Rotaxanes

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A Catalytic Palladium Active-Metal Template Pathway to [2]Rotaxanes**

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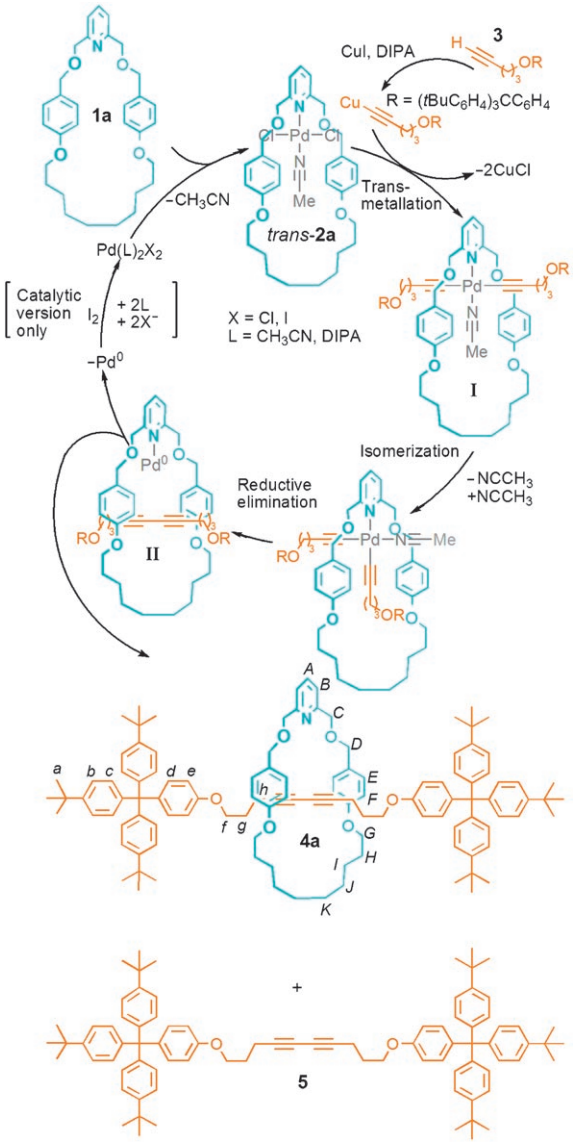
The preparation of rotaxanes and other mechanically interlocked molecules by the oriented assembly of ligands around metal ions is a classic demonstration[1] of the utility and effectiveness of template-directed synthesis.[2] However, besides organizing the organic fragments through its preferred coordination geometry, the metal template is usually otherwise passive during such reactions. To exploit the richness of the metal's chemistry more fully in synthesis, we recently started to explore a strategy for rotaxane formation in which the metal plays a dual role, acting as both a template for threading and catalyzing covalent-bond formation.[3] Unlike "passive" template methodologies, in which the rotaxane product is normally a better ligand for the metal than the non-interlocked components, this type of "active" template can, in principle, be made to work substoichiometrically. The feasibility of such an approach was first demonstrated[3] using tetrahedral Cu^{I} centers, which is both the most well-established[1b,h,4] coordination geometry for metal template rotaxane-forming reactions and an extremely structurally tolerant catalyst[5] for the azide–alkyne 1,3-cycloaddition (a so-called "click" reaction[6]). Herein we report an application of the active-metal template concept to palladium chemistry, which is rather more demanding in terms of template geometry, but somewhat more significant in terms of catalysis.

The explosive growth in the number and variety of palladium-catalyzed transformations over the latter part of the 20th century has seen palladium become the workhorse of modern synthetic chemistry.[7] Palladium-catalyzed processes include the formation of C–O, C–N, C–S, and, most notably, C–C bonds.[7] Although Pd^{II} has a square-planar coordination geometry, it has proved possible to use its two-dimensional motif to assemble rotaxanes[8] and catenanes[9] in classical passive template strategies by utilizing steric control over the required crossover point in the third dimension.[10]

Macrocycle **1a** (Scheme 1)[9] was chosen as a suitable candidate ligand for developing a palladium active-template rotaxane synthesis. X-ray crystallography of a related palladium(II) [2]catenate shows that the *trans*-coordinated chloride ligands protrude out of opposite sides of the macrocycle



Scheme 1. Pd^{II}-mediated active-metal template synthesis of [2]rotaxane **4a**. For yields and conditions see Table 1.

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cavity.[9b] We reasoned that if the chloride ligands of *trans*-**2a**[9b] could be replaced by suitably functionalized stopper groups it would generate a threaded complex (e.g. **I**, Scheme 1). If the palladium center is able to retain the stoppered ligands until it has mediated a covalent bond forming reaction between them (**II**, Scheme 1), a [2]rotaxane would be formed.

This idea was investigated using the palladium(II)-mediated homocoupling of terminal alkynes (Scheme 1).[11–13] Complex *trans*-**2a** was treated with 2.5 equivalents of an appropriately derivatized alkyne (**3**) and CuI (5 mol% with respect to **3**) in diisopropylamine (DIPA; Table 1, entry 1).[14]

Table 1: Effect of reactant stoichiometry and experimental conditions on the Pd^{II}-mediated active-metal template synthesis of [2]rotaxane **4a**.[a]

Entry	**1a** [equiv]	*trans*-**2a** [equiv]	**3** [equiv]	I_2 [equiv]	*t* [h]	Conversion **3** → **4** + **5** [%]	Yield[d] of **4a** [%]
1[b]	–	1	2.5	–	12	>98	43
2[b]	–	1	10	–	12	>98	61
3[b]	0.9	0.1	10	0.5	12	37	<1
4[c]	0.9	0.1	10	0.5	12	57	27
5[c]	0.9	0.1	10	0.5	24	83	35
6[c]	0.95	0.05	15	0.5	72	94	81
7[c]	0.95	0.05	30	0.5	72	49	90

[a] Reactions were carried out at 298 K[18] using anhydrous solvents and protected from moisture (see the Experimental Section);[19] [b] 10 mM *trans*-**2a**, CuI (5 mol% with respect to **3**), DIPA; [c] 14 mM macrocycle (**1a** + *trans*-**2a**) CuI (5 mol% with respect to **3**), DIPA (5 equiv), benzene; [d] with respect to **1a** + *trans*-**2a**.

We were delighted to find that after 12 h at room temperature the desired [2]rotaxane **4a** was formed in 43% yield (based on **2a**). The homocoupling reaction essentially proceeded to completion (>98% conversion into the diyne products, rotaxane **4a**, and non-interlocked thread **5**).[15] Carrying out the reaction using a fivefold excess of **3** increased the yield of [2]rotaxane **4a** to 61% (Table 1, entry 2).

The ^{1}H NMR spectrum of **4a** in $CDCl_3$ (Figure 1b) shows an upfield shift of several signals with respect to the non-interlocked components (Figure 1a,c,d). The shielding, which is typical of interlocked architectures in which the aromatic rings of one component are positioned face-on to another component, occurs for all the nonstopper resonances of the axle (H_{f-h}), indicating that in the metal-free rotaxane the macrocycle is able to access the full length of the thread.[16]

The proposed mechanism for rotaxane formation is shown in Scheme 1. Standard Pd ligand-substitution chemistry[7,17] means that under transmetalation the acetylide units should directly replace the chloride ligands of *trans*-**2a**, initially retaining their relative stereochemistry and thus leading to the threaded *trans* palladium bis(alkyne) adduct **I**. Isomerization of **I** to the *cis* geometry necessary for the reductive elimination must occur without breaking either Pd–acetylide bond, as models show that the unthreaded isomer of the *cis* complex (which would generate noninterlocked macrocycle **1a** and thread **5** rather than [2]rotaxane **4a**) would be preferred on steric grounds. Reductive elimination then generates the Pd^0–rotaxane complex **II** and decomplexation of the weakly binding Pd^0 liberates the free rotaxane **4a**.

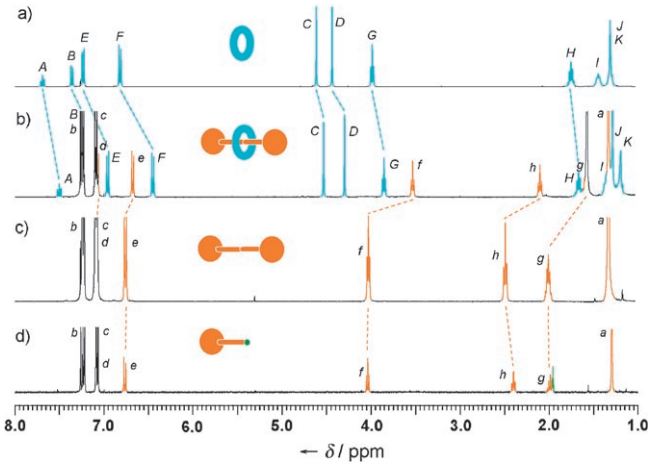
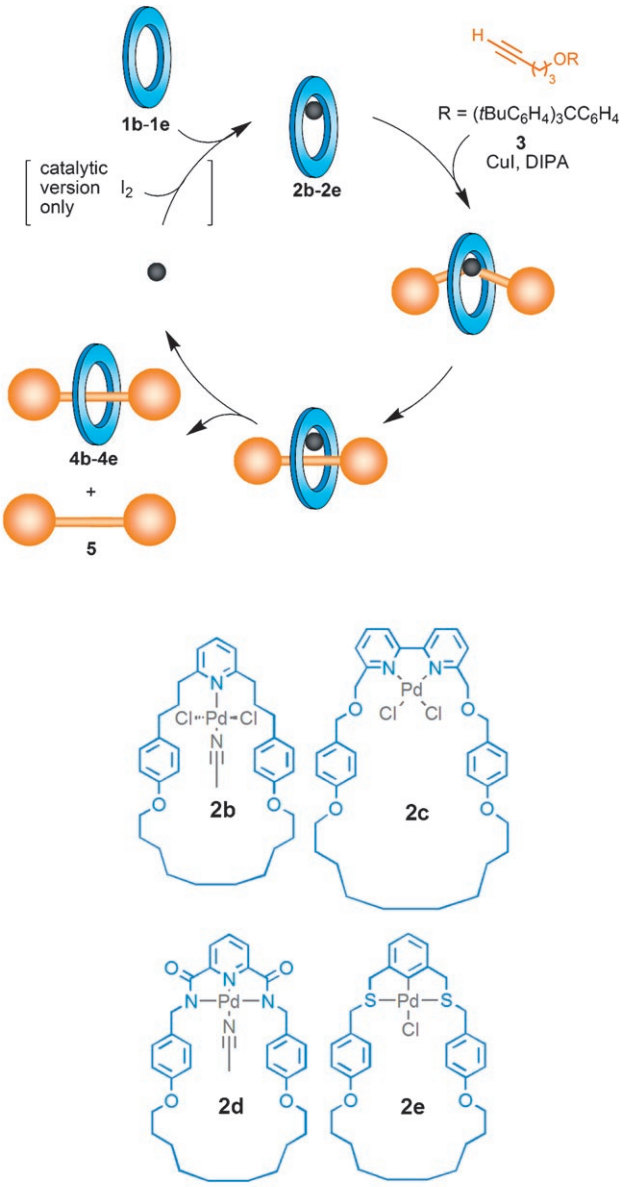


Figure 1. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 300 K) of a) macrocycle **1a**, b) [2]rotaxane **4a**, c) thread **5**, d) half-thread **3**. The assignments correspond to the lettering shown in Scheme 1.

Having achieved an efficient stoichiometric version of the active-metal template reaction, we turned our attention towards developing a synthesis that was catalytic with respect to palladium (Table 1, entries 3–7). This requires the metal to turn over as both a template and a covalent bond forming catalyst. The palladium-mediated alkyne homocoupling reaction is particularly well-suited in this respect because diyne formation is accompanied by reduction of the Pd^{II} to intrinsically weaker coordinating Pd^0. A combination of iodine and oxygen is typically used as the oxidant to render such reactions catalytic.[7]

We initially tried conditions similar to those employed in the stoichiometric rotaxane-forming reaction, but using 10 mol% of *trans*-**2a** in the presence of I_2 (Table 1, entry 3). However, no rotaxane was produced under these conditions and the overall conversion of alkyne to diyne was only 37%. Switching from DIPA to benzene as the solvent led to a significant improvement in both the total yield of diyne products and the formation of [2]rotaxane **4a** (57% and 27%, respectively, entry 4). Increasing the reaction time from 12 to 24 h gave further improvements (83% diyne products; 35% [2]rotaxane, entry 5). Finally, increasing the equivalents of **3**, reducing the loading of **2a** to 5 mol% with respect to **1a**, and further extending the reaction time to 72 h improved the yield of rotaxane **4a** to up to 90% (entries 6 and 7).[18,19]

We used the mono- (**2b**), bi- (**2c**), and tridentate (**2d** and **2e**) macrocycles shown in Scheme 2 (their syntheses are detailed in the Supporting Information) to explore the influence of the nature of the macrocyclic ligand on the active-metal template reaction.[20] Reaction of **2b** or **2c** under the standard stoichiometric conditions resulted in the formation of the corresponding [2]rotaxanes **4b** and **4c**[21] in 38% and 10% yields, respectively (Table 2, entries 1 and 4). The low yield obtained with the bidentate complex **2c** presumably reflects the fact that the two chloride ligands are necessarily *cis* for transmetalation. Even with the larger



Scheme 2. Screening of different macrocyclic ligands for the palladium(II)-mediated active-metal template synthesis of [2]rotaxanes. For yields and conditions see Table 2.

macrocycle cavity of **2c** relative to **2a**, the *cis* orientation significantly decreases the chance of the two alkyne substitutions occurring through opposite faces of the macrocycle.[22] Carrying out the same reactions in the presence of 10 equivalents of **3** increased the yield of [2]rotaxane **4c** to 20% (Table 2, entry 5) but, to our surprise, resulted in a decrease in the yield of rotaxane **4b** from 38% to 30% (Table 2, entry 2). As expected, reaction of **3** with the tridentate palladium complexes **2d** and **2e** failed to generate any reaction products (Table 2, entries 7 and 8), as two labile coordination sites on the metal are necessary for the alkyne homocoupling mechanism (Scheme 1).

As found earlier for **4a** (Table 1, entries 2 and 7), the yield of rotaxane **4c** was greatly improved (from 20% to 76%; Table 2, entries 5 and 6) by changing from stoichiometric to catalytic palladium conditions. In contrast, the yield of rotaxane **4b** decreased to 14% under similar catalytic conditions, although the overall conversion into diyne products **4b**+**5** is a respectable 63% (Table 2, entry 3). It is possible that this disparity occurs because the benzylic oxygen atoms in **2a** can play a role in dynamic ligation to the palladium center. In their absence the macrocycle is a poorer ligand. Thus, when the amount of alkyne **3** present with respect to **2b** is increased (Table 2, entries 2 or 3), the excess alkyne is able to compete with the pyridine macrocycle for the palladium, thereby reducing the yield of rotaxane **4b**.

Table 2: Effect of macrocycle structure on the Pd^{II}-mediated active-metal template synthesis of [2]rotaxanes (Scheme 2).[a]

Entry	Macrocycle–Pd^{II} complex	**3** [equiv]	*t* [h]	Conversion **3**→ **4**+**5** [%]	Yield[e] of **4b–e** [%]
1[b]	**2b**	2.5	18	82	38
2[b]	**2b**	10	18	75	30
3[c]	**2b**	30	72	63	14
4[b]	**2c**	2.5	18	77	10
5[b]	**2c**	10	18	85	20
6[c]	**2c**	30	72	19	76
7[b]	**2d**	2.5	72	0[d]	0[d]
8[b]	**2e**	2.5	72	0[d]	0[d]

[a] Reactions were carried out at 298 K using anhydrous solvents and protected from moisture (see the Supporting Information); [b] stoichiometric conditions (10 mM **2b–e**): macrocycle–Pd complex **2b–e** (1 equiv), CuI (0.05 equiv), DIPA; [c] catalytic conditions (14 mM **1b**+**2b** or **1c**+**2c**): macrocycle **1b** or **1c** (0.95 equiv), macrocycle–Pd complex *trans*-**2b** or *cis*-**2c** (0.05 equiv), benzene, CuI (5 mol% with respect to **3**), I_2 (0.5 equiv), DIPA (5 equiv); [d] no diyne product was detected; [e] with respect to **2b–e** (entries 1, 2, 4, 5, 7 and 8), **1b**+**2b** (entry 3), or **1c**+**2c** (entry 6).

It is interesting to note that the catalytic conditions with **2a** and **2c** provide much cleaner conversions and higher yields of [2]rotaxanes than the stoichiometric conditions. The use of stoichiometric amounts of Pd^{II}, especially with the solvent concentrations of DIPA required for high conversions in the stoichiometric reactions, probably gives rise to side-reactions and other macrocycle–Pd species that do not afford [2]rotaxane.

The template-directed assembly of otherwise difficult-to-access molecules and the catalysis of covalent-bond formation are two of the most useful tasks that transition metals can perform in organic chemistry. The present work demonstrates that the currently rare combination of these apparently disparate functions can produce high-yielding, mild, and effective synthetic routes to complex molecular architectures that require only substoichiometric amounts of metal. Studies directed towards the design and development of other active template systems are in progress.

Experimental Section

General procedure for catalytic rotaxane synthesis: A 5-mL round-bottomed flask, equipped with a drying $CaCl_2$ tube, was charged with a solution of the terminal alkyne **3** (484 mg, 0.84 mmol) in anhydrous benzene (2 mL). Diisopropylamine (28 mg, 0.28 mmol), copper

iodide (8 mg, 42.0 μmol), macrocycle **1a–c** (26.6 μmol), and iodine (4 mg, 14.0 μmol) were added sequentially. A solution of the corresponding palladium–macrocycle complex **2a–c** (1.4 μmol) in anhydrous benzene (1 mL) was slowly added over a period of 12 h with a syringe pump. When addition was complete the reaction mixture was allowed to stir for a further 72 h after which time the crude product was taken into a partition of dichloromethane and a saturated solution of sodium ethylenediaminetetraacetate (Na_4EDTA, 15 mL) and stirred for 1 h. The layers were separated and the aqueous layer extracted with dichloromethane (2×5 mL). The combined organic extracts were then washed with brine (15 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel to afford the corresponding [2]rotaxane (**4a** 90%; **4b** 14%; **4c** 76%).

Full details of the experimental procedures and compound characterization are given in the Supporting Information.

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[15] This reaction is ligand-accelerated: Repeating the reaction with $Pd(MeCN)_2Cl_2$ in place of *trans*-**2a** resulted in only 20% conversion into the homocoupled product **5** during the same reaction time.
[16] All rotaxanes were fully characterized by ^{1}H and ^{13}C NMR spectroscopy, as well as LRESI-MS and HRMS. ^{1}H NMR stack plots of [2]rotaxanes **4b** and **4c** with their non-interlocked components are provided in the Supporting Information.
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[18] Attempts at increasing the reaction rate by heating to 50 °C, with the other reaction conditions as for Table 1, entry 6, resulted in a lower yield of rotaxane **4a** (47%) and lower overall conversions into diyne products (52%).
[19] Several control reactions were carried out to confirm the necessity of both Pd and Cu. When the conditions used for Table 1, entry 2 (i.e. stoichiometric) or Table 1, entry 6 (i.e. catalytic) were repeated in the absence of Pd (i.e. with macrocycle **1a** replacing the Pd complex **2a**), no diyne products were detected by ^{1}H NMR spectroscopy. Thus, under these conditions the Cu^{I}-mediated Glaser alkyne homocoupling[11] does not operate to any significant extent (< 1%). Similarly, when the same reactions were run in the absence of CuI instead of in the absence of Pd, no diyne products were detected by ^{1}H NMR spectroscopy.
[20] The pyridine coordination site on the macrocycle is crucial for rotaxane formation. When the conditions used for Table 1, entry 1 were repeated with the non-pyridine version of macrocycle **1a** (pyridine replaced by benzene), no rotaxane was detected and non-interlocked thread **5** was formed in only 19% yield after 3 days. See the Supporting Information for further details.
[21] A further decomplexation reaction using KCN in MeOH/CH_2Cl_2 was necessary before [2]rotaxane **4c** could be isolated.
[22] For an X-ray crystal structure of **2c** and the corresponding crystallographic data, see the Supporting Information.

