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High-Fidelity Stereochemical Memory in a $Fe^{II}_4L_4$ Tetrahedral Capsule

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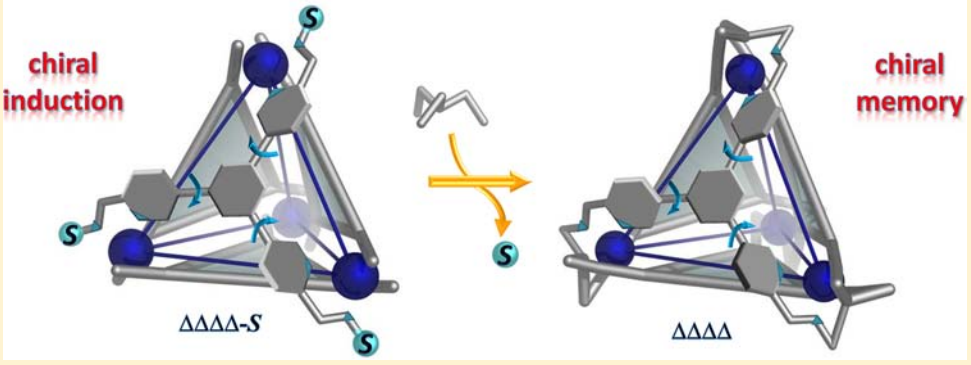
Supporting Information



ABSTRACT: A new class of $Fe^{II}_4L_4$ capsules, based upon a tritopic trialdehyde subcomponent, is reported. One such capsule was prepared diastereoselectively through the incorporation of a chiral amine residue. This amine was displaced by an achiral one, while maintaining the stereochemistry of the cage framework (99% *ee*); this cage retained its stereochemistry even after 4 days at 90 °C. Mechanistic studies indicate the memory displayed by this capsule to be the result of effective stereochemical communication between the metal centers mediated by the rigid 3-fold-symmetric faces, in combination with a stepwise substitution mechanism.

INTRODUCTION

Metal−organic capsules[1] with chirotopic[2] cavities[3−5] have proved useful in stereoselective guest recognition and sensing[4] and as asymmetric reaction vessels.[5] The development of these applications is hindered, however, by the lack of efficient methods for the preparation of large, enantiopure, non-racemizing capsules. To develop such methods, a fundamental understanding must be gained as to the mechanisms whereby stereochemical information is relayed through the frameworks of metal−organic cages.[6]

A general strategy to influence the stereochemistry of self-assembled systems[7] and capsules[3−5,6d,8] is the introduction of additional stereocenters, in the form of either enantiopure building blocks,[3b,d,4b,8b−d] chiral ancillary ligands,[3a,e,5b] chiral guests,[4d,8a] or counterions.[3c,6b] The fixed stereochemistry of these stereocenters thus influences the conformations of new stereocenters formed during self-assembly resulting in diastereomerically enriched structures. The isolation of enantiomerically pure assemblies has been achieved through self-resolution[9] or chiral chromatography[10] of assemblies originally prepared in racemic form,[11,12] as pioneered in the context of Ga_4L_6 clusters by the Raymond group.[13] Systems with stereochemical memory[6a,8a,12−14] are able to process and conserve the information first introduced by a chiral auxiliary after its removal or replacement—the crucial step of this strategy. Thus, these assemblies are still optically active even though the original source of chiral information has been removed.

Recently, the technique of subcomponent self-assembly,[15] involving the formation of dynamic coordinative (N → M) and covalent (N═C)[16] bonds during a single overall process under thermodynamic control, has provided a platform to study the transmission of stereochemical information within $Fe^{II}_4L_6$ complexes of different sizes and different degrees of stereochemical coupling[17] between metal centers.[6c−e] Here we explore the stereochemical memory of a tetrahedral $Fe^{II}_4L_4$ capsule through the substitution of an enantiopure subcomponent with an achiral one. For this study we have developed a new class of face-capped[18] tetrahedral complexes based on C_3-symmetric tris(bidentate) ligands, formed in situ by metal-templated imine condensation[16] of tris(formylpyridyl) benzene **A** and amines (Scheme 1). This system allows for the straightforward imprinting of a given stereochemistry upon the structure through the incorporation of chiral amine subcomponents, as their steric influence determines the configuration of adjacent metal centers.[6d] Strong cooperative stereochemical coupling between the iron(II) stereocenters of the structure enabled retention of configuration upon replacement of the chiral subcomponents. This memory effect allows for the stereoselective preparation of a metal−organic capsule that contains ultimately only achiral subcomponents. Elucidation of the subcomponent substitution mechanism

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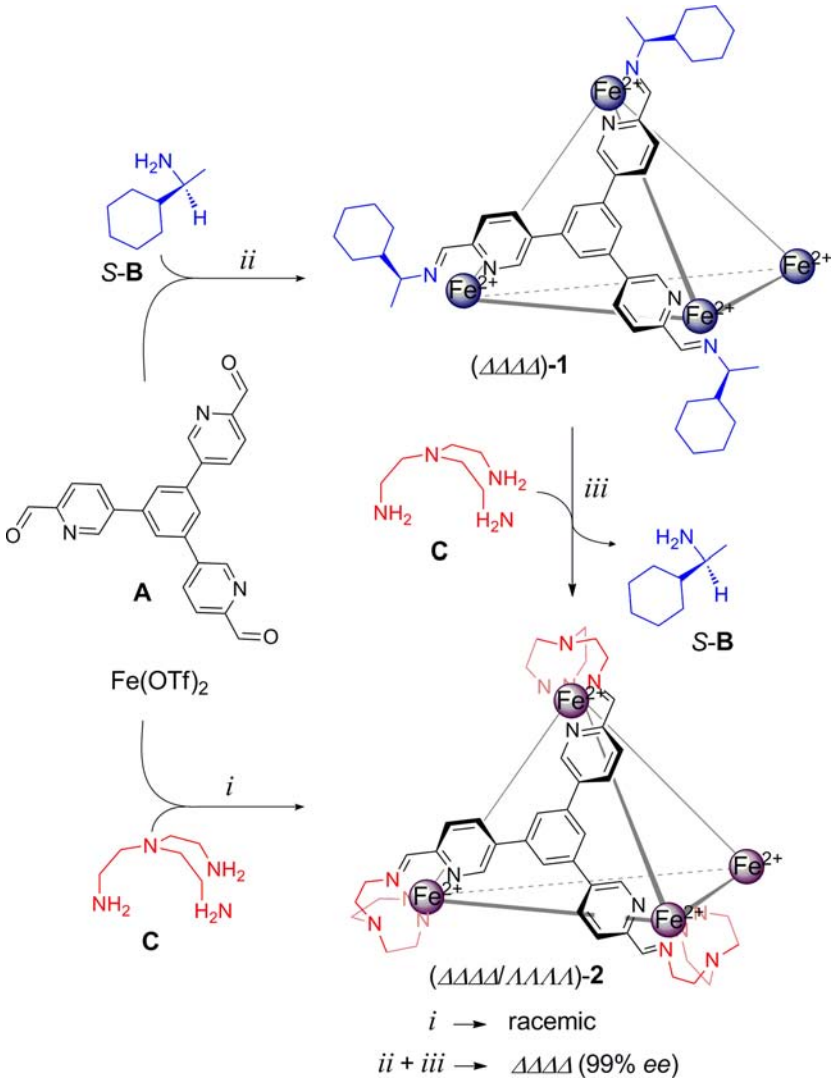
Scheme 1. Preparation of Cages 1 and 2[a]



[a]Route *i*: formation of racemic cage **2** through subcomponent self-assembly;. Route *ii* then *iii*: enantioselective formation of cage **2** through subcomponent substitution; high enantioselectivity requires extra Fe^{II} (see below). Only one ligand face is drawn per structure for clarity.

through the use of circular dichroism (CD) enabled us to rationally optimize the stereoselectivity of the process.

RESULTS AND DISCUSSION

Subcomponent Self-Assembly of Cages 1 and 2. The $Fe^{II}_4L_4$ structures described here (Scheme 1) are assembled from six-coordinate iron(II) ions, trialdehyde **A**, and a chiral monoamine, (*S*)-1-cyclohexylethylamine (*S*-**B**), or a chelating triamine, tris(2-aminoethyl)amine (*tren*, **C**). Subcomponent **A** was synthesized from 1,3,5-tris(boronpinacolate)benzene and 5-bromo-2-formylpyridine by Pd-catalyzed Suzuki–Miyaura cross-coupling reaction;[19] a full description of its synthesis is provided in the Supporting Information. We chose subcomponent *S*-**B** as a chiral amine for this study as it has been shown to strongly induce a single handedness at a proximate metal center in mononuclear Fe^{II} tris(pyridylimine) complexes through steric effects.[20]

The reaction of **A**, *S*-**B**, and $Fe(OTf)_2$ in a 1:3:1 ratio afforded tetrahedral cage **1** as a dark blue crystalline solid (Scheme 1, route *ii*). Vapor diffusion of diisopropyl ether into an acetonitrile solution of **1** produced crystals suitable for analysis by single-crystal X-ray diffraction (Figure 1). The four octahedral Fe^{II} centers are bridged by four C_3-symmetric ligands, each of which caps a face of the tetrahedron. Cage **1** crystallized in the chiral space group $P32_1$ with Δ configurations at all metal centers and approximate *T* point symmetry. The absolute configuration and enantiopurity of the crystal were confirmed by anomalous dispersion effects. The ligands on all faces of **1** adopt the same C_3-symmetric propeller-like configuration, in which the handedness of the propeller is the same as that of the Fe^{II} centers due to the conformational rigidity of the cage framework. The Fe^{II} centers are separated by 11.9 Å, and the volume of the central cavity was calculated to be 133 $Å^3$.[21] A single triflate anion is encapsulated, which is disordered around a C_3 symmetry axis.

ESI-MS and NMR analyses reflect a solution structure of **1** analogous to what is observed in the solid state. The simple ^1H NMR spectrum of **1**, with only one set of ligand resonances, is consistent with the formation of a single diastereomer with *T* point symmetry (Figure 2a). Cage **1** also encapsulates one counterion $CF_3SO_3^-$ (OTf^-) in solution as indicated by its ^{19}F NMR spectrum with two peaks, assigned to encapsulated and

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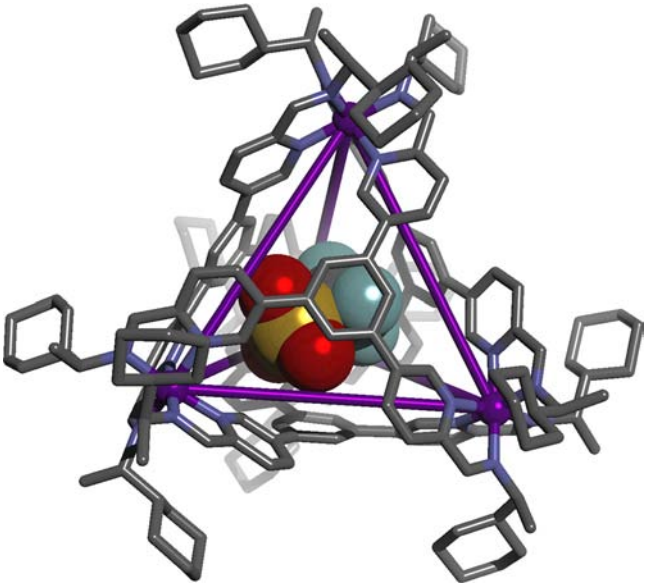

Figure 1. Crystal structure of cage ΔΔΔΔ-**1**. Only one of three orientations of the disordered OTf^- anion inside **1** is shown. Hydrogen atoms and nonencapsulated anions are omitted for clarity.

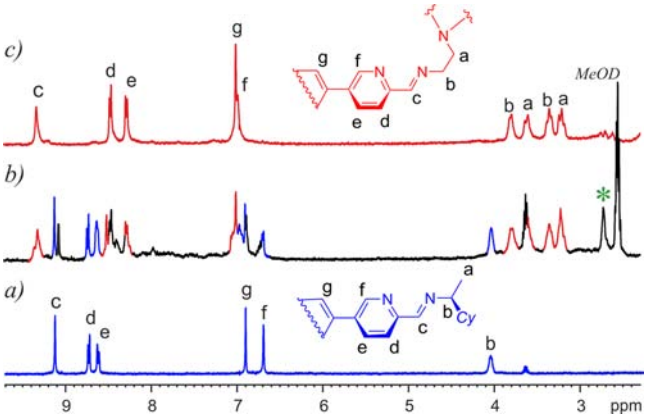

Figure 2. Partial ^{1}H NMR (400 MHz, CD_3CN, 298 K) spectra of (*a*) cage **1**, (*b*) reaction mixture of cage **1** and 5 equiv of **C** after 10 h at 40 °C, and (*c*) pure cage **2**. The CH group of free amine *S*-**B** is denoted with a green *.

free OTf^- (Supporting Information, Figure S15).[22] The CD spectrum of **1** contains intense split-type Cotton effects centered at 580 and 322 nm, confirming the presence of nonracemic stereogenic metal centers. This spectrum is consistent with the diastereoselective formation of the same isomer observed in the solid state, ΔΔΔΔ-(*S*)-**1**.[6d,20,23] Cage **1** prepared from *R*-**B** afforded the mirror image, ΛΛΛΛ-(*R*)-**1**, as indicated by its mirror image CD spectrum (Figure S16, Supporting Information).

The reaction in acetonitrile of trialdehyde **A**, tris(2-aminoethyl)amine (*tren*, **C**), and $Fe(OTf)_2$ in a 1:1:1 ratio yielded tetrahedral cage **2** as the racemate (Scheme 1, route *i*), as confirmed by NMR, ESI-MS, and CD measurements. The simple ^{1}H NMR of **2**, with only one set of ligand resonances (Figure 2c), along with its featureless CD spectrum indicate that this cage structure is formed as a racemic mixture of cage enantiomers, where each cage contains only Δ or Λ metal centers. This observation confirms the anticipated[6d,e,18e] strong stereochemical communication between adjacent metal centers within the Fe_4L_4 face-capped cage framework.

Subcomponent Substitution. On the basis of previous work on imine exchange within related structures,[22,24] we inferred that **2** could also be prepared by substitution of the 12 residues of (*S*)-**B** in ΔΔΔΔ-(*S*)-**1** by 4 equiv of chelating triamine **C** (Scheme 1, route *iii*). We also hypothesized that this substitution should proceed stereoselectively if it occurs in stepwise fashion through sequential selective displacement of the three chiral residues of **B** at one vertex of structure **1** by one molecule of **C**. This hypothesis was based on the observation that the presence of just two chiral subcomponents in a related $Fe^{II}_4L_6$ structure was sufficient to induce all of the cage's Fe^{II} stereocenters to adopt the same handedness, as a result of cooperative stereochemical communication between metal centers.[6d] During a sequential subcomponent exchange process with no disruption of the cage framework, we inferred that racemization of the metal center undergoing substitution at each step would be prevented, as its stereochemistry would remain fixed by the configuration of the neighboring metal centers. On the contrary, a substitution mechanism involving the disassembly of cage **1** would produce racemic cage **2**, as no chiral bias would be operative during its reassembly.

We thus treated a solution of cage ΔΔΔΔ-(*S*)-**1** (1 mM in acetonitrile) with **C** (5 equiv) at 40 °C. The progress of the reaction was monitored by ^{1}H NMR spectroscopy. During the course of the reaction, ^{1}H NMR spectra showed temporary desymmetrization due to the formation of partially substituted species,[25] eventually converging to a spectrum consistent with *T* symmetric **2**, indicating that the reaction had reached completion (Figure 2). Cage **2** isolated from this reaction exhibited optical activity, with an *ee* value estimated to be 35% by CD measurement.[26−28] ESI-MS analysis of the sample showed only pure cage **2** with no traces of unreacted cage **1** or partially substituted species containing chiral *S*-**B**. This result confirmed that the optical activity measured by CD resulted from the tetrahedral cage structure **2** being produced in enantioenriched form.

Control experiments ruled out the possibility that the partial stereochemical memory observed in this system was a consequence of the presence of *S*-**B** in solution during the substitution process: both the preparation of cage **2** from subcomponents **A** and **C** in the presence of 12 equiv of (*S*)-**B** and the heating of a solution of racemic **2** to 70 °C for 12 h in the presence of excess (*S*)-**B** resulted in no optical activity.

Mechanism of Stereochemical Memory. We infer the substitution of 1 equiv of **C** for 3 equiv of **B** during the **1** → **2** transformation to proceed through one of two conceptually distinct pathways: either a stereochemically *retentive* pathway, where the cage framework maintained a degree of structural integrity, or a *disruptive* pathway, where the removal by **C**[29] of one or more Fe^{II} template ions from the framework led to a partial opening of the framework and a scrambling of its stereochemistry. The two pathways are shown schematically in Figure 3. The observations that led us to this conclusion are discussed below.

Upon addition of 6 equiv of **C** to cage **1** (1 mM in acetonitrile), a 30% drop in CD intensity was observed within 10 min at 25 °C (Figure S24b, Supporting Information), although the substitution of **C** for **B** was only observed to proceed on a time scale of hours at 50 °C.[30] After the first abrupt decrease of CD intensity following the addition of **C**, the optical activity appears to remain nearly constant during the

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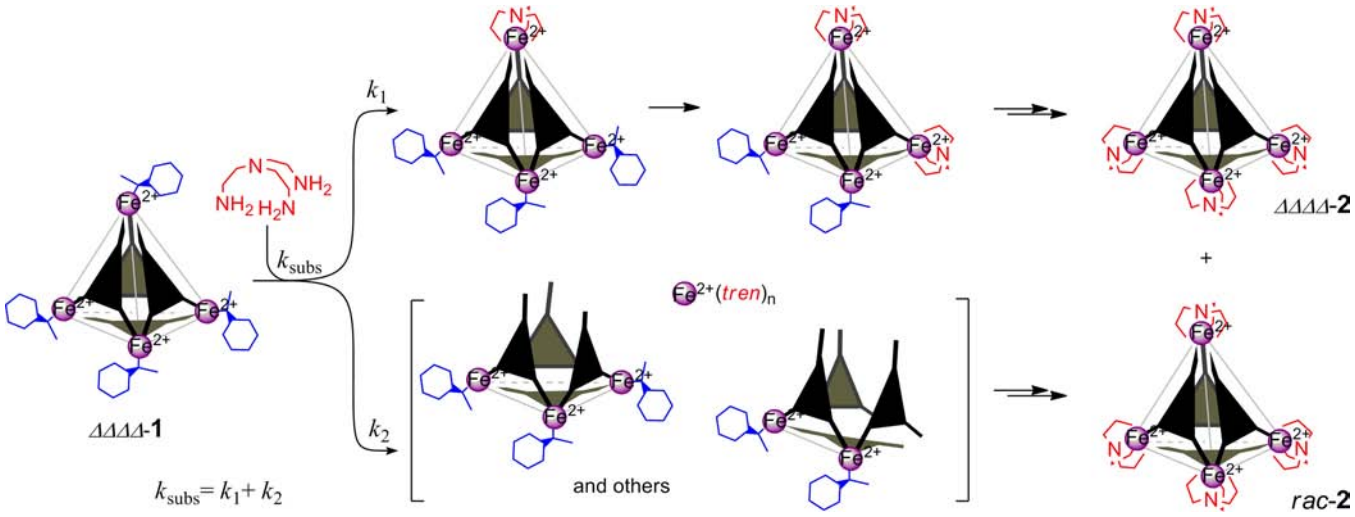

Figure 3. Schematic representation of the two parallel pathways operating during the transformation of cage **1** into cage **2**. Retentive substitution pathway (k_1, top) results in enantiopure cage **2** (stereochemical memory); disruptive substitution pathway 2 (k_2, bottom) results in racemic cage **2** (loss of stereochemical information).

course of the reaction (see for example Figure S26 in the Supporting Information). These observations are consistent with rapid partial demetalation[31] of cage **2**, whereby Fe^{II} complexes with the chelating agent *tren*[29] (**C**) are formed. Demetalation thus results in disruption of the cage framework and the formation of intermediate structures with more conformational freedom than cages **1** or **2**. The configurations of the remaining Fe^{II} vertices of these partially opened intermediates appear to be less strongly influenced by the still-incorporated chiral amine residues, as a consequence of the more loosely bound framework, resulting in racemization of the structure.

Following the complete substitution of **B** for **C**, the optical activity of cage **2** did not degrade even after heating to 90 °C for 10 days (Figure S30, Supporting Information), indicating that this structure is stable toward racemization, once formed. The process of racemization thus appears to occur only during the structural disruption that follows the initial demetalation of **1**.

Although the two pathways of Figure 3 probably represent two poles of a continuum of possibilities in practice, they could be distinguished analytically through their distinct outcomes, as discussed below.

To gain further insight into the substitution mechanism, we set out to perform a simple kinetic analysis. In keeping with our proposed mechanism we applied a kinetic model for parallel reactions (Figure 3). The pseudo-first-order rate constant for the overall substitution process (k_{subs}), the primary reaction step of which consists of the reaction of **C** with cage **1**, can be considered as the sum of the pseudo-first-order rate constants for two concurrent processes with separate pathways: $k_{subs} = k_1 + k_2$. Pathway 1 is stereochemically retentive (stepwise substitution mechanism), and pathway 2 results in racemization (disruptive mechanism). k_{subs} was estimated at different temperatures by monitoring the reaction progress by ^{1}H NMR spectroscopy ($[\mathbf{1}]_0$ = 1 mM, see Supporting Information). The linear temperature dependence of the *ee* value of cage **2** obtained from cage **1** (Figure S23a, Supporting Information) enabled us to estimate the ratios k_1/k_2 at each temperature and consequently the values for k_1 and k_2 (Table 1). Eyring analysis of these kinetic data (Figure 4) provided the

Table 1. Pseudo-First-Order Rate Constants for the Two Active Pathways (k_1, retentive; k_2, disruptive) and the Overall Subcomponent Exchange Process (k_{subs}) of 1[a]

temp (°C)	k_{subs} ($\times 10^{-4}$ s^{-1})	k_1 ($\times 10^{-4}$ s^{-1})	k_2 ($\times 10^{-4}$ s^{-1})
40	1.1 ± 0.1	0.4 ± 0.1	0.7 ± 0.2
50	1.9 ± 0.1	0.5 ± 0.1	1.4 ± 0.2
60	4.5 ± 0.4	0.9 ± 0.1	3.6 ± 0.4
70	6.6 ± 0.2	1.1 ± 0.1	5.5 ± 0.5

[a]Conditions: $[\mathbf{1}]_0$ = 1 mM.

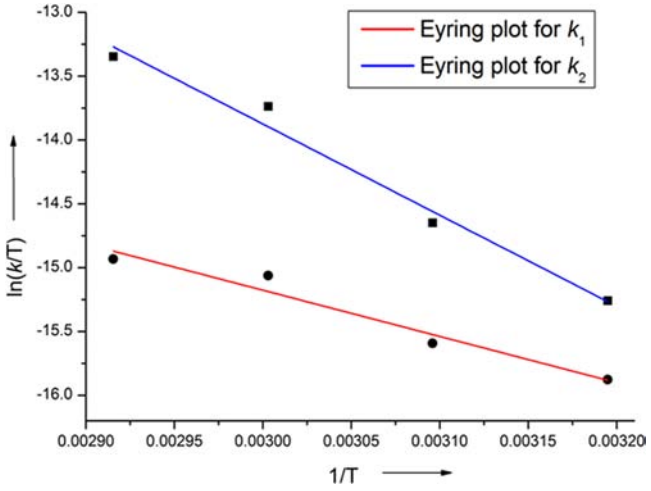

Figure 4. Eyring plots of $\ln(k_1/T)$ and $\ln(k_2/T)$ versus $1/T$ for the determination of the activation parameters for the two substitution pathways.

following thermodynamic parameters for the retentive pathway 1, $\Delta H^{\ddagger}$ = 30 kJ mol^{-1} and $\Delta S^{\ddagger}$ = −230 J mol^{-1} K^{-1}, and the disruptive pathway 2, $\Delta H^{\ddagger}$ = 59 kJ mol^{-1} and $\Delta S^{\ddagger}$ = −135 J mol^{-1} K^{-1}. The less negative value for the entropy of activation and the more positive enthalpy of activation suggest a more dissociated transition state for pathway 2, consistent with the dissociative mechanism proposed for the formation of **2** in racemic form.

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Effects of Concentration and Free Fe^{II}. The racemization rate (pathway 2) was also examined at higher and lower concentrations (Figure S23b, Supporting Information). At lower concentration ($[\mathbf{1}]_0$ = 0.09 mM), a significant decrease in the *ee* value of the resulting cage **2** was observed (estimated value of 6%), whereas at higher concentration ($[\mathbf{1}]_0$ = 3.8 mM) the product cage **2** was observed to form with enhanced enantiopurity (estimated value of *ee* 71%, Table 2).[32] This dependence of the stereochemical memory fidelity on concentration is again consistent with a partial cage disruption mechanism for the racemizing pathway 2, as such a dissociative process would be favored at lower concentrations.

Table 2. Summary of the *ee* Values of Cage 2 Obtained under Different Reaction Conditions[a]

$[\mathbf{1}]_0$ (mM)	equiv of $Fe(OTf)_2$	*ee* (%)[b]
1	0	35
1	4	89
3.8	0	71
3.8	4	99

[a]Reaction temperature 40 °C. [b]*ee* estimated by CD measurements.[27]

We reasoned that the demetalation of cage **1** by **C** could be minimized by the presence of free Fe^{II} in solution during the subcomponent substitution reaction. At lower concentration ($[\mathbf{1}]$ = 0.09 mM), the decrease of CD intensity upon addition of **C** was mitigated in the presence of added Fe^{II} (4 equiv, Figure S27, Supporting Information). Likewise, at higher concentration ($[\mathbf{1}]$ = 3.8 mM), the presence of additional Fe^{II} (4 equiv) in the reaction mixture enabled the conversion of **1** into **2** in nearly enantiopure form (99% *ee*, Figure 5 dashed trace). The optical activity of the product did not diminish following its isolation from the reaction mixture, indicating that purification did not result in enantioenrichment. Consistently, a pronounced decrease of the overall reaction rate for the substitution was also observed in the presence of free Fe^{II}. Whereas the reaction had approached completion in 7 days in the absence of additional Fe^{II}, in its presence, 17 days were required.

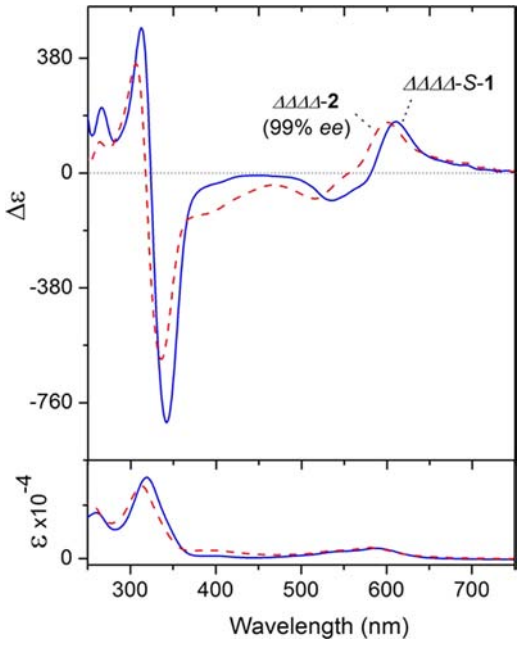

Figure 5. CD (top) and absorption (bottom) spectra of cage ΔΔΔΔ-*S*-**1** (solid traces) and cage **2** obtained through subcomponent substitution (dashed traces) in CH_3CN at 20 °C, [cage] = 6.7×10^{-5} M. $\Delta\varepsilon$ and ε were normalized with respect to [cage].

As noted above, the optical activity of the isolated enantiopure cage **2** is robustly remembered, remaining intact after a month standing at room temperature and even after extended heating (90 °C, 4 days, Figure S31, Supporting Information). However, the addition of 8 equiv of **C** to a solution of **2** in acetonitrile at 60 °C brought about a 15% drop in the CD intensity. This drop could again be prevented by the presence of excess Fe^{II} (4 equiv) in solution, providing further evidence that racemization is caused by the demetalation of the cage vertices by **C** (Figure S31, Supporting Information). This long-lasting stereochemical memory effect and higher resistance to demetalation by **C** may be attributed to the enhanced kinetic inertness of structure **2**, arising from the combination of strongly chelating *tren* trisimine complexes at the vertices with the rigidity of the cage framework.

Stereochemical Memory of Analogues. To further probe the nature of this effect, mononuclear complex **3**[20] and $Fe^{II}_4L_6$ cage **4** were prepared from (*S*)-**B**. Complex **3** was isolated as a mixture containing *fac*-Δ and *mer*-Δ isomers in the ratio 3.6:1. Cage **4** was isolated as a single diastereomer, ΔΔΔΔ-(*S*), as confirmed by ^{1}H NMR and CD measurements (see Supporting Information). Due to the lack of mechanical coupling[17] with other metal centers, treatment of **3** with triamine **C** afforded racemic **5** (Scheme 2). Interestingly, despite the strong stereochemical coupling between neighboring Fe^{II} centers of cages based on 6,6′-diformyl-3,3′-bipyridine,[6d] treatment of **4** with triamine **C** produced only racemic cage **6** (Scheme 2).[33] We infer edge-bridged cages to be more labile than their face-capped analogues, as a result of the greater rigidity of the tritopic ligands of the latter, which would be held in place by two iron(II) centers during stereochemically retentive substitution.

CONCLUSIONS

In conclusion, the high-fidelity retention of stereochemistry displayed by a new Fe_4L_4 cage has enabled its synthesis in enantiopure form through the substitution of chiral subcomponent residues. The strong communication of handedness[6] between the metal centers, effectively mediated by the helical sense of the C_3-symmetric ligands, the robustness of the face-capped structure, and the ease of imprinting stereochemical information through the use of chiral amine residues are the key features that enable stereochemical memory to function in this system. A mechanistic study of this phenomenon has allowed us to separate the stepwise substitution process by which stereochemical information is retained upon substitution from the dissociative one, entailing chiral information loss. This mechanistic understanding of the substitution processes enabled optimization of the efficiency of the stereochemical memory effect of the system. The robustness of the structure of cage **2** prevents its racemization, allowing for long-lasting storage of chiral information. These findings provide a new means for the rational design of functional metal−organic capsules to be assembled with durable stereochemistry[6a] by using reduced amounts of a potentially reusable source of chiral information, a valuable feature for the development of applications.[4,5]

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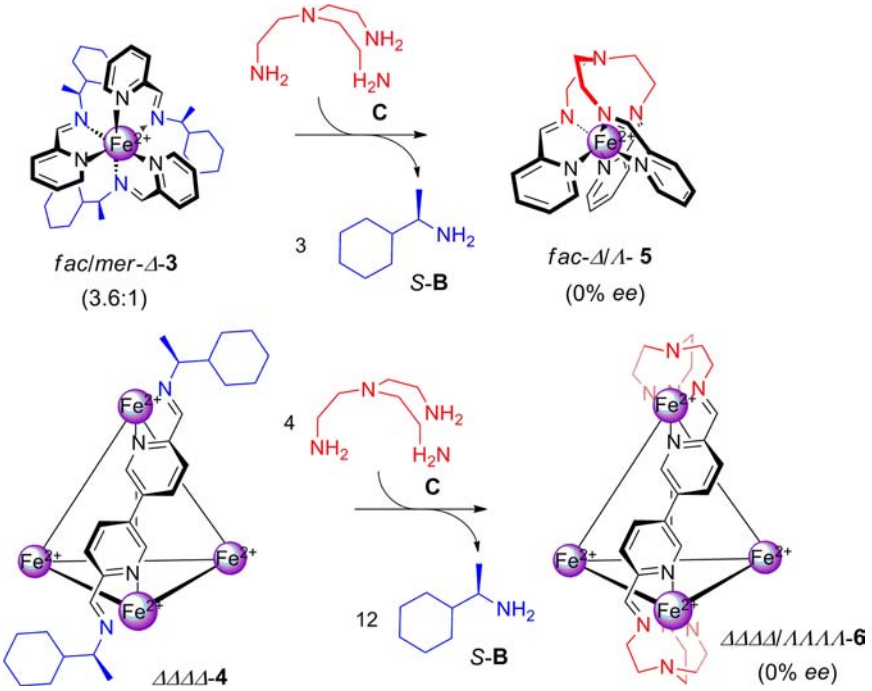
Scheme 2. Mononuclear Complex 5 and $Fe^{II}_4L_6$ Cage 6 Are Obtained Only in Racemic Form through Subcomponent Substitution



EXPERIMENTAL METHODS

General. All reagents and solvents were purchased from commercial sources and used as supplied. 1,3,5-Tris(boronpinacolate)-benzene[34] and 6,6′-diformyl-3,3′-bipyridine[22] were prepared as described in the literature. NMR spectra were recorded on a Bruker Avance DPX400 or Bruker Avance 500 Cryo spectrometer; Chemical shifts are reported in parts per million (δ) referenced to the CHD_2CN residual solvent signal of CD_3CN at δ = 1.94 or the $CHCl_3$ residual solvent peak of $CDCl_3$ at δ = 7.26. ^{19}F chemical shifts (δ) are reported relative to hexafluorobenzene at −164.9 ppm. Electrospray ionization mass spectra (ESI-MS) were obtained on a Micromass Quattro LC, infused from a Harvard Syringe Pump at a rate of 10 μL per minute. CD analyses were performed on an Applied Photophysics Chirascan circular dichroism spectrometer. Satisfactory elemental analyses required the inclusion of water molecules; this water was observed in ^1H NMR spectra of crystallized products. Possible sources of water include the imine condensation reaction and the solvents employed. The syntheses of complexes **3**−**6** and subcomponent **A** are reported in the Supporting Information.

Synthesis of Cage 1. Into a 50 mL Schlenk flask containing CH_3CN (10 mL) were added subcomponent **A** (80 mg, 0.2 mmol), (*S*)-1-cyclohexylethylamine (81.8 mg, 0.64 mmol), and iron(II) triflate [$Fe(OTf)_2$] (71.9 mg, 0.2 mmol). The flask was sealed and subjected to three evacuation/nitrogen fill cycles. After stirring at 70 °C for two days the mixture was allowed to cool to room temperature and filtered. Cage **1** was precipitated as a dark blue crystalline solid by addition of isopropyl ether to the filtrate (yield 144 mg, 66%). ^1H NMR (400 MHz, CD_3CN): δ = 9.11 (s, 12H, imine), 8.73 (d, J = 1.9, 8.0 Hz, 12H, 5-pyridine), 8.63 (d, J = 8.0 Hz, 12H, 4-pyridine), 6.90 (s, 12H, *H*-phenyl center), 6.69 (s, 12H, 2-pyridine), 4.04 (m, 12H, C$^{\alpha}$*H* cyclohexylethylamine), 1.68 (m, 12H, C*H* cyclohexylethylamine), 1.57 (d, J = 6.7 Hz, 36H, CH_3 cyclohexylethylamine), 1.46 (m, 24H, C*H* cyclohexylethylamine), 1.39 (m, 12H, C*H* cyclohexylethylamine), 0.86−1.14 (m, 48H, C*H* cyclohexylethylamine), 0.79 (m, 12H, C*H* cyclohexylethylamine), 0.51 (m, 12H, C*H* cyclohexylethylamine), 0.17 (m, 12H, C*H* cyclohexylethylamine). ^{13}C NMR (125 MHz, CD_3CN): δ = 171.6, 159.8, 152.2, 139.4, 136.5, 135.8, 131.4, 127.4, 70.7, 42.2, 31.8, 27.4, 26.7, 26.6, 25.1, 17.4. ^{19}F NMR (376 MHz, CD_3CN): δ = −79.6 (bs, *exo* OTf^-), −79.8 (s, *endo* OTf^-). ESI-MS: m/z 465.22 [**1**$(OTf)]^{7+}$, 567.60 [**1**$(OTf)_2]^{6+}$, 710.94 [**1**$(OTf)_3]^{5+}$, 925.94 [**1**$(OTf)_4]^{4+}$, 1284.28 [**1**$(OTf)]^{3+}$. Elemental analysis (%) calcd for $C_{200}H_{240}F_{24}Fe_4N_{24}O_{24}S_8{\cdot}6H_2O{\cdot}1.25C_6H_{14}O$: C 54.93, H 5.99, N 7.41; found C 55.11, H 5.74, N 7.16. Satisfactory elemental analyses required the inclusion of water and isopropyl ether molecules; water and isopropyl ether were observed in the ^1H NMR spectrum of the crystallized product, even after drying under vacuum.

Synthesis of Cage 2. *(a). Subcomponent Self-Assembly.* Into a 25 mL Schlenk flask containing CH_3CN (5 mL) were added trialdehyde **A** (11.5 mg, 29.2 μmol) and iron(II) triflate [$Fe(OTf)_2$] (10.3 mg, 29 μmol). The flask was sealed and subjected to three evacuation/nitrogen fill cycles, and tris(2-aminoethyl)amine **C** (4.7 mg, 32.1 μmol) was added via syringe. The mixture was heated to 70 °C overnight. The day after, the solution was allowed to cool to room temperature, and cage **2** was precipitated pure as a purple solid by addition of Et_2O (yield 21.7 mg, 69%).

(b). Subcomponent Substitution. Into a NMR tube containing iron(II) triflate [$Fe(OTf)_2$] (3 mg, 4 equiv, 8.5 μmol) was added 560 μL of a solution of cage **1** in CD_3CN (3.8 mM). The tube was sealed with a rubber septum, subjected to three evacuation/nitrogen fill cycles and 19 μL (12 equiv, 25.5 μmol) of tris(2-aminoethyl)amine (**C**) added via syringe from a stock solution in CD_3OD-d_4 (1.3 M). The mixture was allowed to stand at 40 °C for 17 days. The reaction progress was monitored by ^1H NMR spectroscopy. Cage **2** was precipitated as a purple solid by addition of diisopropyl ether to the reaction mixture (yield 4.7 mg, 65%). When the reaction was performed with no added $Fe(OTf)_2$, only 5 equiv of **C** were used. The reaction reached completion in 1 week, and cage **2** was isolated in 74% yield.

^1H NMR (400 MHz, CD_3CN): δ = 9.33 (s, 12H, imine), 8.48 (d, J = 8.7 Hz, 12H, 5-pyridine), 8.29 (d, J = 8.9 Hz, 12H, 4-pyridine), 7.00 (m, 24H, overlapping *H*-phenyl center + 2-pyridine), 3.80 (m, 12H, -CH_2- tris(2-aminoethyl)amine), 3.62 (d, J = 13.7 Hz, 12H, -CH_2- tris(2-aminoethyl)amine), 3.36 (m, 12H, -CH_2- tris(2-aminoethyl)-amine), 3.21 (t, J = 12.1 Hz, 12H, -CH_2-tris(2-aminoethyl)amine). ^{13}C NMR (125 MHz, CD_3CN): δ = 172.8, 157.3, 152.9, 139.9, 136.7, 134.9, 129.9, 127.6, 59.8, 54.8. ^{19}F NMR (376 MHz, CD_3CN): δ = −79.5 (bs, *exo* OTf^-), −80.2 (s, *endo* OTf^-). ESI-MS: m/z 410.8 [**2**$(OTf^-)_2]^{6+}$, 522.4 [**2**$(OTf^-)_3]^{5+}$, 690.3 [**2**$(OTf^-)_4]^{4+}$, 970.3 [**2**$(OTf^-)_5]^{3+}$. Elemental analysis (%) calcd for

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$C_{128}H_{108}F_{24}Fe_4N_{28}O_{24}S_8 \cdot 9.3H_2O$: C 45.01, H 3.45, N 11.48; found C 44.54, H 3.74, N 11.99.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures and characterization of subcomponent **A** and complexes **3**−**6**, characterization of complexes **1** and **2**, spectroscopic data, k_1, k_2, k_{subs} and activation parameters determination, and the CIF file for **1**. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data have also been deposited with the Cambridge Crystallographic Data Center as entry CCDC 948136

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Notes

The authors declare no competing financial interest.

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(25) The partially substituted intermediates containing 1, 2, or 3 **C** residues were also observed to form sequentially during the course of the reaction monitored by ESI-MS (Figure S22, Supporting Information).

(26) The optical activity measured for the isolated product **2** is equal to the optical activity measured for the reaction mixture before purification.

(27) The ee values for cage **2** were estimated by CD measurement using the following equation: % ee = $\Delta\varepsilon_2^{first}/\Delta\varepsilon_1^{first} \times 100$ where $\Delta\varepsilon_1^{first}$ and $\Delta\varepsilon_2^{first}$ are the maximum CD intensity at the first Cotton effect of cages **1** and **2**, respectively (see ref 6d,e).
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(30) Similar behavior was observed in the reaction of cage **1** with only 1 equiv of **C** (1 mM, 50 °C, 48 h). CD analysis of the reaction mixture showed 28% decrease of the optical activity despite **1** and monosubstituted **1** being the only cage species detected by ESI-MS (see Supporting Information, Figures S24a and S25).
(31) Addition of excess **C** to a solution of $Fe(OTf)_2$ in acetonitrile at room temperature caused an immediate color change from colorless to brown-orange and a downfield shift of the ^{1}H NMR signals of the triamine **C**. Both observations provide further evidence of the interaction of *tren* with Fe^{II} under the reaction conditions, which is in fast exchange in the ^{1}H NMR time scale (Figure S32, Supporting Information).
(32) Further increase in concentration is limited by cage solubility.
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