133.4, 129.2, 128.7, 124.3, 123.7, 115.9, 115.8, 115.7, 56.2, 56.1, 47.1, 12.3 ppm.

Synthesis of Cu^{I} dimer 4: $[Cu(NCMe)_4][BF_4]$ (3.1 mg, 0.01 mmol) was added to a mixture of **1** (2.5 mg, 0.01 mmol), pyridine-2-carboxaldehyde (2.1 mg, 0.02 mmol), and CD_3CN (0.4 mL) in a Teflon-capped NMR tube. The red solution thus obtained was degassed and purged three times with argon. The reaction was complete within 24 h at RT as monitored by ^{1}H NMR spectroscopy. ^{1}H NMR (400 MHz, 298 K, CD_3CN): $\delta = 9.18$ (s, 4H; N=C*H*), 8.60 (s, 4H; pyridyl), 8.19 (t, $J = 7.6$ Hz, 4H; pyridyl), 8.10 (s, 4H; pyridyl), 7.74 (s, 4H; pyridyl), 7.48 ppm (m, 16H; phenylene); ^{13}C NMR (100 MHz, 298 K, CD_3CN): $\delta = 159.4$, 152.2, 150.6, 146.6, 139.7, 137.9, 130.1, 129.5, 128.6, 124.6 ppm; ESI-MS: m/z: 489.4 $[L_2Cu_2]^{2+}$, 1065.6 $[L_2Cu_2(BF_4)]^+$.

Synthesis of Fe^{II} triple helicate 5: $[Fe(NCMe)_6][BF_4]_2$ (0.8 mg, 1.7 μmol) was added to a mixture of **1** (0.6 mg, 2.5 μmol), pyridine-2-carboxaldehyde (0.5 mg, 5 μmol), and CD_3CN (0.4 mL) in a Teflon-capped NMR tube. The dark purple solution thus obtained was degassed and purged three times with argon. The reaction was complete within 60 min at RT as indicated by ^{1}H NMR spectroscopy. ^{1}H NMR (400 MHz, 298 K, CD_3CN): $\delta = 8.75$ (s, 4H; N=C*H*), 8.51 (d, $J = 7.2$ Hz, 4H; pyridyl), 8.40 (t, $J = 7.2$ Hz, 4H; pyridyl), 7.75 (t, $J = 6.4$ Hz, 4H; pyridyl), 7.41 (d, $J = 8.0$ Hz, 8H; phenylene), 7.30 (d, $J = 5.6$ Hz, 4H; pyridyl), 5.45 ppm (d, $J = 8.0$ Hz, 8H; phenylene); ^{13}C NMR (100 MHz, 298 K, CD_3CN): $\delta = 158.7$, 156.4, 150.1, 140.8, 137.0, 136.9, 132.8, 132.3, 127.4, 122.3 ppm; ESI-MS: m/z: 493.1 $[L_3Fe_2(BF_4)]^{3+}$, 1650.1 $[L_3Fe_2(BF_4)_3]^+$.

Perturbation of the equilibrium $1+2 \rightleftarrows 3$ through the formation of 4: Compound **1** (0.6 mg, 2.5 μmol), compound **2** (0.7 mg, 2.5 μmol), triethylamine (0.015 mg, 0.15 μmol), and [D$_3$]acetonitrile (0.4 mL) were placed in an NMR tube with a Teflon screw-cap. All materials dissolved giving a homogeneous solution. The tube's atmosphere was degassed and purged three times with argon. Pyridine-2-carboxaldehyde (0.5 mg, 5 μmol) and $[Cu(NCMe)_4][BF_4]$ (0.8 mg, 2.5 μmol) were added to this solution, which first turned yellow and then orange-yellow. The reaction was followed by NMR spectroscopy, and signals corresponding to methoxy group of **2** were monitored; equilibrium was reached over the course of 240 h. The ratio of **2**:**3** (1.4) was calculated in the same manner as described above.

Equilibration between 5 and 2 (Scheme 4): Compound **1** (0.6 mg, 2.5 μmol), compound **2** (0.7 mg, 2.5 μmol), triethylamine (0.015 mg, 0.15 μmol), and $[D_3]$acetonitrile (0.4 mL) were placed in an NMR tube with a Teflon screw-cap. All materials dissolved giving a homogeneous solution. The tube's atmosphere was degassed and purged three times with argon. Pyridine-2-carboxaldehyde (0.5 mg, 5 μmol) and $[Fe(NCMe)_6][BF_4]_2$ (0.8 mg, 1.7 μmol) were added, leading to a purple solution. The reaction was followed by monitoring the signals attributed to the methoxy group of **2** in the ^{1}H NMR, and equilibrium was reached over the course of 24 h. The ratio of **2**:**3** (77) was calculated as described above.

Transformation of 4 into 5 through transmetallation (Scheme 5): Copper complex **4** (0.6 μmol) was prepared in $[D_3]$acetonitrile (0.4 mL) as described above. The ^{1}H NMR spectrum corresponded to the previously prepared material. $[Fe(NCMe)_6][BF_4]_2$ (0.8 mg, 1.7 μmol) was added to the solution, resulting in the development of a dark purple color. The tube's atmosphere was degassed and purged three times with argon. The ^{1}H NMR spectrum of the product, taken within 60 min of mixing, corresponded to that of **5**.

Transmetallation of Cu^{I} by Fe^{II} within a dynamic combinatorial library: Compound **1** (0.6 mg, 2.5 μmol), compound **2** (0.7 mg, 2.5 μmol), triethylamine (0.015 mg, 0.15 μmol), and $[D_3]$acetonitrile (0.4 mL) were placed in an NMR tube with a Teflon screw-cap. All materials dissolved giving a homogeneous solution. The tube's atmosphere was degassed and purged three times with argon. Pyridine-2-carboxaldehyde (0.5 mg, 5 μmol) and $[Cu(NCMe)_4][BF_4]$ (0.8 mg, 2.5 μmol) were added, leading to the formation of an orange solution. The reaction was followed by NMR spectroscopy, and equilibrium involving **4** (Scheme 2) was reached over the course of 120 h. The ratio of **2**:**3** (1.4) was calculated in the same manner as described above. Subsequently, $[Fe(NCMe)_6][BF_4]_2$ (0.8 mg, 1.7 μmol) was added to the above mixture, which gave a homogeneous dark purple solution. The transformation was monitored by NMR spectroscopy, which indicated complete transformation of **4** into **5** within 1 h. After equilibration for 24 h, the new ratio of **2**:**3** (83) was obtained.

Reaction of 11 with 5 in the presence of 2 (Scheme 6): Compound **1** (0.6 mg, 2.5 μmol), compound **2** (0.7 mg, 2.5 μmol), triethylamine (0.015 mg, 0.15 μmol), and $[D_3]$acetonitrile (0.4 mL) were placed in an NMR tube with a Teflon screw-cap. All materials dissolved giving a homogeneous solution. The tube's atmosphere was degassed and purged three times with argon. Pyridine-2-carboxaldehyde (0.5 mg, 5 μmol) and $[Fe(NCMe)_6][BF_4]_2$ (0.8 mg, 1.7 μmol) was added, which gave a purple solution. The reaction was followed by NMR spectroscopy, and a spectrum corresponding to that of **5** was observed within 1 h. The ratio of **2**:**3** (83) was determined as described above. Subsequent addition of **11** to the solution of **5** resulted in the formation of **12** with simultaneous release of **1** into the solution over the course of 24 h, as monitored by NMR. Equilibration proved notably slower in this case; following equilibration during 21 d, the ratio of **2**:**3** was observed to shift to 0.43.

Acknowledgements

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