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[2]Rotaxanes through Palladium Active-Template Oxidative Heck Cross-Couplings

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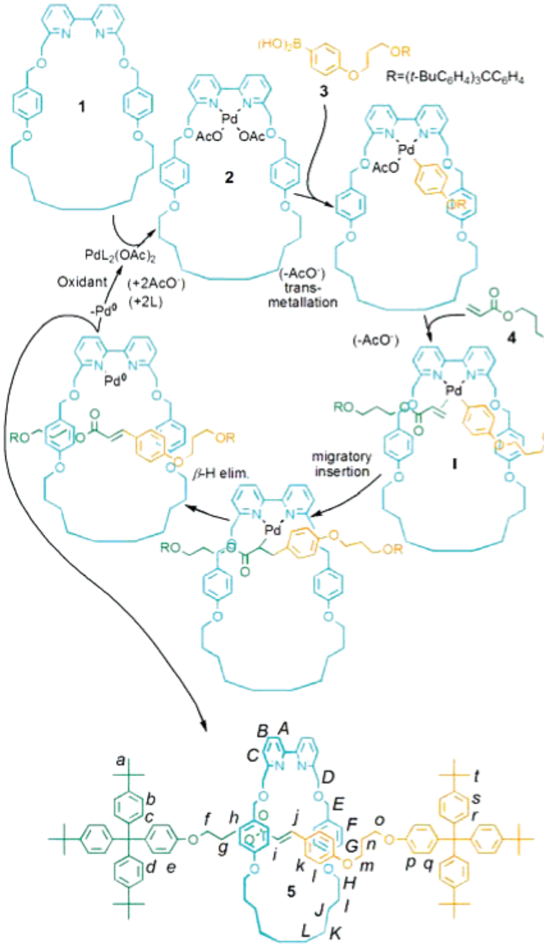
Palladium-catalyzed cross-coupling reactions are extremely powerful tools for organic synthesis, routinely proving the method of choice for the construction of C−C bonds.[1] Recently, Pd(II)-catalyzed cross-couplings have been developed as a novel alternative to the traditional Pd(0) systems, offering a change in both mechanism and reaction parameters.[2] Here we report on the utility of the Pd(II)-catalyzed oxidative Heck cross-coupling over Pd(0)-based methods in the active-metal template synthesis of [2]-rotaxanes.

Active-template syntheses differ from classical template reactions in that a single species acts as both a template AND a catalyst for covalent bond formation.[3] Combining these two roles within the action of the same metal center(s) has several potential advantages over conventional "passive" template syntheses, including inherent efficiency, scope, the possibility of traceless assembly, and—if it is able to turnover at the end of the catalytic cycle—only substoichiometric quantities of the template need to be employed.

The active-template concept has been demonstrated through the synthesis of rotaxanes using reactions such as the Cu(I)-catalyzed azide-alkyne cycloaddition—the CuAAC "click" reaction—and alkyne homocouplings.[3,4] However, to make active-template strategies truly attractive, it will be necessary to apply them to reactions that are synthetically versatile and applicable to a wide variety of different structural motifs. Palladium-catalyzed cross-couplings fit these criteria perfectly, of course. However, our initial attempts to make rotaxanes using Pd(0)-catalyzed reactions with various mono-, bi-, and tridentate macrocycles were unsuccessful, producing only the corresponding non-interlocked threads.[5] We attributed this to the Pd(0) not remaining attached to the macrocycle during key stages of the catalytic cycle. Accordingly, we switched our attention to the oxidative Heck cross-coupling[2] since Pd(II) should be ligated much more strongly than Pd(0) by nitrogen donor atoms[6] in macrocycles such as **1**.

Palladium(II) complex **2** was formed in situ by mixing macrocycle **1** (1 equiv) with a catalytic quantity (10 mol %) of $Pd(OAc)_2$ in 1:1 $CHCl_3/CH_2Cl_2$. Addition of boronic acid **3** (2 equiv), alkene **4** (1 equiv), and benzoquinone (1 equiv), followed by simple stirring under an atmosphere of oxygen at room temperature for 72 h, pleasingly led to the desired [2]rotaxane **5** in 73% yield.[7,8] These base-free conditions produced much higher yields of rotaxane **5** than standard oxidative Heck procedures,[2h] presumably because the formation of undesired homocoupled byproducts is reduced. Reducing the amount of Pd to 1 mol % still produced 66% [2]rotaxane (i.e., the metal template turns over 65 times during the reaction), albeit over a 16 day reaction time.

Scheme 1. Proposed Catalytic Cycle for the Oxidative Heck Active-Template Synthesis of [2]Rotaxane **5** from **1**, **3**, and **4**



+ the corresponding non-interlocked thread. **6**

The proposed mechanism for rotaxane formation is shown in Scheme 1. Transmetalation of the aryl boronic acid **3** with the Pd(II) complex **2**, followed by π-coordination of alkene **4**, affords intermediate **I**. In order to achieve successful rotaxane formation, the two building blocks that ultimately form the thread need to be held on opposite faces of the macrocycle and the palladium needs to retain the stoppered ligands until it has mediated a covalent bond-forming reaction between them. Migratory insertion followed by β-H elimination thus forms a mechanical as well as a covalent bond. Decomplexation of the weakly binding Pd(0) liberates free rotaxane **5**. Reoxidation of Pd(0) to Pd(II) regenerates the catalytically active complex **2** and enables the reaction to be conducted using substoichiometric amounts of palladium.

The ^1H NMR spectrum of rotaxane **5** in $CDCl_3$ (Figure 1b) shows an upfield shift of several signals with respect to the non-interlocked components (Figure 1a and c). The shielding, typical of interlocked architectures in which the aromatic rings of one component are positioned face-on to another component, occurs for all nonstopper resonances of the axle (H_{f-o}), indicating that the macrocycle accesses the full length of the thread in the rotaxane. However, the resonances of the protons on the half of the axle bearing the aryl ring (H_{m-o}) are shielded to a greater extend than those on the other

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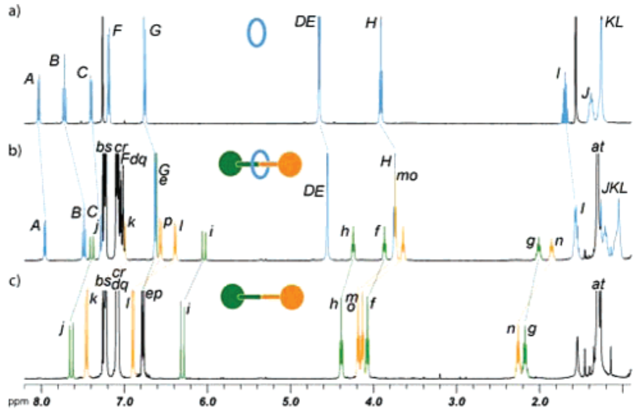
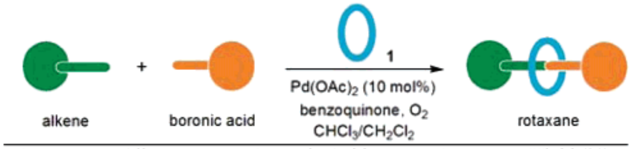
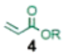
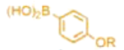
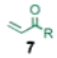
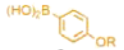
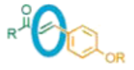
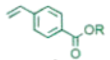
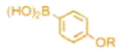
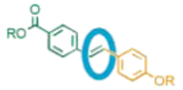
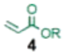
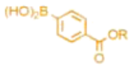
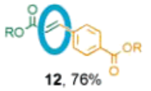
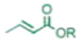
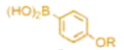
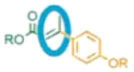
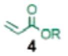


Figure 1. ^1H NMR spectra (400 MHz, $CDCl_3$, 298 K) of (a) macrocycle **1**, (b) [2]rotaxane **5**, (c) thread **6**. The assignments correspond to the lettering shown in Scheme 1.

Table 1. Substrate Scope in the Oxidative Heck Active-Template Synthesis of [2]Rotaxanes[a]



Entry	Alkene	Boronic Acid	Rotaxane, Yield (%)
1	 **4**	 **3**	 **5**, 73%
2	 **7**	 **3**	 **9**, 70%
3	 **8**	 **3**	 **10**, 50%
4	 **4**	 **11**	 **12**, 76%
5	 **13**	 **3**	 **14**, trace
6[b]	 **4**	 **15**	 **16**, 30%[10]

[a] R = $(t\text{-}BuC_6H_4)_3CC_6H_4O(CH_2)_3$–. Reaction conditions: macrocycle **1** (1 equiv), $Pd(OAc)_2$ (10 mol %), alkene (1 equiv), boronic acid (2 equiv), and benzoquinone (1 equiv) in 1:1 $CHCl_3/CH_2Cl_2$ were allowed to stir under O_2 at rt for 72 h. [b] Conditions as for other entries except alkene **4** (1.2 equiv), boronic acid **15** (3 equiv), no benzoquinone, 1:1 $CHCl_3$/DMF as solvent. All reactions were carried out at 16 mM concentration with respect to **1** without the need for dried or distilled solvents.

half (H_{f-h}). This preference of the macrocycle for the aromatic region of the thread is probably a result of both π-stacking interactions and solvation effects.

To examine if this new cross-coupling approach to [2]rotaxanes is tolerant of a range of different cross-coupling partners, we screened a number of alkene and boronic acid functionalized stoppers, generating a variety of [2]rotaxanes (Table 1).[9] Vinyl ketone **7** and styrene derivative **8** can replace vinyl ester **4** as the alkene cross-partner to produce the corresponding rotaxanes **9** and **10** in 70 and 50% yields, respectively. The electron-poor aryl boronic acid **11** can also be used in place of the electron-rich aryl boronic acid **3** without affecting the yield (**12**, 76%). The rotaxane-forming reaction, however, is sensitive to steric hindrance—although trisubstituted alkenes can be formed in high yields using the oxidative Heck method,[2h] the attempted coupling of disubstituted alkene **13** with boronic acid **3** resulted in only traces of the corresponding rotaxane **14**.[9] Alkene boronic acid **15** also proved suitable as a substrate, giving butadiene [2]rotaxane **16** in 30% yield.[10]

The introduction of active-template palladium cross-coupling routes to [2]rotaxanes opens up the possibility of using one of the most powerful bond-forming methodologies in organic chemistry for the assembly of mechanically interlocked architectures. The reaction is mild, substrate-tolerant, and essentially traceless with respect to the thread, and as little as 1% of the catalytic Pd(II) template is required.

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Supporting Information Available: Full experimental procedures and characterization of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) For stoichiometric active-metal template Ullman and Glaser coupling rotaxane syntheses, in which the metal does not turnover, see: Saito, S.; Takahashi, E.; Nakazono, K. *Org. Lett.* **2006**, *8*, 5133−5136.

(5) An outline of these macrocycle−Pd(0) investigations is given in the Supporting Information. Pd(0)-catalyzed Suzuki reactions have been used as the stoppering reaction in the synthesis of cyclodextrin rotaxanes; see: (a) Terao, J.; Tang, A.; Michels, J. J.; Krivokapic, A.; Anderson, H. L. *Chem. Commun.* **2004**, 56−57. (b) Klotz, E. J. F.; Claridge, T. D. W.; Anderson, H. L. *J. Am. Chem. Soc.* **2006**, 128, 15374−15375. (c) Stone, M. T.; Anderson H. L. *Chem. Commun.* **2007**, 2387−2389.

(6) Studies[2f−h] suggest that bidentate N ligands such as bipyridine and phenanthroline are the most effective at promoting oxidative Heck reactions at room temperature. Carrying out the reaction in Table 1, entry 1, with a monodentate pyridine macrocycle resulted in no rotaxane formation and only 10% conversion to the thread.

(7) Use of $Cu(OAc)_2$ or I_2 as the oxidant produced no rotaxane; O_2 as the sole oxidant produced only 26% rotaxane (other reagents and conditions as per Table 1, entry 1). See Supporting Information for further details.

(8) According to Jung and co-workers,[2h] the base-free oxidative Heck cross-coupling shows the greatest efficiency in polar aprotic solvents. However, our rotaxane-forming reactions did not proceed efficiently in DMF (16% yield of **5**), probably due to the low solubility of the cross-coupling partners. A 1:1 mixture of $CHCl_3/CH_2Cl_2$ was found to be the optimal solvent system for the studies presented here. See Supporting Information for further details.

(9) Much lower yields of rotaxane (<5%) were obtained using pinacol boronic esters in place of boronic acids, even though the former generally gives higher yields in base-free oxidative Heck reactions.[2h] This difference is probably due to steric effects.

(10) Unoptimized yield. Rotaxane **16** proved difficult to isolate free from the accompanying byproduct thread.

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