

Triple-stranded Helicates as a Synthetic Template: Synthesis of Pyridine-containing Macrocyclic Compounds

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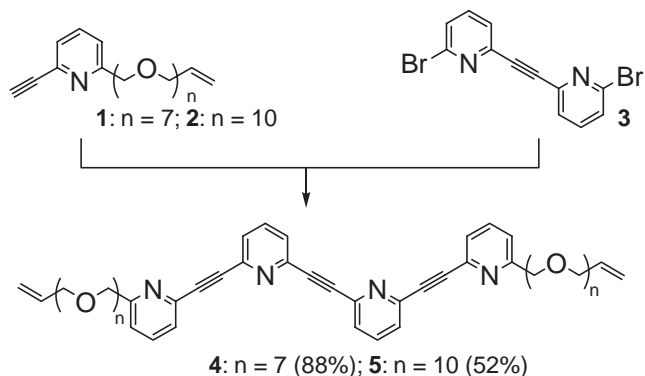
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Triple-stranded helicates possessing polyether side chains have been prepared from the reaction of oligo(ethynylpyridines) with copper(I) ions. Ring-closing metathesis of the helicates by using Grubbs' catalyst has led to the formation of pyridine-containing macrocyclic compounds.

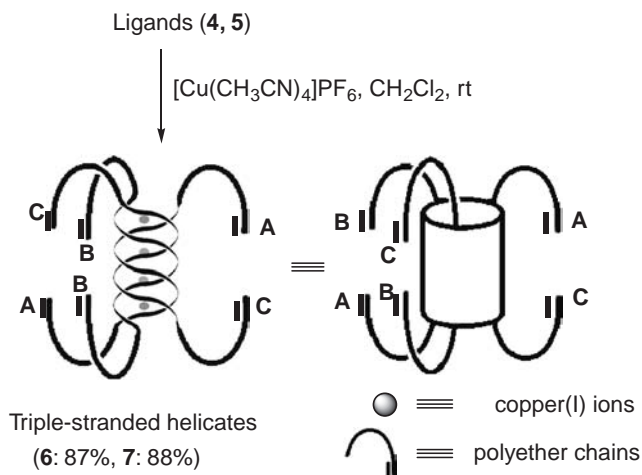
Supramolecular *helicates*, which are discrete helical supramolecular complexes constituted by one or more covalent organic strands wrapped about and coordinated to a series of ions defining the helical axis, possess fascinating structures, and are excellent model systems for the study of mechanisms in supramolecular chemistry.¹ Among these helicates, various reports have been published on the self-assembly of double- and triple-stranded helicates from polydentate nitrogen ligands and metal ions.² The use of these helicates in organic synthesis would be expected to provide us a facile entry into a new stage of helicate chemistry. However, no triple-stranded helicates in organic synthesis have been documented in the literature to date, although there have been several papers on the use of double-stranded helicates.³ We recently reported the copper(I) ion mediated self-assembly of triple-stranded helicates from oligo(2-ethynylpyridines).⁴ In this paper, we describe the synthesis of triple-stranded helicates possessing polyether side chains and their potential as a synthetic template for the formation of pyridine-containing macrocyclic compounds.

Ring-closing metathesis (RCM) by using Grubbs' catalyst is one of the best synthetic methods for preparing macrocyclic compounds.⁵ Therefore, ligands **4** and **5**, available for RCM approach, were designed. 2-Ethynylpyridine derivatives **1** and **2**^{4,6} and bis(6-bromo-2-pyridyl)acetylene (**3**),⁴ which were key intermediates for the synthesis of ligands **4** and **5**, were prepared from 2,6-dibromopyridine according to the literature procedure, respectively.

The cross-coupling reaction of **3** with the corresponding 2-



Scheme 1. Preparation of ligands **4** and **5**.

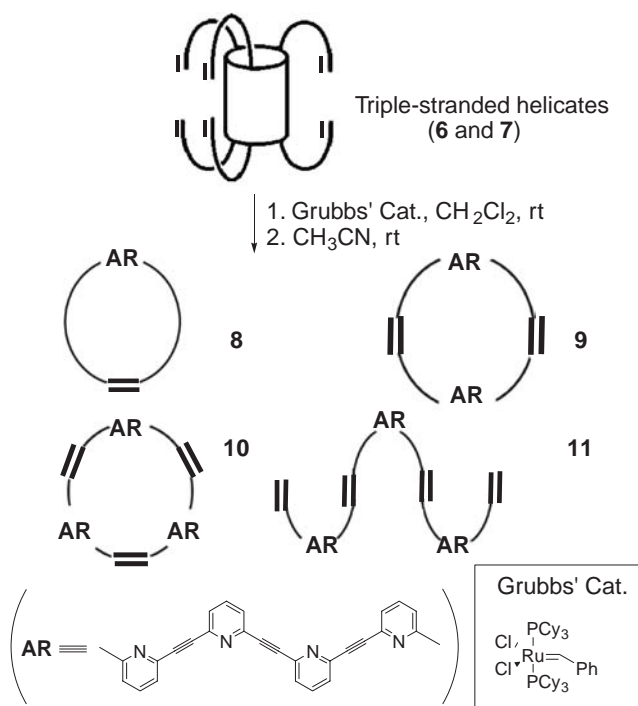


Scheme 2. Self-assembly of triple-stranded helicates **6** and **7**.

ethynylpyridine derivatives **1** and **2** (2.5 equiv.) in the presence of a catalytic amount of $Pd(PPh_3)_4$ in diethylamine at 80 °C afforded the desired ligands **4** and **5** in 88 and 52% yields, respectively (Scheme 1). All the ligands obtained in this study were characterized by spectroscopy (NMR, IR, and FABMS) and elemental analysis.

As shown in Scheme 2, the synthesis of triple-stranded helicates was achieved by the complex-forming reaction of ligands in this study with copper(I) ions according to our previous paper.⁴ For instance, the reaction of **4** with 1.4 equiv. of $[Cu(CH_3CN)_4]PF_6$ in dichloromethane (CH_2Cl_2) at room temperature resulted in the immediate formation of yellow solutions, indicating a fast complexation with copper(I) ions, from which copper(I) complex **6** was obtained in 87% yield. Elemental analysis of **6** showed the complex **6** to be $[Cu_4(4)_3](PF_6)_4$. The reaction of **5** with 1.4 equiv. of $[Cu(CH_3CN)_4]PF_6$ under the similar condition gave triple-stranded helicates **7**: $[Cu_4(5)_3](PF_6)_4$ in 88% yield.

The RCM of triple-stranded helicate **6** in the presence of Grubbs' ruthenium benzylidene complex ($[RuCl_2\{P(C_6H_{11})_3\}_2(=CHPh)]$) at a substrate concentration of 0.1 mM in CH_2Cl_2 at room temperature, followed by dissociation of copper(I) ions by addition of a large excess amount of acetonitrile at room temperature, afforded pyridine-containing macrocyclic products **8a** (cyclic monomer), **9a** (cyclic dimer), and **10a** (cyclic trimer) in 25, 30, and 31% yields, respectively, along with **11** (non-cyclic trimer) in 8% yield and recovery of ligand **4** (3%). The RCM of triple-stranded helicate **7** under the same condition afforded macrocyclic products **8b**, **9b**, and **10b** in 27, 38, and 33% yields, respectively, without non-cyclic product. These results are summarized in Table 1. Cyclic compounds

**Table 1.** Ring-closing metathesis of triple-stranded helicates

Run	Helicates	Yield/% ^a				Recovery of ligand
		8	9	10	11	
1	6	25	30	31	8	3
2	7	27	38	33	nd ^b	nd

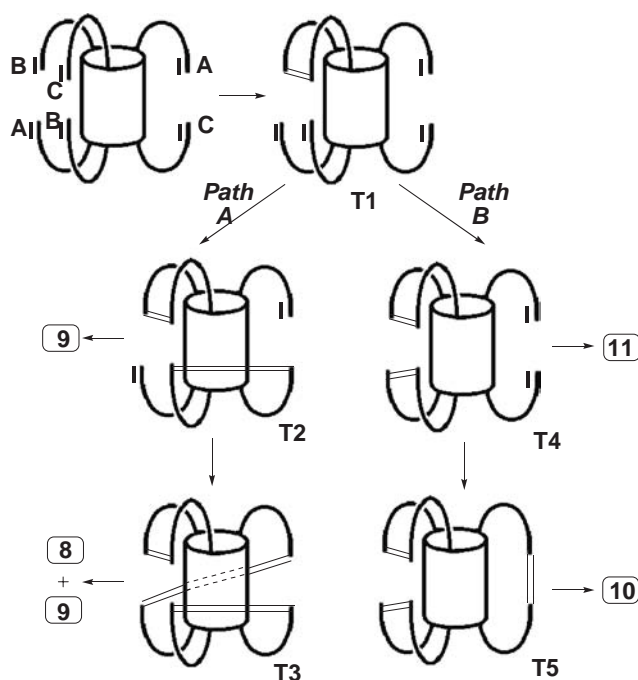
^aIsolated yield. ^bNot detected.

obtained in this study appeared mixture of *cis/trans* alkenes in a 3:2 ratio, according to the ¹H NMR spectrum. All new products obtained this study were characterized by spectroscopy (NMR and FABMS) and elemental analysis.

In contrast to RCM of helicates, it was noteworthy that no products were obtained when the RCM of ligands **4** and **5** were performed under the same conditions. This result indicates that the structure of triple-stranded helicate plays an important role in the formation of macrocyclic compound, that is, triple-stranded helicate acts as a template.

A proposed mechanism for the RCM of triple-stranded helicates is illustrated in Scheme 4. RCM reaction first takes place exclusively on the site of ethylenic termini B–C (as well as A–B, or C–A) in triple-stranded helicate to produce intermediate **T1**. The next reaction of **T1** in B–C site via Path A gives **T2** to afford cyclic dimer **9** after demetallation. RCM of **T2** in A–A site leads to the formation of **T3**, and then after its demetallation, cyclic monomer **8** and cyclic dimer **9** are produced. On the other hand, the reaction of **T1** in A–B site via Path B gives **T4** to afford non-cyclic product **11** after demetallation. The following RCM of **T4** in C–A site leads to the formation of **T5**, and then after its demetallation, cyclic trimer **10** is produced.

In conclusion, we have demonstrated that RCM of triple-stranded helicate proceeds smoothly to yield pyridine-containing macrocyclic compounds (for instance, 76-membered ring for **8b**,

**Scheme 4.** A proposed mechanism for the RCM of triple-stranded helicates. Each of A, B, and C shows ethylenic termini of one ligand in the helicate.

152-membered ring for **9b**, and 228-membered ring for **10b**). These macrocyclic compounds would be expected to have the potential for molecular recognition. Furthermore, the finding of cyclic monomer **8** may lead us to novel cyclic compound such as catenane derivative by adjustment of the number of pyridine ring or length of polyether side chain. These studies are now in progress.

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