

Designing Multistep Transformations Using the Hammett Equation: Imine Exchange on a Copper(I) Template

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Abstract: Herein, we quantify how imine exchange may be used to selectively transform one metallo-organic structure into another. A series of imine exchange reactions were studied, involving a set of 4-substituted anilines, their 2-pyridylimines and 1,10-phenanthrolyl-2,9-diimines, as well as the copper complexes of these imine ligands. Electron-rich anilines were found to displace electron-poor anilines in all cases. Linear free energy relationships (LFERs) were discovered connecting the electron-donating or -withdrawing character of the 4-substituent of an aniline, as measured by the Hammett σ_{para} parameter, to that aniline's ability to compete with unsubstituted aniline to form imines. The quality of these LFERs allowed for quantitative predictions: to obtain the desired degree of selectivity in an imine exchange between anilines A and B, the required σ_{para} differential could be predicted using a variant of the Hammett equation, $\log(K_{\text{AB}}) = \rho(\sigma_{\text{A}} - \sigma_{\text{B}})$. We validated this methodology by designing and executing a three-step transformation of a series of copper(I)-containing structures. Each step proceeded in predictably high yield, as calculated from σ differentials. At each step in the series of transformations, macrocyclic structures could be created or destroyed through the selection of mono- or di-amines as subcomponents. The same methodology could be used to predict the formation of a diverse dynamic library of helicates from a set of four aniline precursors, as well as the collapse of this library into one helicate upon the addition of a fifth aniline.

Introduction

Metallo-organic self-assembly^{1–4} represents a fascinating subfield of supramolecular chemistry, not only because of the static architectures that may be constructed using its principles,⁵ but also for the sake of the dynamic rearrangements that some of these architectures may undergo.⁶ Recent examples include the reorganization of two separate coordination cages to form a single catenate,⁷ the pH-driven threading/unthreading of two helices,⁸ the dynamic interconversion of different structures based upon solvent and template effects,^{9,10} the templated formation of specific porphyrin assemblies from dynamic libraries,¹¹ and the rearrangements of libraries of metallomacrocycles in response to ionic signals.¹² Dynamic reassembly

reactions likewise generate the function at the hearts of a growing number of synthetic molecular machines.^{13–17}

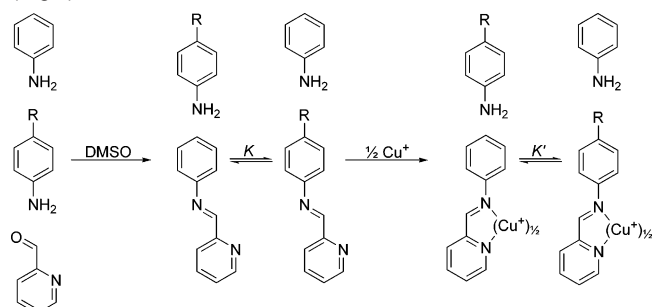
We have recently reported a series of self-assembled metallo-organic structures that are capable of rearranging not only at their labile metal-ligand bonds,¹⁸ but also at the dynamic covalent⁶ imine bonds that hold these structures together.^{18–20} The acidity differential between two amines could be used as a driving force to effect imine exchange with high selectivity: Under acidic conditions, the more basic of two amines is preferentially protonated, leaving the less basic amine free to incorporate into an imine under equilibrium conditions.

In the present work, we examine how electronic effects may provide a thermodynamic driving force for imine exchange within Cu^I-imine complexes. We have investigated substitution reactions involving structures incorporating both monocopper bis-pyridylimine²¹ and dicopper bis(phenanthrolyldiimine)^{20,22,23}

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Scheme 1. Formation of Equilibrium Mixtures of Imines from Unsubstituted and 4-Substituted Anilines with Pyridine-2-carbaldehyde (Left); Reaction of These Imines with Copper(I) To Form New Equilibrium Mixtures of Imine Complexes (Right)^a



^a Competition equilibrium constants before (K) and after (K') the addition of copper(I) were determined for the series of 4-substituted anilines shown in Table S1 (Supporting Information).

subunits. A linear free energy relationship was found between the equilibrium constant of an imine exchange reaction and the electron-donating ability of a given aniline's 4-substituent, as measured by the Hammett σ_{para} parameter.^{24,25} This correlation enabled us to design progressive transformations in which electron-rich anilines displaced electron-poor anilines. Successive transformations were thus possible in the same reaction flask, with each imine-exchange step proceeding in greater than 95% yield. The anilines so introduced may form parts of larger building blocks, allowing structural complexity to be created or transformed during the substitution reaction. Structural diversity could also be predictably created and destroyed: When mixtures of electron-poor anilines were employed together as building blocks, a diverse collection of complexes was formed. The addition of a single electron-rich aniline resulted in quantitative displacement of all electron-poor anilines, giving a single imine complex.

Results and Discussion

The mixture of equimolar amounts of pyridine-2-carbaldehyde, aniline, and a 4-substituted aniline resulted in conversion of the pyridine-2-carbaldehyde into a mixture of two imines, as shown in Scheme 1 (left). The presence of 1 equiv of each aniline pushed the conversion to completion; no residual aldehyde was observed under these reaction conditions. The mixture of two imines and two anilines reached equilibrium in all cases within 48 h at room temperature. Equilibrium constants could be determined by integrating the ¹H NMR resonances corresponding to the free 4-substituted and unsubstituted anilines.

The addition of copper(I) tetrafluoroborate resulted in the quantitative formation of a mixture of imine complexes (Scheme 1, right). A new equilibrium, measured by an equilibrium constant K' , was reached in all cases within 48 h at room temperature. In cases in which both anilines were incorporated, ESI-MS showed that the expected statistical mixture of homoleptic and heteroleptic complexes was present. We were not able to distinguish between homo- and hetero-complexes by

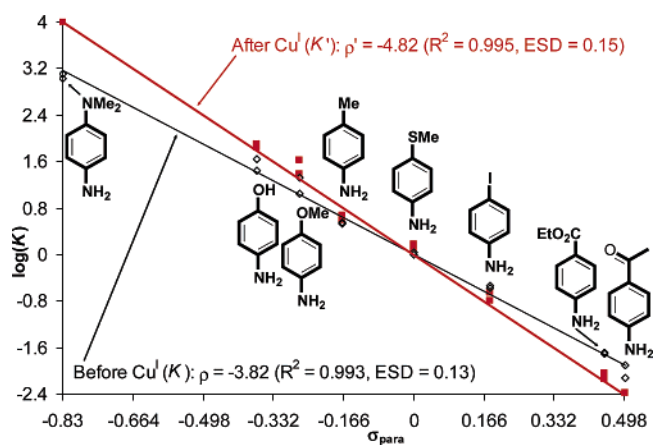


Figure 1. Hammett plots for the thermodynamic competition of anilines to form imines (as shown in Scheme 1) in the presence and absence of copper(I), including the linear regressions used to obtain ρ and ρ' ; data from both independent runs are plotted and analyzed together.

NMR spectroscopy, but it was not necessary to do so to determine the relative amounts of the two anilines incorporated. The equilibrium constants K' , obtained through integration of the ¹H resonances corresponding to the free 4-substituted and unsubstituted anilines, thus refer to a conceptually simplified system in which each equivalent of heteroleptic complex is counted as one-half of an equivalent of each of the homoleptic complexes shown in Scheme 1. Details as to the determination of equilibrium constants are provided in the Supporting Information. The anilines investigated, together with their substituents' σ_{para} values²⁶ and the logarithms of the equilibrium constants K and K' obtained in the absence and presence of copper(I), are presented in Table S1 in the Supporting Information. Each data point was collected twice, in two independent experimental runs.

When anilines bearing 4-substituents more electron withdrawing than acetyl, such as nitro ($\sigma_{\text{para}} = 0.78$), were employed, we were not able to observe the corresponding imine to form in competition with unsubstituted aniline. In the absence of competition, these anilines were also not observed to form imines in the absence of copper(I); imines were formed only to a limited extent in the metal's presence.

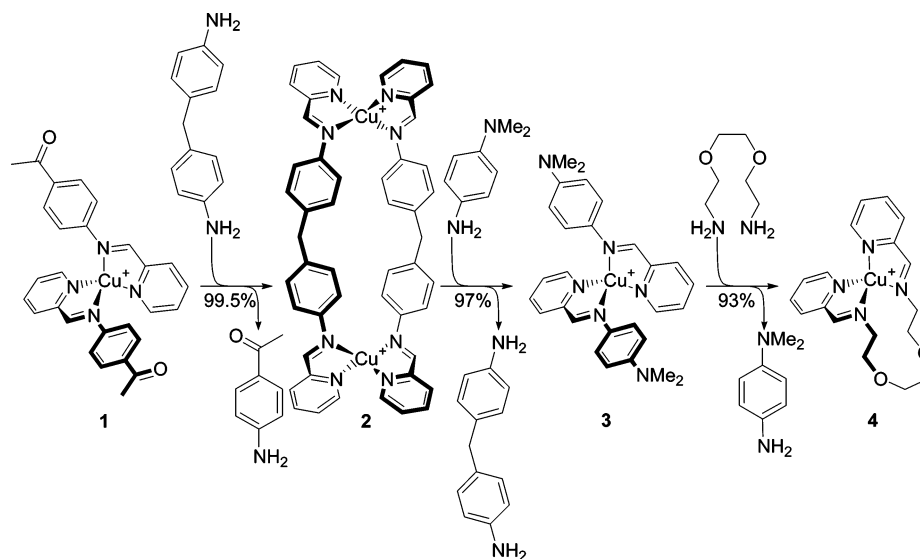
When the logarithms of the equilibrium constants K and K' were plotted against the Hammett σ_{para} values²⁶ of the anilines' 4-substituents, a pair of linear free energy relationships (LFERs) was revealed (Figure 1). These data thus followed the Hammett equation, $\log(K/K_0) = \sigma\rho$,^{24,25} with $K_0 = 1$, trivially.

Both ρ and ρ' , corresponding to the equilibria before and after the addition of copper(I), are negative and large, which indicates that the incorporation of an electron-rich aniline residue strongly stabilized both imine ligands and copper(I) complexes. This observation is consistent with the findings of Gagné et al. in the context of Pt(salicylaldimine) complexes.²⁷ The observation that ρ' was of greater magnitude than ρ indicated that the cationic metal complex was more stabilized by the presence of electron-donating groups than was the neutral ligand, which makes intuitive sense. The ratio of the two ρ values, $\rho'/\rho = 1.26$, may be seen as an amplification factor^{28,29} relating the logarithms of the two equilibrium constants and indicating to what degree

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Scheme 2. A One-Pot Series of Transformations, Using Substituent Effects and the Chelate Effect To Provide Driving Forces for Imine Exchange



the proportion of the majority imine will be enhanced through the addition of copper(I).

The R^2 and estimated standard deviation (ESD) values calculated during the linear least-squares fit suggested that these data may be of sufficient quality and reproducibility to allow conclusions to be drawn relevant to the use of these electronic effects to control subcomponent substitution; a statistical analysis³⁰ is presented in the Supporting Information. For an arbitrary pair of 4-substituted anilines A and B, the equilibrium constant for a competition experiment of the type shown in Scheme 1 may be defined as $K_{AB} = K_A/K_B$, or $\log(K_{AB}) = \log(K_A) - \log(K_B)$, where K_A and K_B are the equilibrium constants for the competitions between unsubstituted aniline and substituted anilines A and B, respectively. Combining this equation with the Hammett equation, we obtained eq 1:

$$\log(K_{AB}) = \rho(\sigma_A - \sigma_B) \quad (1)$$

Equation 1 allows one to predict the equilibrium constant for the competition reaction between an arbitrary pair of anilines, either in the presence (using $\rho' = -4.82$) or in the absence ($\rho = -3.82$) of copper(I). This equation also permits one to determine the σ differential required to obtain a given selectivity in substitution. The greater magnitude of ρ' indicates that higher selectivity may more readily be obtained in the presence of copper(I); for example, for a substitution reaction between anilines A and B to proceed in greater than 95% yield, it is necessary to have a difference between σ_A and σ_B of at least 0.53 in the presence of copper, versus 0.67 in the metal's absence.

Because the anilines shown in Figure 1 span a range of 1.33 σ units, one may consider the programming of two subsequent transformations between three distinct structures, in which both imine exchange reactions proceed in greater than 95% yield. The substituted anilines could be incorporated into larger molecules, allowing the introduction of structural complexity

through subcomponent substitution. Scheme 2 demonstrates the realization of this idea: Three distinct subsequent transformations were carried out in the same reaction vessel. The anilines' σ differentials were used as driving forces for the first two of these substitutions. The entropy gain associated with the formation of a more chelating ligand³¹ served to push the last reaction forward.

The series of reactions shown in Scheme 2 demonstrated the use of successive subcomponent substitutions to generate, destroy, and regenerate structural complexity. Dimeric macrocycle (mesocate³²) **2**, previously reported by the group of Hannon³³ and characterized structurally by Kruger et al.,³⁴ has a topology fundamentally different from that of mononuclear complex **1**. The mononuclear topology may be readily regenerated upon treatment of **2** with dimethylaminoaniline to generate **3**, which may then be converted into monomeric macrocycle **4**,¹⁸ which has its own distinct topology. Although the structural complexity of macrocycles **2** and **4** is not great, the creation of complexity is a necessary precondition for the generation of function, a worthwhile ultimate goal.

Using eq 1, one would predict imine exchange yields of 97.5% for both the **1**→**2** and the **2**→**3** transformations, using the σ_{para} value for 4-aminotoluene and ignoring the entropic effects of macrocycle formation or destruction. Because heteroleptic complexes are also present, the true yields of **2**, **3**, and **4** are less than the imine exchange yields presented above.

In addition to the mononuclear complexes described above, we have also studied imine exchange equilibria in the context of phenanthroline diimines and dicopper helicates^{20,22,23} constructed from these ligands, as shown in Scheme 3.

As in the case of the mono-imine systems of Scheme 1, no free aldehyde was noted in any of the equilibrium reaction mixtures. The equilibrium constants K_{phen} and K'_{phen} were again determined examining only the relative equilibrium concentrations of free unsubstituted and substituted anilines, resulting in

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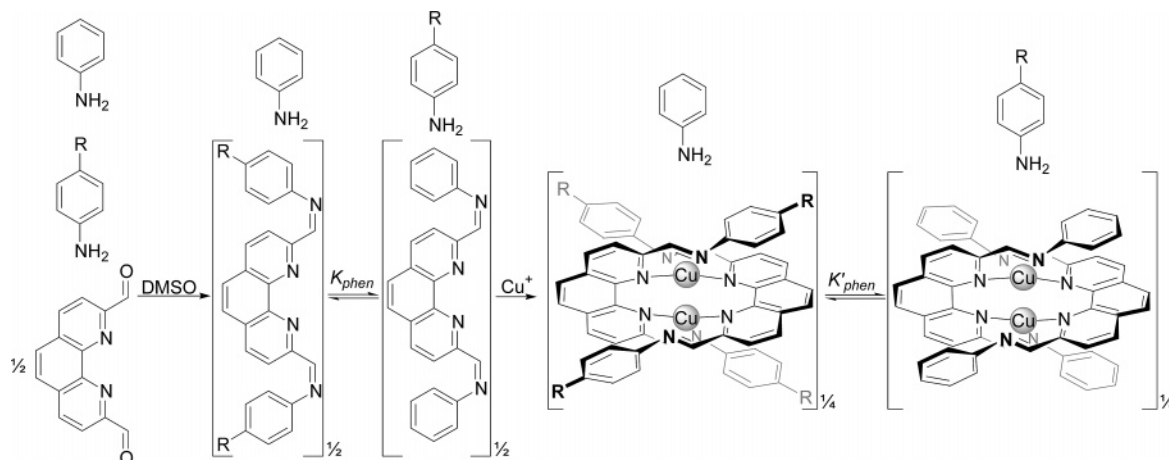
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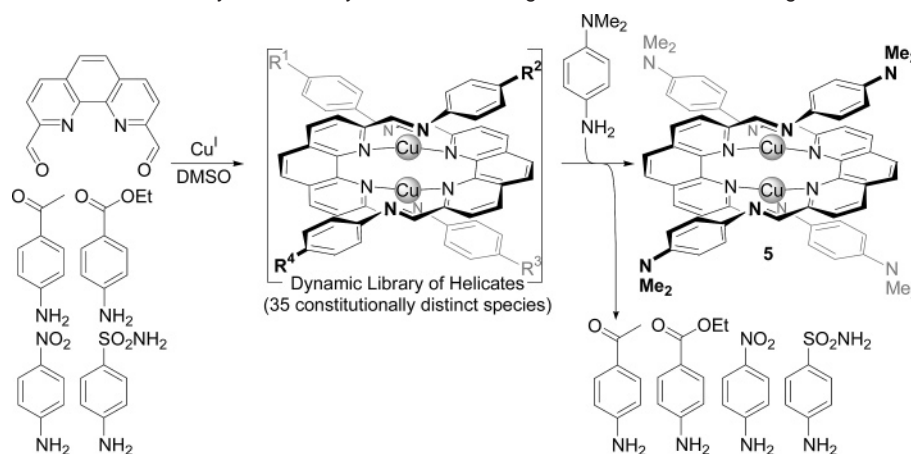
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Scheme 3. Formation of Equilibrium Mixtures of Imines from Unsubstituted and 4-Substituted Anilines (from Table S1, Supporting Information) with 1,10-Phenanthroline-2,9-dicarbaldehyde (Left); Reaction of These Imines with Copper(I) To Form New Equilibrium Mixtures of Dicopper Double-Helicates (Right)



Scheme 4. Creation and Destruction of a Dynamic Library of Helicates Using σ Differentials as a Driving Force



a conceptually simplified system in which structures containing both anilines are counted as partial contributors to the concentrations of the two homo-imine complexes. The Hammett plots corresponding to this system, before and after the addition of copper(I), are shown in Figure 2.

These ρ values are similar in magnitude to those observed in the mononuclear case; we have chosen to formulate the

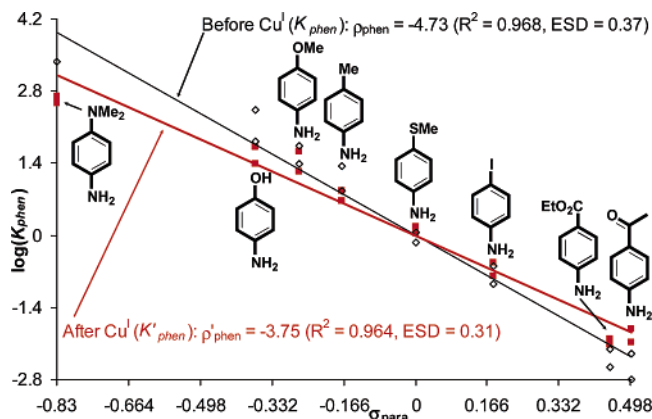


Figure 2. Hammett plot for the thermodynamic competition of 4-substituted anilines with unsubstituted aniline to form diimines in the presence and absence of copper(I) (as shown in Scheme 3), including the linear regressions used to obtain ρ_{phen} and ρ'_{phen} ; data from both independent runs are plotted and analyzed together.

equilibrium expressions to allow direct comparison of these values (details are provided in the Supporting Information). As can be seen in Figure 2, the linear least-squares fits are of lower quality and the data are less reproducible than was observed in the mononuclear case; a statistical analysis³⁰ is presented in the Supporting Information. In contrast with the mononuclear case of Scheme 1, the addition of copper(I) slightly diminishes the magnitude of the substituent effects for the helicates of Scheme 3: $\rho_{\text{phen}} < \rho'_{\text{phen}}$, whereas $\rho > \rho'$. Although the magnitudes of the standard deviations in the ρ_{phen} and ρ'_{phen} values permit less confidence than in the cases of ρ and ρ' , an orbital explanation might cautiously be invoked to account for this difference. The pseudotetrahedral coordination geometry of copper(I) is more flattened (distorted toward square planar) in the case of the helicates.^{20,22,23} This distortion raises the energy of the d_{z^2} orbital and allows for more efficient mixing between filled metal d orbitals and empty ligand π^* orbitals,³⁵ both of these effects acting to increase the degree of $d-\pi^*$ back-bonding. The increased energetic importance of this back-bonding, which is enhanced in the cases of electron-poor ligands, might counteract part of the stabilization afforded by the incorporation of more electron-rich aniline residues, leading to the observed reduction of the magnitude of ρ_{phen} upon copper(I) coordination.

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The mixture of a set of four different electron-poor 4-substituted anilines with 1,10-phenanthroline-2,9-dicarbaldehyde and copper(I) formed a dynamic combinatorial library^{9,29,36–38} of helicates, as shown in Scheme 4. We were not able to assign all 35 of the constitutionally distinct species expected to be present within the complicated mass spectrum of this library; the multitude of peaks observed nonetheless covers the expected range for dications from 530 to 610 *m/z*. The use of numerical methods, as developed in the groups of Otto³⁹ and Severin,²⁸ could allow predictions to be made as to the composition of these libraries, based upon the anilines' concentrations and the σ values of their 4-substituents. The quality of these predictions would be limited by the quality of the linear Hammett correlation shown in Figure 2 (ESD = 0.31) and the narrow range of σ values ($0.45 \leq \sigma \leq 0.78$) represented by this set of substituents; fine predictions would be difficult to make with confidence.

It is, however, possible to predict clearly that a diverse mixture of compounds should be observed on the basis of the narrow range of σ values employed: no single one of the four initially present anilines is able to quantitatively displace the others. A more electron-rich aniline, however, would be expected to readily eject all of the others, reducing the diverse mixture to a single complex. As shown in Scheme 4, the reaction of the dynamic library of electron-poor helicates with 4-dimethylaminoaniline (4 equiv) resulted in the collapse of this library, with the generation of helicate **5** as the unique product observed. The large σ differential ($\Delta\sigma \geq 1.28$) between dimethylaminoaniline and the four electron-poor anilines of Scheme 4 allows one to predict an essentially quantitative formation of helicate **5** (>99.5%) using eq 1, in agreement with observation.

Conclusions

Substituent electronic effects may thus readily be employed to drive ligand subcomponent substitution. The quantification of these effects using the Hammett equation²⁴ allowed us to predict product identities and yields with good accuracy. Several transformations may follow each other in the same reaction flask, allowing the creation, destruction, and recreation of macrocyclic geometries. The driving force provided by substituent effects may also be used to control and shape the constitution of a dynamic combinatorial library, allowing the generation and destruction of molecular diversity within mixtures.

To generate potentially useful function from such rearrangement reactions, it will be necessary to make them reversible^{8,40} or cyclic^{15,41} in nature. We are currently investigating the use of pH changes to this end; our previous investigations^{18,20,21} have revealed that pK_a differences may be exploited to effect the substitution of an arylamine for an alkylamine at low pH, despite the higher nucleophilicity of alkylamines under neutral conditions. Competition with protons might thus allow us to reverse the selectivity described herein, allowing us to generate repetitive motion, which lies at the heart of biological motors.⁴²

The use of Hammett correlations will also allow us to undertake mechanistic studies, by investigating reaction rates instead of equilibrium constants. Starting from imine exchange reactions involving unbound imines, comparison of substituent effects with imine exchanges involving metal complexes should allow for the presence of the metal to be quantified, giving insight as to whether exchange occurs while the ligand is coordinated. Such studies are currently underway.

Experimental Section

Measurement of Equilibrium Constants for Pyridyl–Imine Exchange (Scheme 1). A stock solution was prepared by mixing pyridine-2-carbaldehyde (0.0386 g, 0.36 mmol), aniline (0.033 mL, 0.36 mmol), and *d*⁶-DMSO (6.0 mL) together in a 10-mL Schlenk flask. The flask was sealed, and the atmosphere was purified of dioxygen by three evacuation/argon purge cycles. For each 4-substituted aniline shown in Figure 1, the following procedure was followed. The 4-substituted aniline (0.030 mmol) was loaded into a Teflon screw-capped NMR tube containing the stock solution (0.5 mL). The tube's atmosphere was purged of dioxygen with three evacuation/argon purge cycles. The equilibration was followed during 48 h at room temperature, after which time the evolution was found to have ceased in all cases. The equilibrium constant was then determined from the ratio of the integrated ¹H NMR signals of the free 4-substituted and unsubstituted anilines (see the Supporting Information). Tetrakis(acetonitrile)copper(I) tetrafluoroborate (0.0047 g, 0.015 mmol) was then added, giving a dark red solution. The tube's atmosphere was purged of dioxygen with three evacuation/argon purge cycles. Following 48 h of equilibration at room temperature, evolution was again found to have ceased. Integration of the ¹H NMR signals corresponding to substituted and unsubstituted anilines was again used to determine the equilibrium constant. Characterization data for all complexes are provided in the Supporting Information.

Measurement of Equilibrium Constants for Phenanthrolyl–Diimine Exchange (Figure 2). A stock solution was prepared by mixing 1,10-phenanthroline-2,9-dicarbaldehyde (0.0431 g, 0.18 mmol), aniline (0.033 mL, 0.36 mmol), and *d*⁶-DMSO (6.0 mL) together in a 10-mL Schlenk flask. The flask was sealed, and the atmosphere was purified of dioxygen by three evacuation/argon purge cycles. For each 4-substituted aniline shown in Figure 1, the following procedure was followed. The 4-substituted aniline (0.030 mmol) was loaded into a Teflon screw-capped NMR tube containing 0.5 mL of the stock solution. The tube's atmosphere was purged of dioxygen with three evacuation/argon purge cycles. The equilibration was followed during 48 h at room temperature, after which time the evolution was found to have ceased in all cases. The equilibrium constant was then determined from the ratio of the integrated ¹H NMR signals of the free 4-substituted and unsubstituted anilines (see the Supporting Information). Tetrakis(acetonitrile)copper(I) tetrafluoroborate (0.0047 g, 0.015 mmol) was then added, giving a dark solution. The tube's atmosphere was purged of dioxygen with three evacuation/argon purge cycles. Following 48 h of equilibration, evolution was again found to have ceased. Integration of the ¹H NMR signals corresponding to substituted and unsubstituted anilines was again used to determine the equilibrium constant.

Successive Subcomponent Substitution (Scheme 2). Stock solutions of each component noted below (0.07–0.13 mmol) in *d*⁶-DMSO (approximately 0.4 mL) were prepared in NMR tubes, and the concentration of each component relative to the known concentration of *t*-BuOH (0.025 M), used as an internal standard, was measured by NMR integration. The volume noted for each successive addition was then measured using a syringe. The tube's atmosphere was purged of dioxygen with three evacuation/argon purge cycles after each addition, and then the sample was heated to 50 °C during 24 h; evolution had in all cases ceased after this time. Copies of all spectra are provided in the Supporting Information.

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A solution of 4'-aminoacetophenone in d^6 -DMSO (0.140 mL, 0.222 M) was added to a solution of pyridine-2-carbaldehyde in d^6 -DMSO (0.160 mL, 0.194 M) in an NMR tube with a Teflon screw-cap. Solid tetrakis(acetonitrile)copper(I) tetrafluoroborate (0.0051 g, 0.0162 mmol) was then added, giving a dark red solution, the NMR spectrum of which corresponded to complex **1**. A solution of 4,4'-methylenedianiline in d^6 -DMSO (0.096 mL, 0.162 M) was then added, resulting in a ^1H spectrum corresponding to that of complex **2**; the imine exchange yield was estimated to be 99.5% by ^1H integration. A solution of N,N' -dimethyl-*p*-phenylenediamine in d^6 -DMSO (0.154 mL, 0.202 M) was then added, leading to the displacement of 4,4'-methylenedianiline and the formation of complex **3** in 97% yield, as measured by ^1H integration. A solution of 2,2'-(ethylenedioxy)bis(ethylamine) in d^6 -DMSO (0.117 mL, 0.133 M) was then added, leading to the displacement of N,N' -dimethyl-*p*-phenylenediamine and the formation of complex **4** (93% by ^1H integration). No **1**, **2**, or **3** were noted in the final product mixture by ESI-MS.

Creation and Destruction of a Dynamic Library (Scheme 4). Into an NMR tube with a Teflon screw cap were loaded 1,10-phenanthroline-2,9-dicarbaldehyde (0.0054 g, 0.023 mmol), 4'-aminoacetophenone (0.0062 g, 0.046 mmol), ethyl-4-aminobenzoate (0.0076 g, 0.046 mmol), sulfanilamide (0.0079 g, 0.046 mmol), and 4-nitroaniline (0.0063 g, 0.046 mmol) followed by d^6 -DMSO (0.5 mL). The tube's atmosphere was purged of dioxygen with three evacuation/argon purge cycles. Tetrakis(acetonitrile)copper(I) tetrafluoroborate (0.0074 g, 0.023 mmol) was then added, giving a dark red solution that turned dark green after a few minutes. The sample was again purged of dioxygen with three

evacuation/argon purge cycles and left for 6 h at 50 °C. The ^1H NMR spectrum showed a series of broad peaks in the usual range for dicopper double-helicates (9–7 ppm),²⁰ and the ESI-MS showed a multitude of peaks over the expected range from 530 to 610 m/z , consistent with the presence of a diverse dynamic library of helicates. The subsequent addition of N,N' -dimethyl-*p*-phenylenediamine (0.0077 g, 0.048 mmol) led to the displacement of all of the electron-poor anilines and the formation of complex **5** as the unique copper complex observed by ESI-MS ($m/z = 535.5$) and NMR (^1H NMR (400 MHz, 300 K, d^6 -DMSO): $\delta = 8.91$ (s, 4H, imine), 8.42 (d, $J = 8.4$ Hz, 4H, 4-phenanthrolyl), 8.13 (d, $J = 8.1$ Hz, 4H, 3-phenanthrolyl), 7.68 (s, 4H, 5-phenanthrolyl), 6.01 (d, $J = 8.8$ Hz, 8H, phenylene), 8.80 (d, $J = 8.9$ Hz, 8H, phenylene), 2.77 (s, 24H, methyl)).

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Supporting Information Available: Characterization data for copper(I) complexes of all of the 2-pyridylimine complexes derived from the 4-substituted anilines studied, details as to the determination of equilibrium constants, and a table of the data used for the Hammett plots of Figures 1 and 2. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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