Molecular Shuttles

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Active Template Synthesis of Rotaxanes and Molecular Shuttles with Switchable Dynamics by Four-Component Pd^{II}-Promoted Michael Additions**

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Active template synthesis,[1] in which a substrate acts as both the template for a threaded complex and the catalyst for the covalent bond forming step that captures the interlocked product, is a new addition to the strategies available[2,3] for the assembly of rotaxanes. Unlike traditional "passive template" methods,[3] the intercomponent interactions responsible for rotaxane formation in an active template reaction do not normally "live on" in the final product.[4] Removing the need for permanent recognition features increases the structural diversity that can be introduced into interlocked architectures but also loses one of the key features of rotaxanes that has been so successfully exploited in the early generations of artificial molecular machines.[5] Herein we report on the first active template reaction in which the template interactions between macrocycle and thread persist in the resulting rotaxane. A macrocycle-coordinated palladium(II) center promotes the formation of carbon–carbon bonds between three other building blocks by successive Michael additions while positioning the reactants so that the final covalent bond forms through the macrocycle to produce [2]rotaxanes in up to 99% yield (Scheme 1 and Table 1). The Pd–nitrile coordination bond that directs and controls the synthesis is retained in the rotaxane product, enabling the preparation of both degenerate station molecular shuttles (with controllable dynamics, Scheme 2) and stimuli-switchable molecular shuttles (Scheme 1) through a simple one-pot multicomponent assembly process.

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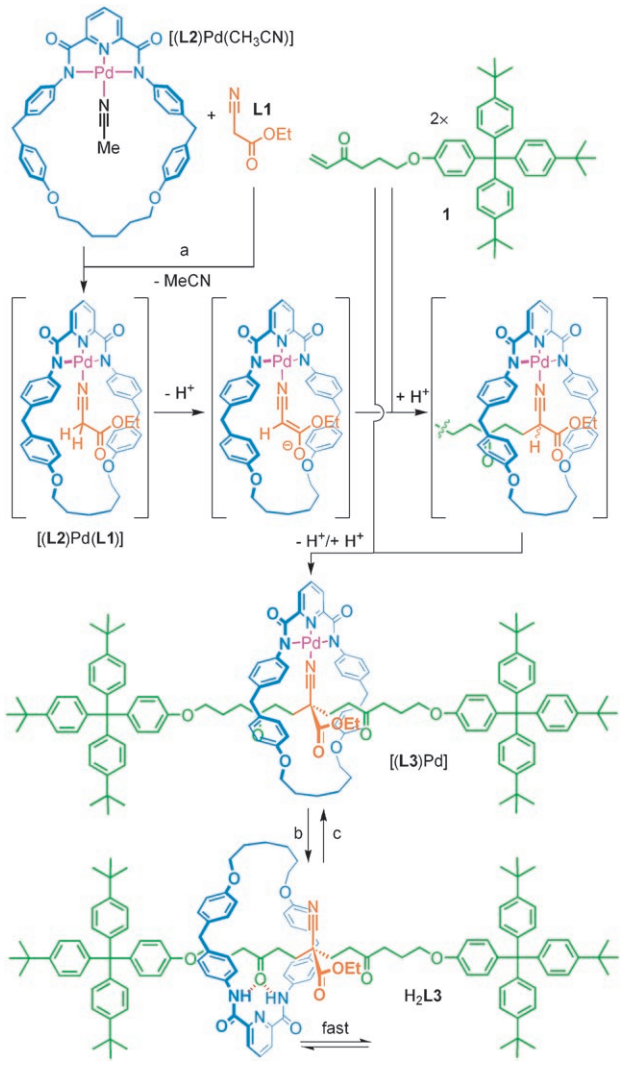
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. Synthesis of metal-coordinated [2]rotaxane [(**L3**)Pd] by an active template Pd^{II}-promoted double Michael addition, and its decomplexation to hydrogen-bonded molecular shuttle H_2**L3**. a) DIPEA, CH_2Cl_2 (see Table 1 for the effects of reagent stoichiometry on the yield of rotaxane [(**L3**)Pd]); b) 1 M HCl (aq):CH_2Cl_2 (1:1), reflux, 92%. In $CDCl_3$ the macrocycle in H_2**L3** shuttles rapidly on the NMR time-scale between the two thread ketone groups, even at 250 K; c) Pd(OAc)$_2$ (2.2 equiv), CH_3CN:CH_2Cl_2 (1:1), 18 h, 313 K, 99%.

The basis for the recognition-element-persistent active template reaction lies in a range of tridentate pyrroloimidazolone[6] and bisoxazoline[7] pincer Pd^{II} complexes that

Table 1: Optimization of the active template Pd^{II}-promoted Michael addition synthesis of rotaxane [(**L3**)Pd][a]

Entry	Thread components [equiv][b]	DIPEA [equiv]	Total conversion [%][c]	Yield of [(**L3**)Pd] [%]
1[d]	1.0	1.0	69	47
2[e]	1.0	0.1	70	53
3[f]	1.0	0.1	76	60
4[f]	1.5	0.1	77	85
5[f]	2.0	0.1	71	96
6[f]	2.5	0.1	67	>99

[a] Reaction conditions: [(**L2**)Pd(CH_3CN)], thread components **1** (×2) and **L1**, DIPEA, CH_2Cl_2. [b] 2:1 stoichiometry of **1**:**L1**. [c] For **L1** + [(**L2**)Pd(CH_3CN)] + 2×**1** → [(**L3**)Pd] + noninterlocked thread. [d] 5 days at room temperature. [e] 19 days at room temperature. [f] 7 days at 313 K.

catalyze asymmetric 1,4-conjugate additions of α-cyano esters to alkyl vinyl ketones in the presence of *N*,*N*-diisopropylethylamine (DIPEA).[8] It seemed that a suitably constructed tridentate macrocycle–Pd^{II} complex[9] might promote the double Michael addition between ethyl cyanoacetate (**L1**) and two suitably derivatized vinyl ketone "stoppers" (**1**) to generate [2]rotaxanes with the intercomponent recognition motif intact (Scheme 1).

Palladium(II)–macrocycle complex [(**L2**)Pd(CH_3CN)] was prepared in five steps from commercially available materials (see the Supporting Information). Treatment of [(**L2**)Pd(CH_3CN)] with ethyl cyanoacetate in CH_2Cl_2 and subsequent removal of the solvent and acetonitrile under reduced pressure afforded complex [(**L2**)Pd(**L1**)], which crystallized from a saturated solution in CH_2Cl_2/Et_2O in a form suitable for investigation by X-ray diffraction.[10] The solid-state structure of both [(**L2**)Pd(**L1**)] (Figure 1a and b) and [(**L2**)Pd(CH_3CN)] (see the Supporting Information)

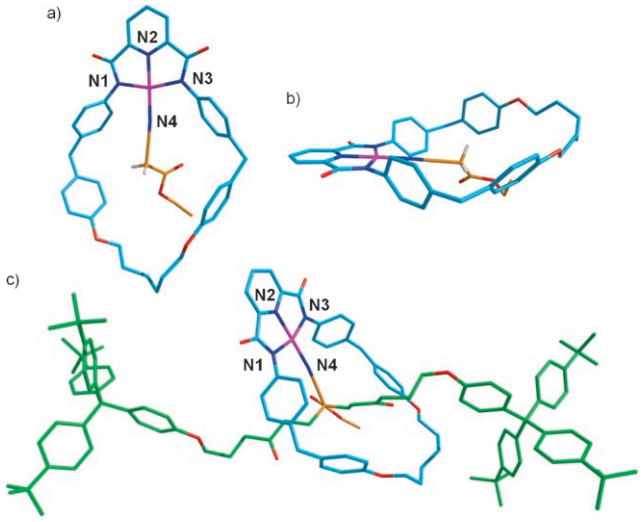


Figure 1. X-ray crystal structures[10] of [(**L2**)Pd(**L1**)] from a) face-on and b) side-on views and c) rotaxane [(**L3**)Pd]. Selected bond lengths [Å] and angles [°]: [(**L2**)Pd(**L1**)]: N1–Pd 2.02, N2–Pd 1.92, N3–Pd 2.04, N4–Pd 2.02; N1-Pd-N3 161.7, N2-Pd-N4 177.9. [(**L3**)Pd]: N1–Pd 2.02, N2–Pd 1.92, N3–Pd 2.03, N4–Pd 2.00; N1-Pd-N3 161.8, N2-Pd-N4 178.9.

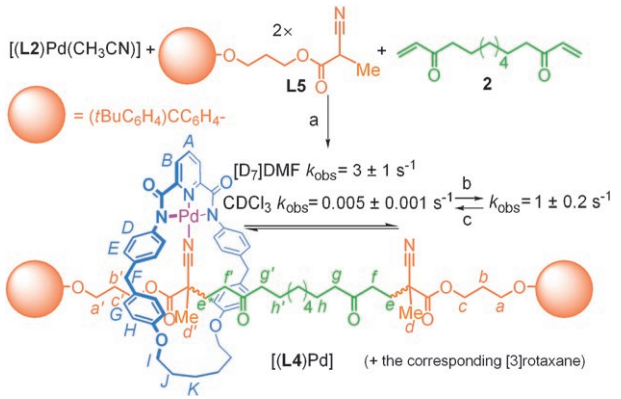
shows that the coordination mode[11] of $\mathbf{L2}^{2-}$ and the shape of the ring holds the nitrile ligand occupying the fourth Pd^{II} coordination site centrally within the macrocycle cavity. The crystal structures suggested that the first alkylation of the α-methylene group should result in one face of the macrocycle being blocked such that the second Michael addition must proceed from the other side, generating a [2]rotaxane.

Pleasingly, the four component assembly of [(**L2**)Pd(CH_3CN)], **1** (×2), and **L1** at room temperature in CH_2Cl_2 in the presence of DIPEA led to [2]rotaxane [(**L3**)Pd], initially in 47% yield (Scheme 1 and Table 1, entry 1). The assignment of [(**L3**)Pd] as a rotaxane was initially made by mass spectrometry (no dissociation of the components observed in the fragmentation pattern without cleavage of a stopper) and ^1H NMR spectroscopy (for a stack plot of the spectra of [(**L3**)Pd] and the corresponding thread showing upfield shifts of the encapsulated regions of the rotaxane axle,[12] see the Supporting Information). Confirmation of the mechanically interlocked structure came from demetalation of [(**L3**)Pd] (1M HCl (aq):CH_2Cl_2 (1:1), 92%, Scheme 1, step b), which gave the weakly hydrogen bonded rotaxane H_2**L3** rather than the dethreaded components. The ^1H NMR spectrum (see the Supporting Information) shows that the macrocycle in H_2**L3** preferentially resides over, and rapidly shuttles between, the two thread ketone groups in $CDCl_3$, even at 250 K. Finally, single crystals of [(**L3**)Pd] were grown from a saturated solution in butanone/methanol. The solid-state structure[10] (Figure 1c) confirms that the Pd–nitrile coordination bond is maintained in the metalated rotaxane and is responsible for holding the macrocycle and thread in the well-defined co-conformation observed in solution.

The rotaxane-forming reaction shown in Scheme 1 was optimized in terms of reagent stoichiometry and conditions (Table 1). The amount of base was decreased to 10 mol% to minimize the background non-palladium promoted reaction (Table 1, entry 2).[13] A concomitant increase in reaction temperature (to 313 K,[14] Table 1, entry 3) was then required for the reaction to achieve significant conversion within a reasonable timeframe (76% yield of double Michael addition products after 7 days). Under these conditions and using a modest excess of the thread building blocks (2.5 versus 1.0 equiv), the yield of [2]rotaxane [(**L3**)Pd] was increased to over 99% (Table 1, entry 6). Thus, this active template reaction is among the most efficient, albeit rather slowly proceeding, rotaxane-forming procedures reported to date.

Since the nitrile functionality is preserved in the product of the active template reaction, it can in principle be used as a binding site or "station" for the macrocycle–Pd component in a molecular shuttle. To incorporate two such units into a rotaxane, the reaction pattern for formation of the thread was reversed, so that shuttle [(**L4**)Pd] was synthesized by Michael additions of two "mono-stoppered" α-cyano esters (**L5**) to bis(vinyl ketone) spacer **2** in the presence of [(**L2**)Pd(CH_3CN)] (Scheme 2, step a).

There are few examples[15] of metal-complexed molecular shuttles, and the investigation of their dynamics is of interest. At room temperature in $CDCl_3$, the exchange of the palladium-coordinated macrocycle between the thread nitrile groups in [(**L4**)Pd] is slow on the NMR timescale. Ligand



Scheme 2. Active template synthesis of a metal-coordinated molecular shuttle, [(**L4**)Pd], with stimuli-responsive dynamics. a) **L5** (2 equiv), **2** (1 equiv), [(**L2**)Pd(CH_3CN)] (1 equiv), DIPEA (0.1 equiv), CH_2Cl_2, 313 K, 5 days; 27% [2]rotaxane [(**L4**)Pd] + 32% of the corresponding [3]rotaxane; b) pyridine (1 equiv); c) TsOH (1 equiv).

exchange at Pd^{II} centers proceeds predominately via associative pathways,[16] possibly through folding at the low concentrations employed herein, and no assistance for this mechanism is intrinsically available from noncoordinating solvents such as $CDCl_3$. Two-dimensional exchange spectroscopy (2D-EXSY)[17] gave the room-temperature pseudo-first-order rate constant $k_{obs} = 5 \times 10^{-3}\ s^{-1}$, which is equivalent to an activation free energy of approximately 20 kcal mol^{-1} (details of the kinetic measurements are given in the Supporting Information). In [D_7]DMF, the separated signals in the ^{1}H NMR spectrum caused by slow shuttling of the macrocycle at room temperature (Figure 2b) coalesced at 390 K (Figure 2c). EXSY experiments at 300 K determined the shuttling rate in [D_7]DMF ($k_{obs} = 3\ s^{-1}$) to be 600 times faster than in $CDCl_3$, corresponding to a rate k_{bi} for the bimolecular process involving solvent participation of $0.2\ M^{-1}s^{-1}$.

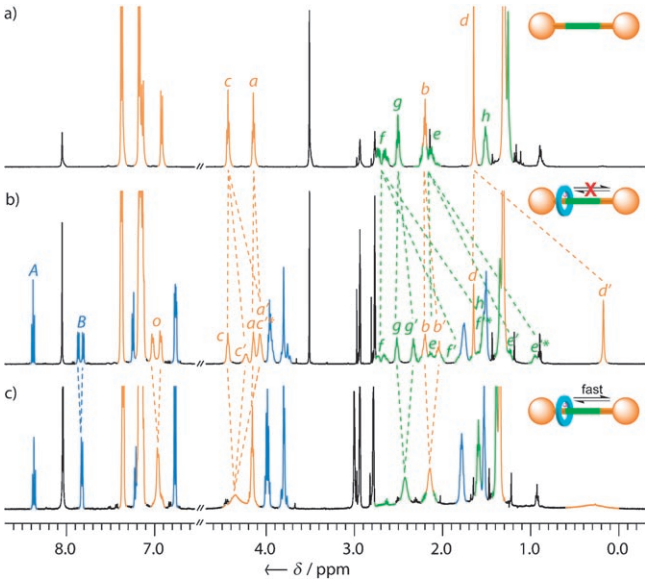


Figure 2. Partial ^{1}H NMR (500 MHz, [D_7]DMF) spectra of a) the free thread at 298 K; b) molecular shuttle [(**L4**)Pd] at 298 K; and c) molecular shuttle [(**L4**)Pd] at 390 K. The assignments correspond to the lettering shown in Scheme 2. Signals labeled * are parts of sets of diastereotopic protons.

A bimolecular mechanism could also be made to operate in $CDCl_3$ by simply adding pyridine (Scheme 2, step b). EXSY experiments showed that at 300 K addition of just one equivalent of pyridine led to a 200-fold increase in the rate of macrocycle shuttling in [(**L4**)Pd] to $1\ s^{-1}$, corresponding to a bimolecular rate constant $k_{bi} = 95\ M^{-1}s^{-1}$. In other words, a molecule of pyridine is around 500 times more effective at accelerating the shuttling rate in [(**L4**)Pd] than a molecule of DMF.[18]

Subsequently neutralizing the added pyridine with one equivalent of TsOH (Scheme 2, step c) returned the shuttling rate to its original value in $CDCl_3$, providing powerful and reversible control over the macrocycle dynamics by reagent addition.

The Pd^{II}-catalyzed Michael addition of α-cyano esters to vinyl ketones provides an exceptionally high yielding multicomponent active metal template reaction in which the template motif is retained in the rotaxane product. The reaction is operationally simple to perform and can generate [2]rotaxanes in essentially quantitative yields with only a modest excess of the thread-forming components. The reaction can be applied to the construction of metal-complexed molecular shuttles in which the dynamics of the shuttling can be controlled by the addition of external reagents. The search for other active template reactions that offer different or improved rotaxane design features compared with existing strategies is ongoing in our laboratory.

Experimental Section

Experimental procedure for the active template synthesis of rotaxane [(**L3**)Pd]: DIPEA (0.7 μL, 0.004 mmol) was added to a solution of [(**L2**)Pd(CH_3CN)] (30 mg, 0.040 mmol), **1** (120 mg, 0.20 mmol), and **L1** (10.7 μL, 0.10 mmol) in CH_2Cl_2 (0.4 mL). The solution was stirred for 7 days at 313 K after which time the solvent was removed under reduced pressure and the crude residue was subjected to column chromatography on silica gel (0–1% MeOH in CH_2Cl_2, gradient elution) to yield [(**L3**)Pd] as a yellow solid (81 mg, 99%). Full details and compound characterization are provided in the Supporting Information.

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[10] The crystal data and experimental details of the structural refinement for [(**L2**)Pd(CH_3CN)], [(**L2**)Pd(**L1**)], and [(**L3**)Pd] are provided in the Supporting Information. CCDC-670786 ([(**L2**)Pd(CH_3CN)]), CCDC-670785 ([(**L2**)Pd(**L1**)]), and CCDC-670784 ([(**L3**)Pd]) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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