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Diels−Alder Active-Template Synthesis of Rotaxanes and Metal-Ion-Switchable Molecular Shuttles

James D. Crowley,† Kevin D. Hänni,† David A. Leigh,*,† and
Alexandra M. Z. Slawin‡

*School of Chemistry, University of Edinburgh, The King's Buildings, West Mains Road,
Edinburgh EH9 3JJ, United Kingdom, and School of Chemistry, University of St. Andrews,
Purdie Building, St. Andrews, Fife KY16 9ST, United Kingdom*

Received February 4, 2010; E-mail: David.Leigh@ed.ac.uk

Abstract: A synthesis of [2]rotaxanes in which Zn(II) or Cu(II) Lewis acids catalyze a Diels−Alder cycloaddition to form the axle while simultaneously acting as the template for the assembly of the interlocked molecules is described. Coordination of the Lewis acid to a multidentate endotopic 2,6-di(methyleneoxymethyl)pyridyl- or bipyridine-containing macrocycle orients a chelated dienophile through the macrocycle cavity. Lewis acid activation of the double bond causes it to react with an incoming "stoppered" diene, affording the [2]rotaxane in up to 91% yield. Unusually for an active-template synthesis, the metal binding site "lives on" in these rotaxanes. This was exploited in the synthesis of a molecular shuttle containing two different ligating sites in which the position of the macrocycle could be switched by complexation with metal ions [Zn(II) and Pd(II)] with different preferred coordination geometries.

Introduction

Active-template synthesis is a strategy for the construction of mechanically interlocked structures in which the metal ion acts as both a template for entwining or threading the components and a catalyst for capturing the interlocked final product by covalent bond formation.[1,2] In doing so, the metal often changes the strength of coordination and preferred geometry of its ligands several times during the reaction. Despite this complexity of mechanism, several different metal-catalyzed reactions have already proven suitable for the active-metal-template synthesis of both rotaxanes and catenanes, including the copper(I)-catalyzed terminal alkyne−azide cycloaddition (the CuAAC "click" reaction),[3] palladium-[3d,4] and copper-catalyzed[5] alkyne homocouplings and heterocouplings, and palladium-catalyzed oxidative Heck couplings[6] and Michael additions.[7] However, unlike traditional "passive" metal-template methods, permanent recognition motifs are not intrinsically required on each of the components to be interlocked in active-template syntheses (i.e., the assembly can be traceless). This means that one of the most widely exploited features of rotaxane template assembly[8]—that the intercomponent recognition motif "lives on" in the rotaxane, providing a preferred binding site for the ring on the thread that can be exploited in "molecular shuttles"—is not automatically present using active-template syntheses.

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† University of Edinburgh.

‡ University of St Andrews.

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Here we report on the active-template synthesis of rotaxanes utilizing the Lewis acid-catalyzed[9] Diels−Alder[10] cycloaddition. The reaction proceeds in the presence of either Zn(II) or Cu(II) salts with weakly coordinating triflate anions, generating [2]rotaxanes in up to 91% yield. The active-template reaction "selects" 2-substituted cyclopentadienes over 1-substituted cyclopentadienes, generating one rotaxane isomer with 90−99% selectivity as opposed to the four isomers produced for the noninterlocked thread. Unusually for an active-template reaction, the template site is fully incorporated into the interlocked product, meaning that metal-chelated molecular shuttles can readily be prepared. This is exemplified through the synthesis of a molecule shuttle in which the position of the macrocycle can be switched by varying the coordination requirements of the metal ion present [trigonal-bipyramidal Zn(II) or square-planar Pd(II)].

Design of a Lewis Acid-Catalyzed Diels−Alder Active-Template Reaction. A wide range of Lewis acids, most often transition-metal salts, have been shown to efficiently catalyze Diels−Alder cycloadditions.[9] α,*β*-Unsaturated 2-acyl-oxazolidinones, imidazolidones, and pyrazolidinones[11] are particularly effective substrates and provide a well-defined chelation geometry around the metal center as the Lewis acid-activated double bond reacts with the diene. Inspired by some literature systems,[12] we postulated that coordination of some simple Lewis acid metal salts with a tridentate macrocycle should lead to a metal−ligand geometry with two replaceable ligands protruding through opposite faces of the macrocycle. An acryloyl imidazolidone unit ("stoppered" at one end) that is chelated to the metal center would generate a threaded complex in which the activated double bond is exposed to an incoming diene. If the diene were also stoppered at one end, Lewis acid-catalyzed cycloaddition through the cavity would lead to a [2]rotaxane.

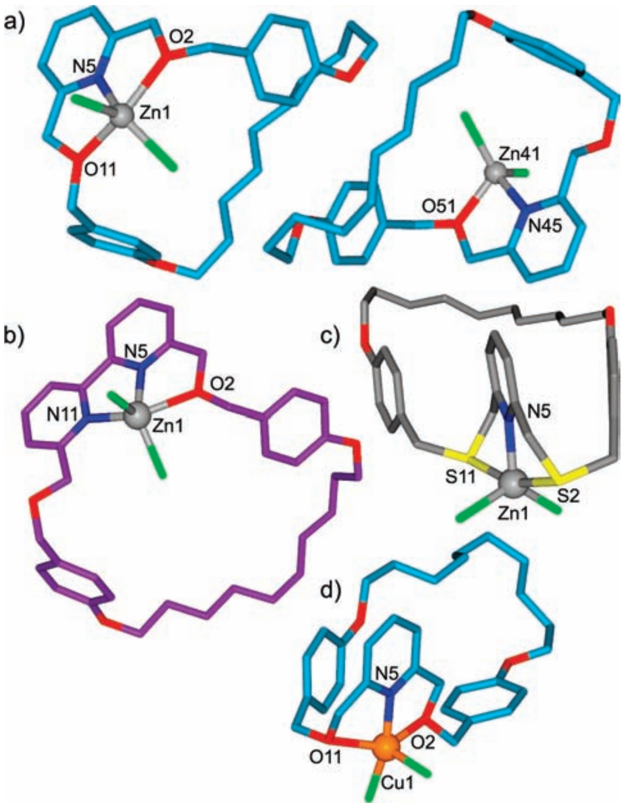

Figure 1. X-ray crystal structures of Lewis acid−macrocycle complexes: (a) [**1a**Zn]Cl$_2$ (the two Zn(II) environments, trigonal bipyramidal and tetrahedral, should be noted); (b) [**1b**Zn]Cl$_2$; (c) [**1c**Zn]Cl$_2$; (d) [**1a**Cu]Cl$_2$.

Results and Discussion

Various pyridine-based ligands, such as pyridine-2,6-bis(oxazoline) (pybox),[13] bipyridyl,[14] and bisoxazolines (box),[13,15] have been shown to efficiency catalyze Lewis acid-promoted cycloaddition reactions. A series of X-ray crystal structures of multidentate pyridine- and bipyridine macrocycles (**1a**, **1b**, **1c**) complexed to ZnCl$_2$ or CuCl$_2$ (Figure 1) were obtained, and they confirmed that the geometries of the coordinated Lewis acids were potentially suitable for rotaxane formation, even though the exchangeable ligands were not always directed through the cavity in the solid state. Rotaxane formation from dieneophile **2**, diene **3**, and complexes of macrocycle **1a** with various Lewis acids was investigated (Scheme 1 and Table 1). A complex between macrocycle **1a** (1 equiv) and the Lewis acid (1 equiv) in CH$_2$Cl$_2$ was formed in situ. Addition of acryloyl imidazolidone **2** (1 equiv) at room temperature and diene **3** (1 equiv) at −78 °C was following by stirring at −78 °C for 20 h and at room temperature for a further 4 h. Initial experiments with ZnCl$_2$ were unsuccessful (Table 1, entry 1), possibly because the two chloride ligands may have been too strongly coordinated to the metal. However, we were delighted to find that switching to Zn(OTf)$_2$ afforded [2]rotaxane **4a** in 8% yield (Table 1, entry 2). Changing the Lewis acid from zinc triflate to copper triflate increased the yield of [2]rotaxane to 47% (Table 1, entry 3). Increasing the amounts of **2** and **3** and extending the reaction time (48 h at −78 °C followed by 48 h at room temperature) improved the yield of **4a** to 42% with Zn(OTf)$_2$ and 83% with Cu(OTf)$_2$ (Table 1, entries 4 and 5).

The proposed mechanism for rotaxane formation is shown in Scheme 1. Replacement of the two labile ligands by the oxygen atoms of the acryloyl imidazolidone unit affords the threaded complex **II**, in which the activated double bond must react with the "stoppered" cyclopentadiene **3** on the macrocycle face opposite the dieneophile stopper group. Demetalation with ammonia [for Cu(II)] or Na$_4$EDTA [for Zn(II)] generates the metal-free rotaxane **4a**. Using the same reaction conditions as in Table 1, entry 5 but with only 30 mol %

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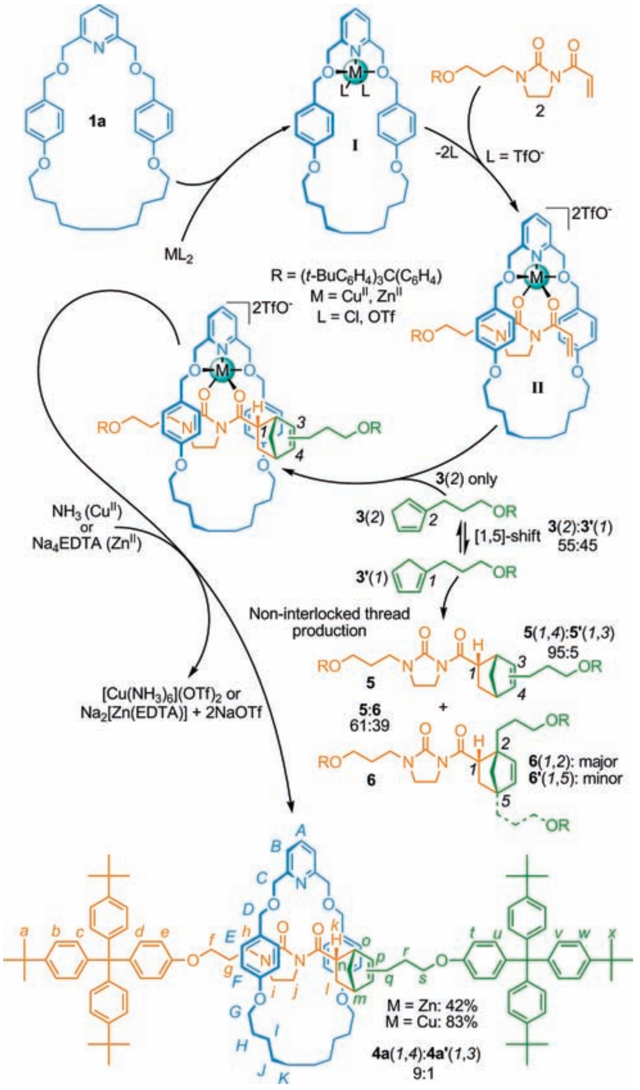
Scheme 1. Diels−Alder Active-Metal-Template Synthesis of [2]Rotaxane **4a** from Macrocycle **1a**, Dienophile **2**, and Diene **3**[a]



[a] For reaction conditions and reagent stoichiometries, see Table 1.

Table 1. Effect of Reactant Stoichiometry and Experimental Conditions on the Diels−Alder Active-Template Synthesis of Rotaxane **4a**[a]

entry	Lewis acid	equiv of **2**	equiv of **3**	*t* (h)	yield of **4a** (%)[d]
1[b]	ZnCl$_2$	1	1	24	0
2[b]	Zn(OTf)$_2$	1	1	24	8
3[b]	Cu(OTf)$_2$	1	1	24	47
4[c]	Zn(OTf)$_2$	1.2	2	96	42
5[c]	Cu(OTf)$_2$	1.2	2	96	83

[a] Reactions were carried out using anhydrous CH$_2$Cl$_2$ and 9 mM **1a** under a nitrogen atmosphere (see the Experimental Section). [b] Reaction conducted at −78 °C for 20 h followed by RT for 4 h. [c] Reaction conducted at −78 °C for 48 h followed by RT for 48 h. [d] Calculated with respect to **1a**.

copper triflate reduced the yield of [2]rotaxane **4a** to 37%, suggesting that the rotaxane sequesters the metal ion, preventing turnover of the active template to any significant extent during the reaction.

Diene Isomer Selection during the Active-Template Reaction. The cyclopentadiene derivative **3** used to form the thread exists as an ∼55:45 mixture of the 1- and 2-substituted isomers (**3′** and **3**, respectively) at 298 and 258 K, as determined by ^{1}H NMR spectroscopy. The energy barrier for the [1,5]-sigmatropic shift of monosubstitued cyclopentadienes, such as the one that converts 1-methyl-1,3-cyclopentadiene into 2-methyl-1,3-cyclopentadiene,[16] is only ∼28 kcal mol^{-1}, so the two isomers of **3** interchange many times during the reaction period at the temperatures used for the active-template reaction. Interestingly, when subjected to the active-template reaction conditions, only the 2-substituted isomer of **3** was found to react with the activated double bond protruding through the cavity of the macrocycle, since no rotaxane with a 1,2- or 1,5-substitution pattern for the thread was detected in the product mixture. Furthermore, 90% of the endo adduct [2]rotaxane formed was the 1,4-isomer **4a**, with the other 10% being the 1,3-isomer **4a′**(*1,3*) (the assignments of the isomers were determined by ROESY experiments; see the Supporting Information). In contrast, all four isomers of the noninterlocked thread [**5**(*1,4*), **5′**(*1,3*), **6**(*1,2*), and **6′**(*1,5*)] were formed when the thread-forming Diels−Alder reaction was carried out with a nonmacrocyclic ligand for the Lewis acid (Scheme 1). Thus, the active-template reaction selects heavily for the 2-substituted cyclopentadiene reactant and the 1,4-cycloaddition rotaxane product.

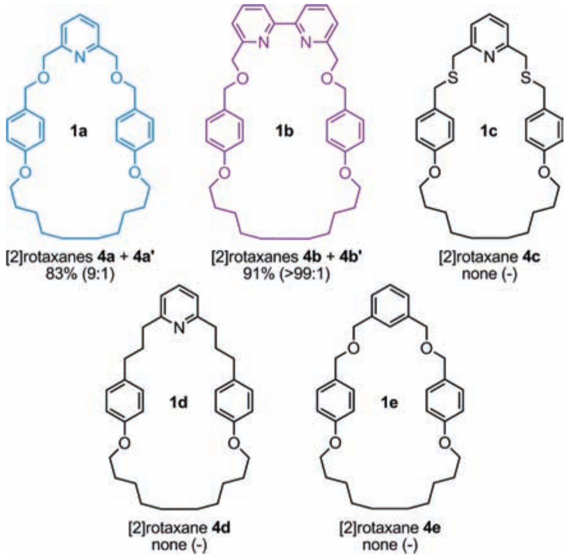


Figure 2. Influence of the macrocyclic ligand on the Diels−Alder active-metal-template rotaxane formation reaction analogous to that shown in Scheme 1 with reagents and conditions as for Table 1, entry 5. The ratio of the 1,4- and 1,3-isomers of each rotaxane is shown in parentheses after the rotaxane yield.

To explore the influence of the nature of the macrocyclic ligand on the active-metal-template cycloaddition reaction shown in Scheme 1, we substituted **1a** with the four different macrocycles **1b**−**e** (Figure 2). Reaction of bipyridyl macrocycle **1b** under these conditions generated the corresponding [2]rotaxane **4b** in 91% yield in a (*1,4*)/(*1,3*) ratio of >99:1. Substitution of the benzylic ether oxygen atoms of **1a** with the strongly coordinating sulfur atoms in **1c**, which would reduce the Lewis acidity of the metal center, or the noncoordinating methylene groups in **1d** completely inhibited rotaxane formation. Use of **1e** without the pyridine nitrogen atom also switched off rotaxane formation. It appears that at least one strongly coordinating pyridine group is necessary

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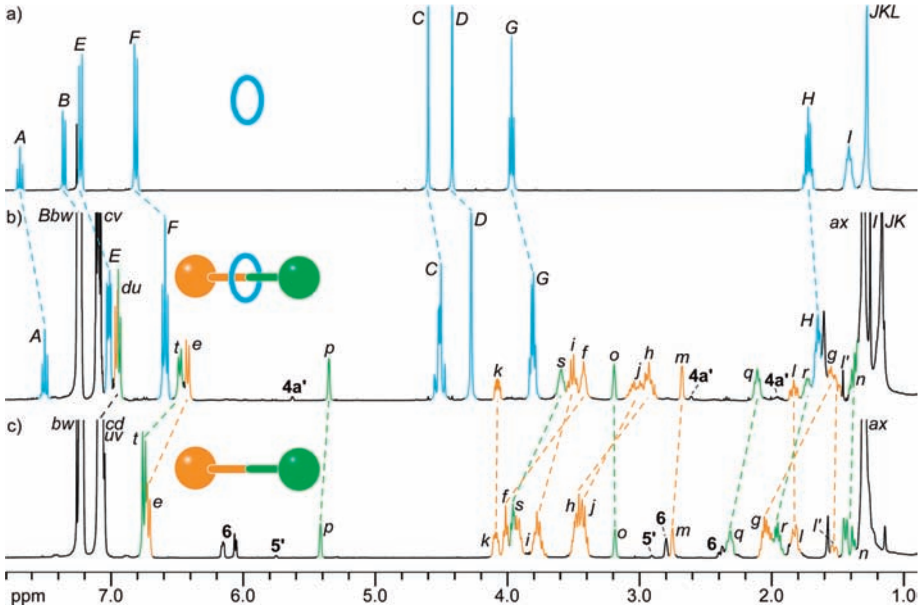
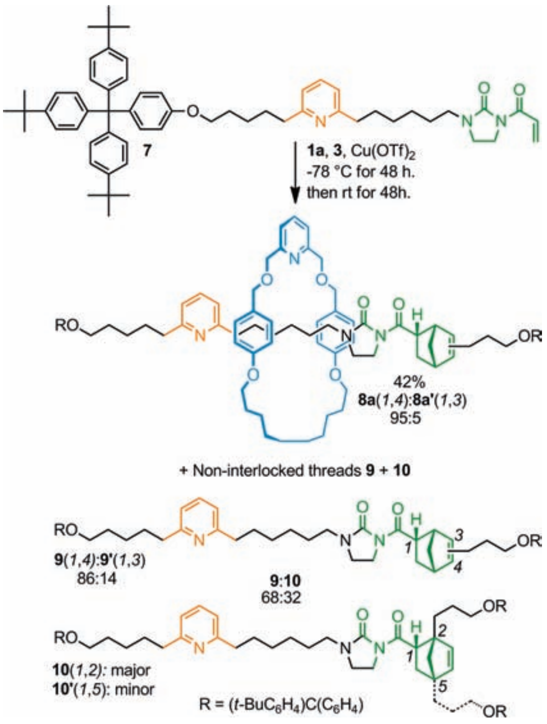


Figure 3. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 328 K) of (a) macrocycle **1a**, (b) [2]rotaxane **4a**:**4a′** (9:1), and (c) noninterlocked threads **5** and **6** (61:39). The assignments of **1a**, **4a**, **5**, and **6** correspond to the lettering shown in Scheme 1. In (b), the resonances of minor rotaxane isomer **4a′** are not assigned to specific protons. In (c), the resonances of the noninterlocked thread are, for the most part, not assigned to specific isomers.

to bind the Lewis acid within the macrocyclic cavity and that the additional weakly ligating donor atoms are needed to hold the chelated alkene in the orientation necessary for the active-template cycloaddition.

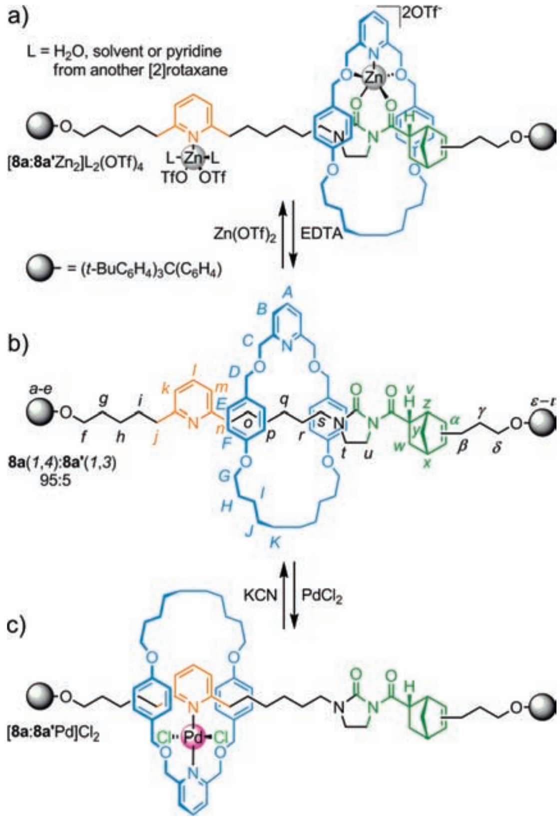
^{1}H NMR Spectroscopy of [2]Rotaxane 4a:4a′. The ^{1}H NMR spectrum of [2]rotaxane **4a** (and the minor isomer **4a′**) in $CDCl_3$ at 328 K shows an upfield shift of several signals with respect to the noninterlocked components (Figure 3). The shielding, typical of interlocked architectures in which the aromatic rings of one component are positioned face-on to another component, occurred for all of the aliphatic nonstopper resonances of the axle (H_{f-h}, H_{q-s}, H_i, and H_j), indicating that the macrocycle

Scheme 2. Assembly of Molecular Shuttle **8a**:**8a′** from the Diels−Alder Active-Metal-Template Reaction of Macrocycle **1a**, Dienophile **7**, and Diene **3**^{a}



^{a} Reagents and conditions: **1a** (1 equiv), $Cu(OTf)_2$ (1 equiv), **7** (1.2 equiv), **3** (2 equiv), CH_2Cl_2, −78 °C for 48 h followed by RT for 48 h.

Scheme 3. Determination of the Macrocycle Position by the Metal Coordination Geometry in Molecular Shuttle **8a**:**8a′**^{a}



^{a} (a) Macrocycle position upon coordination to Zn(II): [**8a**:**8a′**Zn_2]$L_2(OTf)_4$. (b) Metal-free rotaxane **8a**:**8a′**. (c) Macrocycle position upon coordination to Pd(II): [**8a**:**8a′**Pd]Cl_2.

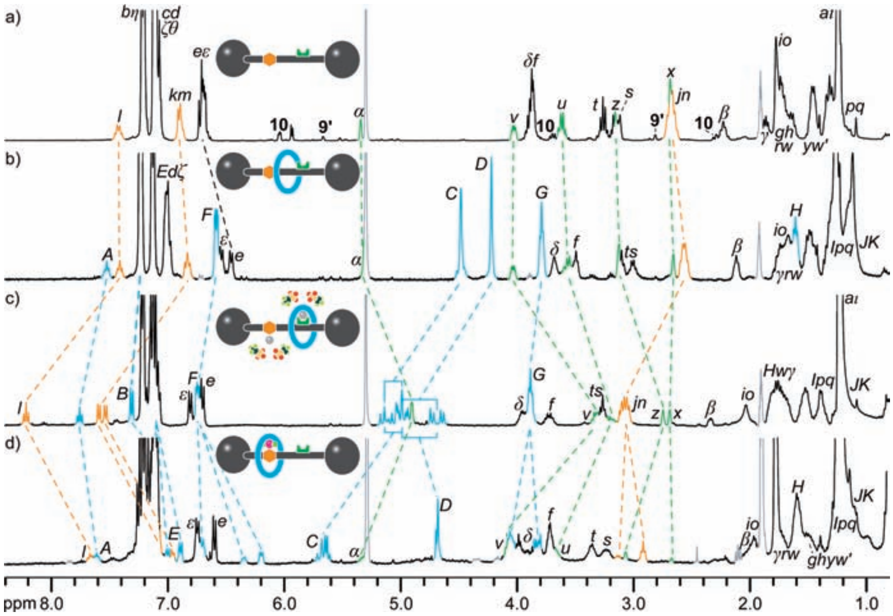


Figure 4. ^{1}H NMR spectra (400 MHz, 298 K, 9:1 CD_2Cl_2/CD_3CN) of (a) threads **9** and **10** (68:32), (b) [2]rotaxane **8a**:**8a′** (95:5), (c) [2]rotaxane−Zn(II) complex [**8a**Zn_2]$L_2(OTf)_4$, and (d) [2]rotaxane−Pd(II) complex [**8a**Pd]Cl_2. The assignments correspond to the lettering shown in Scheme 3.

spends more time over the less hindered parts of the thread in the metal-free rotaxane, avoiding the bulky norbornene unit.

Coordination Control of the Macrocycle Position in a Two-Station Molecular Shuttle. Unusually for an active-template reaction, the metal binding site in the rotaxane-forming Diels−Alder cycloaddition remains essentially unchanged in the rotaxane product. To demonstrate the utility of this feature in more complex rotaxanes, molecular shuttle **8a**:**8a′** was prepared from pyridine-containing dienophile building block **7** and diene **3** (Scheme 2). The yield of [2]rotaxane **8a**:**8a′** (42%) was remarkably good and a high (*1,4*)/(*1,3*) ratio (95:5) was maintained despite the presence of the pyridine unit in building block **7**, which can compete with the macrocycle for complexation with the Lewis acid, offering the building blocks an unhindered site for the Lewis acid-catalyzed reaction to form the thread. The pyridine unit and the α-carbonyl imidazolidone functionalities that persist in [2]rotaxane **8a**:**8a′** could be used as binding sites with different preferred coordination geometries to control the position of the metal-coordinated macrocycle on the thread (Scheme 3).

As with the simpler rotaxane **4a**:**4a′**, the room-temperature ^{1}H NMR spectrum of **8a**:**8a′** (400 MHz, 298 K, 9:1 CD_2Cl_2/CD_3CN) shows an upfield shift of the aliphatic and pyridine signals with respect to those of the noninterlocked thread, particularly H_{f-h}, $H_{\beta-\delta}$, and H_{k-m} (Figure 4a,b), indicating that the macrocycle moves freely but spends most of its time over the less-hindered parts of the thread. Upon the addition of 1 equiv of $Zn(OTf)_2$ to the NMR tube containing **8a**:**8a′**, the ^{1}H NMR spectrum became complex, suggesting that multiple coordinated species were present and probably in exchange. However, saturating all of the rotaxane binding sites by adding an additional 4 equiv of $Zn(OTf)_2$ (5 equiv total) led to a greatly simplified spectrum (Figure 4c). This spectrum shows significant upfield shifts of the α-carbonyl imidazolidone moiety (H_α, H_υ, H_u, and H_z) and downfield shifts of the pyridine station (H_{j-n}) with respect to the metal-free rotaxane (Figure 4b), indicating that the macrocycle is held over the α-carbonyl imidazolidone unit as part of a trigonal-bipyrimidal-coordinated Zn(II) complex while the thread pyridine group is coordinated to a second Zn(II) ion (structure [**8a**:**8a′**Zn_2]$L_2(OTf)_4$ in Scheme 3a). Demetalation (Na_4EDTA, RT, 1 h) of the zinc complex liberated the metal-free rotaxane **8a**:**8a′**.

Addition of $PdCl_2$ to **8a**:**8a′** results in formation of a different rotaxane complex, [**8a**:**8a′**Pd]Cl_2 (Scheme 3c). However, in the ^{1}H NMR spectrum of [**8a**:**8a′**Pd]Cl_2 (Figure 4d), it is the protons adjacent to the thread pyridine unit (H_j and H_n) that are shielded by the macrocycle aromatic rings (consistent with the chemical shifts of a previously reported[17] palladium-complexed rotaxane), while signals of the α-carbonyl imidazolidone moiety appear at chemical shifts similar to those of the noninterlocked thread (Figure 4b). Demetalation of [**8a**:**8a′**Pd]Cl_2 with KCN ($MeOH/CH_2Cl_2$ 1:1, RT, 1 h) again afforded metal-free [2]rotaxane **8a**:**8a′**.

Conclusions

The Diels−Alder cycloaddition is one of the most celebrated and best-known transformations in organic synthesis. Its use to form rotaxanes in high yields (up to 91%) through an active-template reaction is yet another indication of its tremendous versatility.[18] The Diels−Alder reaction is unusual among active-template reactions in that it produces rotaxanes in which the metal binding sites on both the macrocycle and the thread persist in the rotaxane. This can be exploited to construct molecular shuttles in which the position of the macrocycle can be controlled by the coordination requirements of metal ions coordinated to the rotaxane. Such metal-ion-switchable systems have historically required lengthy syntheses (10−20 steps),[19] so the active-template Diels−Alder reaction should provide a valuable addition to methods for the assembly of interlocked molecular-level architectures.

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Experimental Section

General Experimental Procedure for Diels−Alder Active Template Rotaxane Synthesis. A dry Schlenk tube was charged with Zn(II) or Cu(II) triflate (1.0 equiv, 0.014 mmol) and macrocycle (1.0 equiv, 0.014 mmol) under a nitrogen atmosphere. Dry CH_2Cl_2 (0.5 mL) was added, and the mixture was stirred at room temperature for 30 min. A solution of acryloyl imidazolidone stopper **2** (1.2 equiv, 0.017 mmol) in dry CH_2Cl_2 (0.5 mL) was added, and the mixture was stirred for a further 30 min. The mixture was cooled to −78 °C and stirred for 5 minutes, after which a solution of diene **3** (2 equiv, 0.028 mmol) in dry CH_2Cl_2 (0.5 mL) was added. The reaction mixture was stirred at −78 °C for 2 days and then allowed to stir at room temperature for a further two days. The reaction was quenched with ammonia (35% in water), and the aqueous layer was extracted twice with CH_2Cl_2. The organic layers were combined, washed three times with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by column chromatography (5:45:55 MeCN/hexane/CH_2Cl_2) provided the [2]rotaxane as a colorless film (**4a**, 83%; **4b**, 91%; **8a**, 42%). Full details of the experimental procedures and compound characterizations are given in the Supporting Information.

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Supporting Information Available: Experimental procedures and spectral data for all compounds and details of the X-ray analyses of [**1a**Zn]Cl_2, [**1b**Zn]Cl_2, [**1c**Zn]Cl_2, and [**1a**Cu]Cl_2, including CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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