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End-Cap Exchange of Rotaxane by the Tsuji–Trost Allylation Reaction

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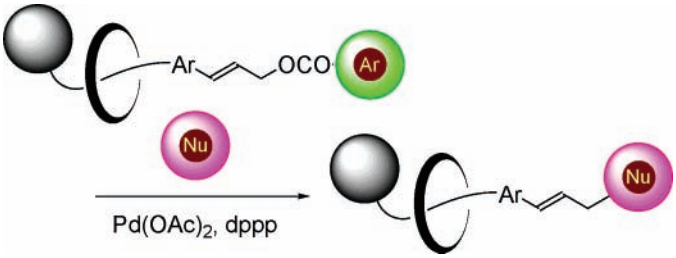
ABSTRACT



Rotaxanes possessing a cinnamyl ester group at the axle terminal were prepared. The terminal end-cap was modified with a bulky malonate ester in excellent yield by the Tsuji–Trost allylation reaction, which was carried out in the presence of a palladium catalyst.

A rotaxane is an interlocked compound comprising a macrocyclic wheel and a dumbbell-shaped axle as components.[1] The bulky substituents present at the terminal ends of the axle prevent the dethreading of the axle from the wheel. Reactions of rotaxane that involve a modification of the main skeleton are extremely limited because the bond-scission may lead to the destruction of the interlocked structure. The rotaxanes whose end-cap group can be chemically replaced are considered beneficial because several types of rotaxanes with desired structures and functional groups can be prepared from a common intermediary rotaxane by the same chemical procedure. Stoddart has reported the successful end-cap exchange of phosphonium salt-terminated rotaxanes by the Wittig reaction.[2] Leigh also reported the end-cap exchange reaction by the transesterification reaction.[3] However, since these reactions were carried out under strongly basic conditions, the base-sensitive functional groups show incompatibility with these reactions. In the course of our study on the chemical modification of interlocked compounds,[4] palladium-catalyzed coupling reactions have caught our attention.[5,6] The palladium-catalyzed coupling reactions are important from the view of end-cap

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exchange reactions for the following reasons: (i) the course of the reaction can be controlled by the type of palladium complex used and (ii) the reaction proceeds under mild conditions such that high tolerance toward functional groups is realized. However, a bond scission occurs when a palladium complex activates a rotaxane, and this may lead to the destruction of the interlocked structure. This destruction may be avoided by the use of a bulky palladium complex as a catalyst. In this paper, we report a highly efficient end-cap exchange reaction of rotaxanes by the Tsuji−Trost allylation reaction (Figure 1).

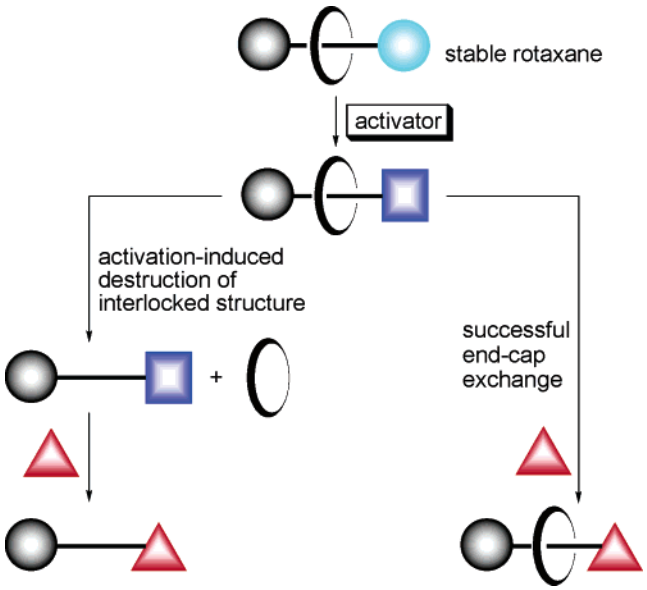
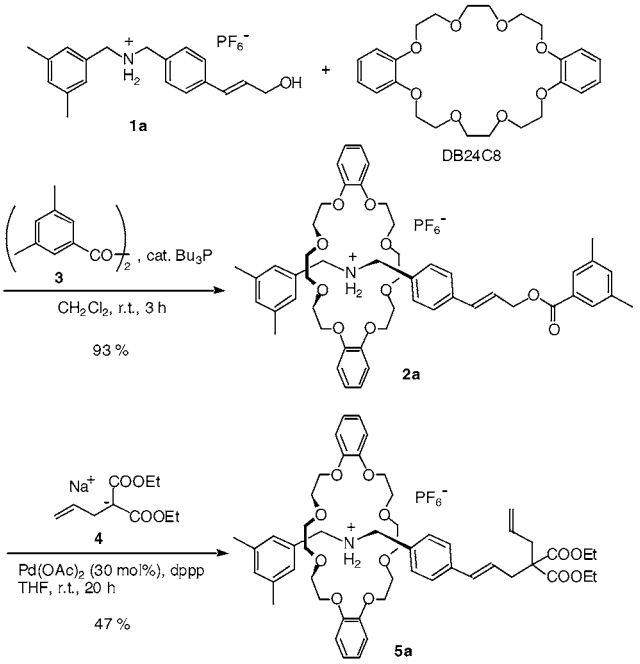


Figure 1. Schematic representation of the successful end-cap exchange reaction of rotaxane. The reactive group (blue square) must be larger than the cavity of the wheel component even after its activation to avoid the activation-induced destruction of the interlocked structure.

A rotaxane system comprising the dibenzo-24-crown-8 (DB24C8) and a secondary ammonium salt (established by Busch and developed by Stoddart[7]) was used for the end-cap exchange reaction in this study. A secondary ammonium salt bearing a terminal hydroxy group **1a** was end-capped with a bulky acid anhydride **3** in the presence of DB24C8 to give the corresponding rotaxane **2a** in 93% yield (Scheme 1).[8]

Scheme 1



The Tsuji−Trost allylation reaction involves the coupling of the allyl ester group with nucleophiles such as the malonate ester anion. If the malonate ester anion is protonated by the ammonium group present in a rotaxane, the Tsuji−Trost reaction will not proceed. However, we have reported that the ammonium group of rotaxanes is barely acidic due to the strong intramolecular hydrogen-bonding interaction with the surrounding crown ether.[9] Therefore, we could safely expect that the malonate ester anion maintains nucleophilicity even in the presence of the ammonium group of rotaxanes.

The Tsuji−Trost allylation reaction of sodium diethyl allylmalonate (**4**), bearing an acid-sensitive allyl group and base-sensitive ester groups, with the cinnamyl ester group of **2a** was investigated in THF using palladium(II) acetate−dppp as the catalyst system in which dppp was selected as the bulky ligand. The reaction proceeded unexpectedly slowly. When the reaction was carried out with 30 mol % of palladium(II) acetate, 47% of the desired rotaxane **5a** was obtained with a 12% recovery of **2a** after 20 h, although cinnamyl benzoate gave the corresponding allylation product in 70% yield under the same reaction conditions within 3 h

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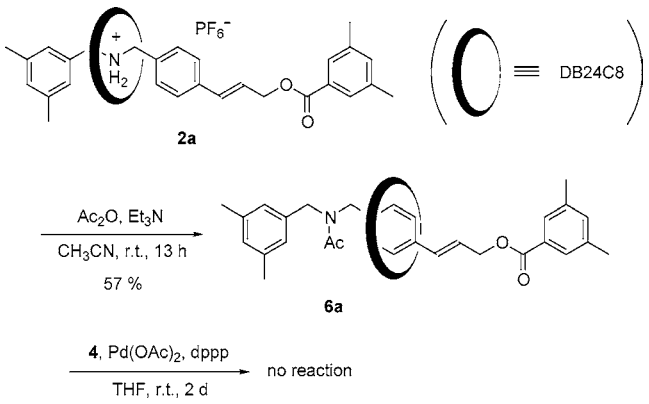
with complete conversion. The reactivity of the cinnamyl group in **2a** was greatly suppressed (Scheme 2).

Scheme 2



There are two possible reasons for the decrease in reactivity. One of them is the deactivation of the catalyst by the action of the ammonium group and the other is that the cinnamyl ester group is protected by the bulky DB24C8 wheel. To demonstrate the effect of the ammonium group, rotaxane **6a** was prepared by the acylative neutralization of **2a**,[9] and the Tsuji−Trost allylation reaction was investigated using **6a**. When the reaction was carried out under the above-mentioned conditions, no reaction occurred, and **6a** was recovered quantitatively. This clearly indicates that the DB24C8 component disturbed the allylation reaction due to steric hindrance.[10] Since the DB24C8 component cannot thread over the acetamide group, DB24C8 was present around the cinnamyl group in **6a**.

To avoid the retardation of the reaction by the wheel component, rotaxanes **2b** and **2c** with longer axles were prepared from **1b** and **1c** in 72% and 64% yields, respectively (Scheme 3). The Tsuji−Trost allylation reactions of **2b** and **2c** proceeded smoothly to afford the desired rotaxanes **5b** and **5c** in good yields. The results are summarized in Table 1. The yield of **5** increases with a decrease in the amount of the catalyst. When 5 mol % of palladium(II) acetate was used as the catalyst, **5b** was obtained in 96% yield.[11] The fact that **5** was obtained in excellent yields indicates that the ammonium group in rotaxane did not prevent the Tsuji−Trost allylation reaction. Even though the reaction proceeded slowly, $Pd_2(dba)_3$ can also be used as a catalyst.

Scheme 3

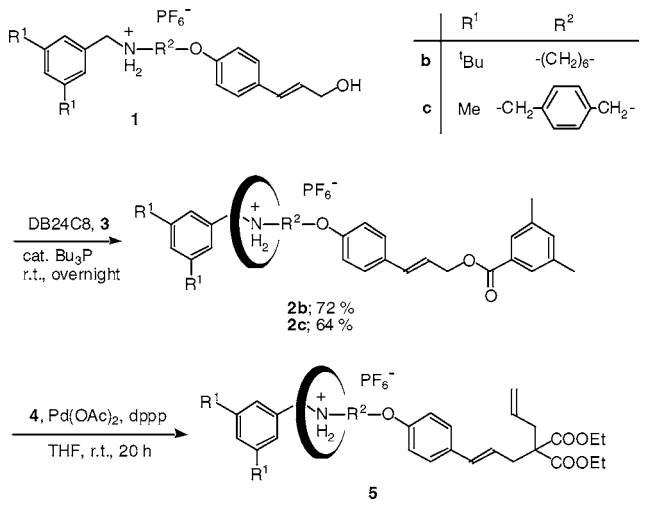


Table 1. Allylation of **4** with Rotaxanes **2b** and **2c** Catalyzed by Palladium Complexes[a]

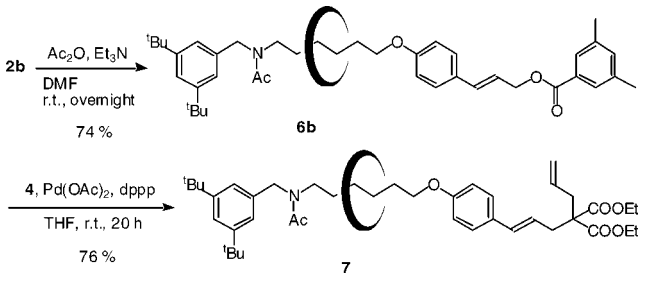
rotaxane	Pd catalyst (mol %)	dppp/mol %	yield/%
2b	$Pd(OAc)_2$ (20)	30	79
2b	$Pd(OAc)_2$ (10)	15	85
2b	$Pd(OAc)_2$ (5)	10	96
2c	$Pd(OAc)_2$ (20)	30	83
2c	$Pd(OAc)_2$ (10)	15	86
2c	$Pd_2(dba)_3$ (5)	15	51

[a] Reactions were carried out with 3 equiv of **4** in THF at rt for 20 h. Yields were determined by isolation.

It should be noted that the direct preparation of **5** from any ester of **1**, DB24C8, and **4** by the Tsuji−Trost allylation end-capping reaction is impossible. Unlike the ammonium group present in a rotaxane, the ammonium group in the crown ether complex is easily neutralized by **4** that leads to a loss in the intermolecular interactions, because the complexation of the crown ether is under equilibrium.

Next, we investigated the effect of acylative neutralization of **2b** on the end-cap exchange reaction. For this experiment, rotaxane **6b** was prepared in a manner similar to that described above and was subjected to the Tsuji−Trost allylation reaction. Rotaxane **7** was obtained in 76% yield by a successful end-cap exchange reaction (Scheme 4). Since **2b** afforded **5b** in 85% yield under the same reaction conditions, the reactivity of **6b** was slightly lower than that of **2b**. It is obvious that the DB24C8 component acted as a sterically protective group[10] in the allylation of **6b**, although

Scheme 4



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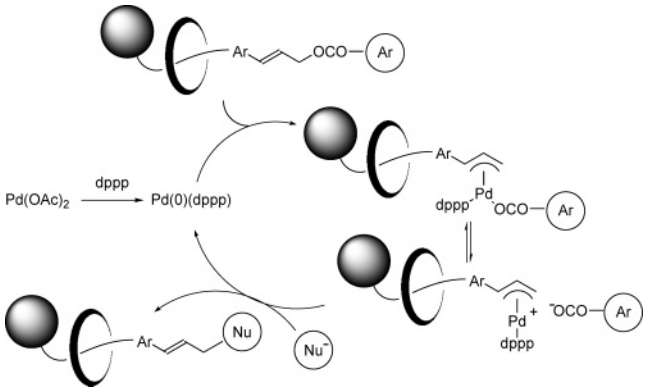
the steric effect of the DB24C8 component was smaller in **6b** than in **6a** due to the longer axle of **6b**.

The mechanism of the end-cap exchange reaction is illustrated in Scheme 5. Palladium(0) species produced from

Scheme 5



palladium(II) acetate is coordinated by the bulky dppp ligand. The oxidative addition of the Pd(0)−dppp complex to the cinnamyl group affords the allylpalladium(II) complex. The dissociation of the carboxylate ligand is possible while the rotaxane structure being retained, since the allylpalladium group acts as a sterically bulky end-cap. When sodium diethyl allylmalonate attacks the allylpalladium species, it yields the allylation product along with the regeneration of the palladium(0)−dppp complex. Since the attack of the nucleophile and the release of the palladium moiety occur simultaneously, the end-cap exchange proceeds without the destruction of the rotaxane structure.

In conclusion, we have demonstrated that the Tsuji−Trost allylation reaction is one of the most effective methods to carry out the end-cap exchange without triggering the destruction of the rotaxane structure. Since several palladium complex-catalyzed coupling reactions are known, it is possible to design various types of end-cap exchange reactions for rotaxanes. Based on the high functional group tolerance of palladium complex-catalyzed reactions, rotaxanes with a wide variety of functional groups can be synthesized. Further, the bulky palladium complex itself can act as the effective end-cap of rotaxanes.

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Supporting Information Available: Experimental procedure and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) **Typical Procedure.** To a dispersion of sodium hydride (7.8 mg, 0.33 mmol) in THF (0.5 mL) was added diethyl allylmalonate (66 μL, 0.33 mmol), and the mixture was stirred until the solution became transparent. Rotaxane **2b** (128 mg, 0.109 mmol), dppp (4.6 mg, 11.2 μmol), and palladium acetate (1.3 mg, 5.8 μmol) were added under an argon atmosphere, and the reaction mixture was allowed to stand at room temperature for 20 h. After water was added, the product was extracted with chloroform. The organic layer was dried over magnesium sulfate, the solvent was evaporated in vacuo, and the product was purified by preparative GPC (chloroform) to obtain 129 mg (96%) of **5b** as a pale yellow viscous oil: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.55 (br, 2H, NH_2), 7.38−7.10 (m, 7H, Ar−H and NH_2), 6.90 (s, 8H, Ar−H in crown), 6.78 (d, J = 8.5 Hz, 2H, Ar−H), 6.37 (d, J = 15.8 Hz, 1H, Ar−CH=C), 5.92−5.80 (m, 1H, C=CH−C), 5.79−5.62 (m, 1H, CH=C), 5.18−5.09 (m, 2H, C=CH_2), 4.64−4.60 (m, 2H, Ar−CH_2−N), 4.46−4.07 (m, 12H, O−CH_2), 3.85−3.68 (m, 10H, O−CH_2), 3.65−3.55 (m, 4H, O−CH_2), 3.42−3.34 (m, 4H, O−CH_2), 3.22−3.09 (m, 2H, N−CH_2), 2.77 (d, J = 7.3 Hz, 2H, C=C−CH_2), 2.68 (d, J = 7.2 Hz, 2H, C=C−CH_2), 1.53−0.95 (m, 32H, CH_2 and CH_3) ppm.