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C−C Bond-Forming Click Synthesis of Rotaxanes Exploiting Nitrile *N*-Oxide

Tohru Matsumura, Fumitaka Ishiwari, Yasuhito Koyama,* and Toshikazu Takata*

Department of Organic and Polymeric Materials, Tokyo Institute of Technology, 2-12-1 (H-126), Ookayama, Meguro, Tokyo 152-8552, Japan

ttakata@polymer.titech.ac.jp; ykoyama@polymer.titech.ac.jp

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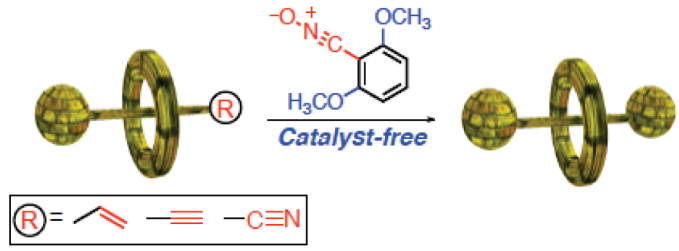
ABSTRACT



A click end-capping reaction exploiting nitrile *N*-oxide to rotaxane was described with emphasis of productivity of the protocol via stable C−C bond formation. Establishment of a pH-driven molecular shuttling system was also demonstrated by practical neutralization of the *sec*-ammonium group of the rotaxane axle with potassium hydroxide.

Rotaxane is part of a fascinating class of supramolecules consisting of interlocked macrocyclic and dumbbell-shaped components. The rotaxane scaffolds are expected to be an indispensable motif for nanoscale devices such as a molecular motor or for polyrotaxane networks with specific characteristics.[1] Although synthetic studies directed toward the versatile motifs have been reported,[2] the synthesis of rotaxane itself is still not easy owing to the need for multistep elaborations or labor-intensive purification of the resulting compound. Moreover, the skeleton often includes labile linkages such as ester, urethane, and so on because of the synthetic requirement to limit further modification of rotaxane. Hence, the development of productive and labor-saving methods for the synthesis of interlocked molecules could allow easy access to highly sophisticated supramolecular systems. For this purpose, click chemistry,[3] exploiting the Huisgen dipolar cycloaddition of azides to alkynes, has generated particular interest in the usefulness in the supramolecular chemistry.[4] However, the problems of safety of the azide moiety concerning toxicity and explosiveness are some of the limitations.[5]

Recognizing such issues, we became intrigued by the potential usefulness of stable nitrile *N*-oxide as a substitute

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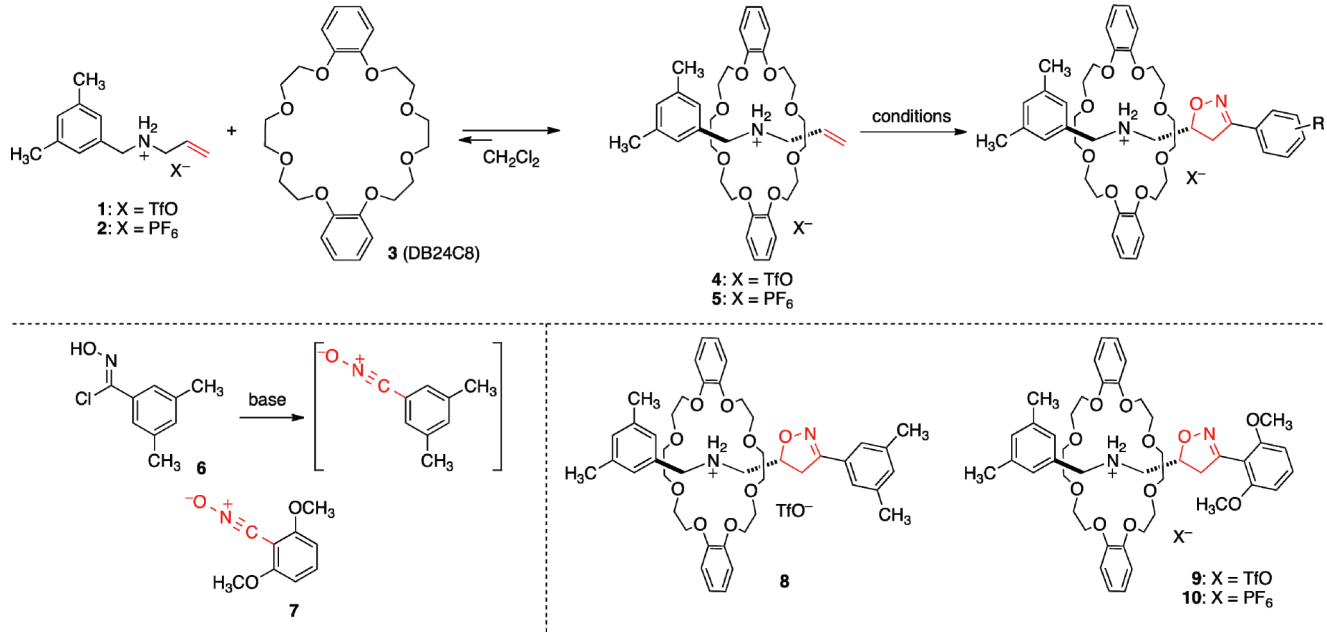
Table 1. Click End-Capping Reaction Exploiting Nitrile *N*-Oxide for Rotaxane Synthesis[a]



entry	pseudorotaxane	end-capping agent	additive	temp /°C	time	[2]rotaxane	Yield /%
1	**4**	**6**	Et_3N	rt	5 d	**8**	0
2	**4**	**6**	AgOTf	0 °C	30 min	**8**	25
3	**4**	**6**	MS 4A	rt	1 d	**8**	19
4	**4**	**6**	MS4A	reflux	13 d	**8**	47
5	**4**	**7**	–	rt	20 h	**9**	61
6	**5**	**7**	–	rt	1 d	**10**	97
7	**5**	**7**	–	reflux	2 h	**10**	85
8[b]	**5**	**7**	–	reflux	20 min	**10**	80

[a] General condition: A mixture of an axle component (0.18 mmol), DB24C8 (0.21 mmol), an end-capping agent (0.23 mmol), and additive was stirred in CH_2Cl_2 (0.5 mL). [b] Solvent: $ClCH_2CH_2Cl$.

for azides, which would enable the efficient conversion of not only alkynes but also alkenes and nitriles to selectively give isoxazole, isoxazoline, and oxadiazole without any catalyst.[6,7] Since the end-capping reaction of pseudorotaxane absolutely requires a mild condition to avoid decomposition of the labile complex, the use of nitrile *N*-oxide as the end-capping agent would provide a reliable synthetic method of interlocked compounds.[8] On the other hand, the resulting rotaxane skeleton consists only of chemically stable linkages and therefore enables versatile chemical modifications of the rotaxane.[9]

Herein, we describe the effective synthesis of rotaxanes via click reaction exploiting nitrile *N*-oxide to pseudorotaxane possessing alkene, alkyne, or the nitrile group on the axle terminal. A molecular shuttling system was fruitfully constructed by a simple neutralization of the resulting rotaxane with potassium hydroxide (KOH).

Table 1 features the conversion of pseudorotaxane into [2]rotaxane consisting of dibenzo-24-crown-8-ether (DB24C8, **3**) and *sec*-ammonium salt as the axle moiety. Treatment of *sec*-ammonium salt (**1** or **2**) in the presence of DB24C8 (**3**) gave pseudorotaxane (**4** or **5**) possessing a terminal olefin

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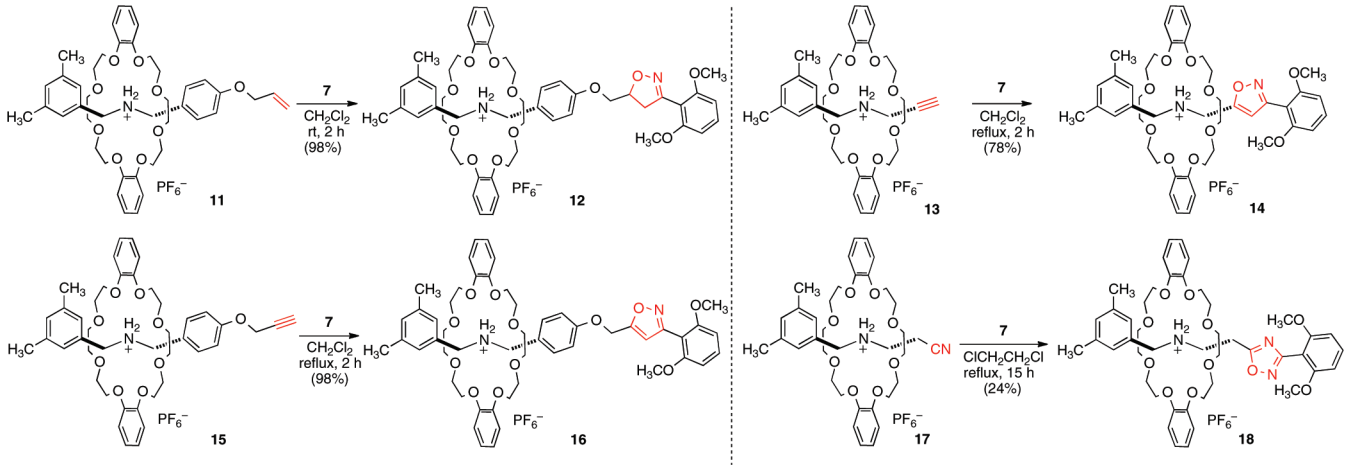
Scheme 1. Synthesis of [2]Rotaxanes Comprising Hetero Aromatics[a]



[a] The reactions were performed using axle component, DB24C8 (1.2 equiv per axle component), and stable nitrile *N*-oxide **7** (1.3 equiv per axle component).

moiety that hopefully served for the isoxazole formation to give the corresponding rotaxane (**8**−**10**). However, initial attempts using benzohydroxamoyl chloride derivative **6** were not so productive. The combination of **6** with Et_3N to generate nitrile *N*-oxide in situ only afforded the dumbbell-shaped molecule with a lack of the wheel component (Table 1, entry 1). Use of AgOTf or MS 4A[10] resulted in relatively low yields of rotaxane **8** as a single product (Table 1, entries 2−4). After considerable efforts, we found that [2]rotaxane **9** was nicely obtained by treatment of **4** with stable nitrile *N*-oxide **7**[11] through use fo bulky substituents in CH_2Cl_2 without any catalyst (Table 1, entries 5−8). Finally, treatment of hexafluorophosphate salt **5** as the pseudorotaxane with **7** at room temperature afforded the rotaxane **10** in 97% yield as a single product (Table 1, entry 6). The regiochemistry of **8** and **10** was determined by the HMBC correlations.[12] On the other hand, the elevated temperature shortened the reaction time, though the yield was slightly lowered. The decrease of yield clearly depends on the entropy-driven dessociation of the pseudorotaxane (entries 7 and 8).

Having the stable nitrile *N*-oxide **7** as a crucial end-capping agent in hand, we examined its utility for various [2]rotaxane preparations. Scheme 1 shows the end-capping reactions of pseudorotaxanes possessing various dipolarophiles at the axle termini. According to the same procedure as for entry 7 of Table 1, the vinylene terminus of **11** worked well to obtain isoxazole-containing [2]rotaxane **12** in 98% yield at room temperature after only 2 h. The high reactivity is probably attributed to the steric hindrance of **11** being less than **5**. The use of acetylene **13** or **15** also underwent the click end-capping to give the corresponding isoxazoline-containing [2]rotaxane **14** or **16** as a single product in a high yield, respectively (**14**: 78%, **16**: 98%). On the other hand, the use of cyano-functionalized **17** gave 1,2,4-oxadiazole-containing [2]rotaxane **18** in 24% yield. DB24C8-free dumbbell-shaped ammonium salt was obtained as the main product because the basity of the oxadiazole formed probably causes the decomposition of pseudorotaxane **17**. Notably, all reactions proceeded regioselectively, as evaluated by the HMBC correlations,[12] and importantly, the formation of [2]rotaxanes was performed by the chemically stable C−C bond in the cases of the pseudorotaxane having an alkene and an alkyne terminus.

Figure 1 features the application to a molecular shuttling system by showing the spectral change of ^{1}H NMR from (a) ammonium-type rotaxane **16** to (b) free amine-type rotaxane **19**. In spectrum a, the signal originating from the isoxazole skeleton along with the disappearance of signal of terminal alkyne of pseudorotaxane **15** afforded the direct evidence for the formation of **16**. In addition, the characteristic signals of benzyl protons of the axle component of **16** appeared as broad peaks due to the geminal coupling, strongly supporting the rotaxane formation in accordance with the literatures.[8] The neutralization reaction of the *sec*-ammonium moiety in **16** was performed by pouring a DMSO solution of **16** into 3 M aq KOH.[13] The corresponding free amine-type rotaxane **19** was quantitatively obtained. As shown in the spectrum of **19**, the signals of the benzyl protons of the axle component were upfield-shifted, indicating the neutralization of the ammonium moiety.[14] Moreover, some signals of the axle effected a deshielding effect from DB24C8

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(12) Structural assignments of **8**, **10**, **12**, **14**, **16**, and **18** were based on the HMBC correlations. The HMBC observed between the hetero ring protons was diagnostic in each case.

(13) The use of an excess amount of KOH in polar solvents such as DMSO or DMF was absolutely needed in the neutralization process, strongly suggesting the low acidity of the ammonium group surrounded by the crown ether of **16**. For a related report, see: Kihara, N.; Tachibana, Y.; Kawasaki, H.; Takata, T. *Chem. Lett.* **2000**, *29*, 506–507.

(14) Nakazono, K.; Takata, T. *Chem.—Eur. J.* **2010**, . in press.

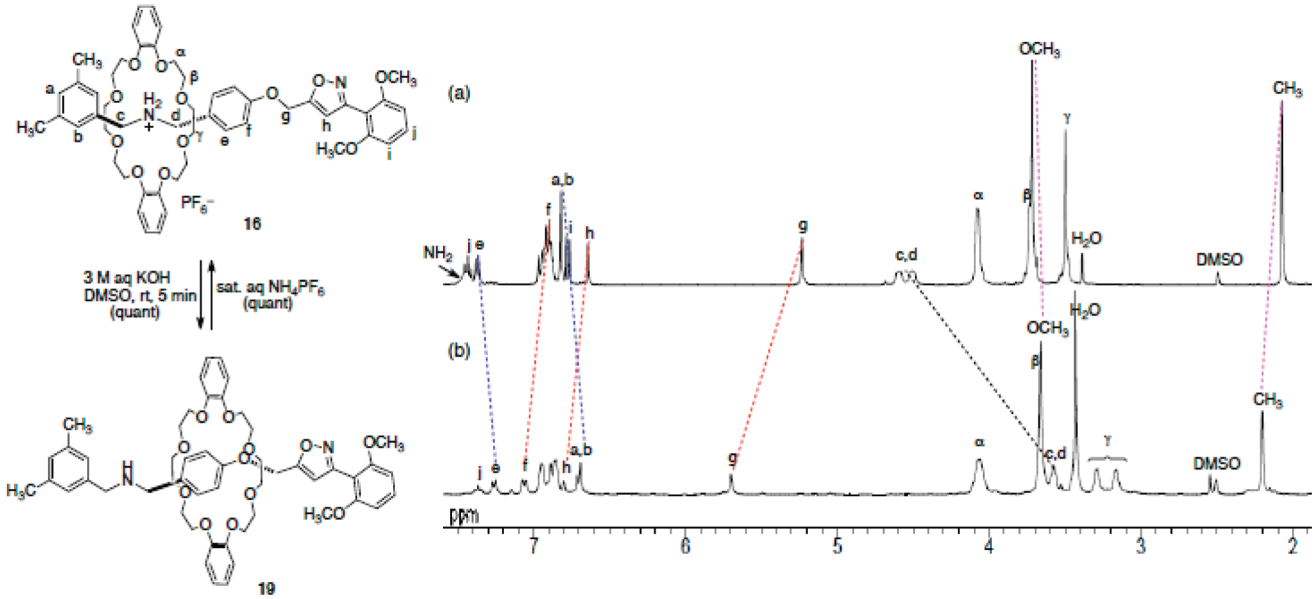

Figure 1. Spectral change of the molecular shuttling system: ^{1}H NMR spectra of (a) rotaxane **16** and (b) free amine-type rotaxane **19** (DMSO-d_6, 400 MHz, 298 K).

and were the most characteristic toward understanding the translation of the wheel component: Signals a−c around DB24C8 were upfield-shifted; on the contrary, signals f−h located far from DB24C8 were downfield-shifted. On the other hand, the signals of the Ar-CH_3 and Ar-OCH_3 protons of the end groups showed inverse behavior to such signals, probably depending on the shielding effect from DB24C8.

Again, treatment of **19** with satd aq NH_4PF_6 furnished **16**, suggesting the establishment of a pH-driven molecular shuttling system.[15]

In conclusion, the present paper has disclosed a simple and powerful synthetic method of various heteroaromatics-containing [2]rotaxanes without any catalyst and its application to a molecular switch, with emphasis of productivity of the protocol via stable C−C bond formation. Further studies directed toward the functionalization of the resulting rotaxanes by the chemical modifications of the heteroaromatics are currently underway.

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Supporting Information Available: Full experimental details for all compounds, including ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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