

Template-Directed Olefin Cross  
Metathesis

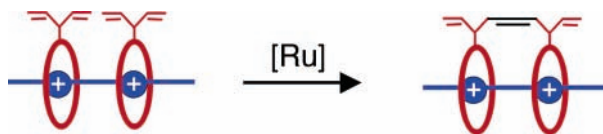
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## ABSTRACT



A template containing two secondary dialkylammonium ion recognition sites for encirclement by olefin-bearing dibenzo[24]crown-8 derivatives has been used to promote olefin cross metatheses with ruthenium–alkylidene catalysts. For monoolefin monomers, the rates of metatheses and yields of the dimers are both amplified in the presence of the template. Likewise, for a diolefin monomer, the yield of the dimer is enhanced in the presence of the template under conditions where higher oligomers are not formed.

Nature employs template-directed synthesis<sup>1,2</sup> by using noncovalent bonding and  $\pi$ – $\pi$  stacking, in the formation of DNA, RNA, and proteins, to obtain well-defined biopolymers in respect to their precise lengths and specific sequences. For chemists to be able to synthesize artificial heteropolymers with such well-defined structures, an alternative set of molecular recognition motifs and catalysts have to be identified and developed. Ruthenium–alkylidene-mediated olefin metathesis,<sup>3</sup> using catalysts such as **1** and **2** shown in

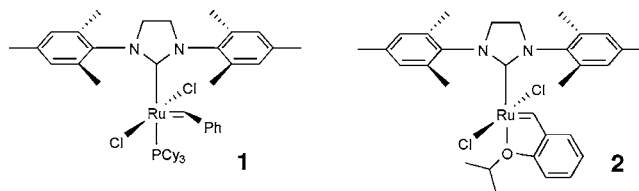


Figure 1. Ruthenium–alkylidene catalysts **1** and **2**.

Figure 1, has proved to be a highly convenient method for the synthesis of natural products<sup>4</sup> and artificial polymers,<sup>5</sup> as well as mechanically interlocked compounds,<sup>6</sup> e.g., catenanes and rotaxanes. Ring-closing metathesis<sup>3</sup> (RCM),

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(4) For some recent examples, see: (a) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238. (b) Cheung, A. K.; Murelli, R.; Snapper, M. L. *J. Org. Chem.* **2004**, *69*, 5712–5719. (c) Chen, J.; Forsyth, C. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2148–2152. (d) Nicolaou, K. C.; Montagnon, T.; Vassilikogiannakis, G.; Mathison, C. J. N. *J. Am. Chem. Soc.* **2005**, *127*, 8872–8888.

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used in concert with the molecular recognition that exists<sup>7,8</sup> between secondary dialkylammonium ions ( $\text{RCH}_2\text{NH}_2^+-\text{CH}_2\text{R}$ ) and dibenzo[24]crown-8 (DB24C8), which readily form [2]pseudorotaxanes in aprotic solvents as a result of highly stabilizing  $[\text{N}^+-\text{H}\cdots\text{O}]$  hydrogen bonds and  $[\text{C}-\text{H}\cdots\text{O}]$  interactions, has led previously<sup>6,9</sup> to the template-directed synthesis<sup>1,2</sup> of catenanes,<sup>6f</sup> rotaxanes,<sup>6d</sup> and a molecular bundle<sup>6e</sup> under thermodynamic control.

Olefin cross metathesis (CM) has also been investigated with peptides<sup>10</sup> and peptide-based templates<sup>11</sup> where the formation of the new carbon–carbon bond is controlled by the preorganization exerted by the conformation of the peptide chain. Herein, we report an approach utilizing a template-mediated CM, employing the  $(\text{RCH}_2\text{NH}_2^+-\text{CH}_2\text{R})/\text{DB24C8}$  recognition motif, in the formation of dimeric crown ethers, a satisfactory outcome of our preliminary efforts to template the synthesis of oligomeric and polymeric structures by acyclic diene metathesis (ADMET).

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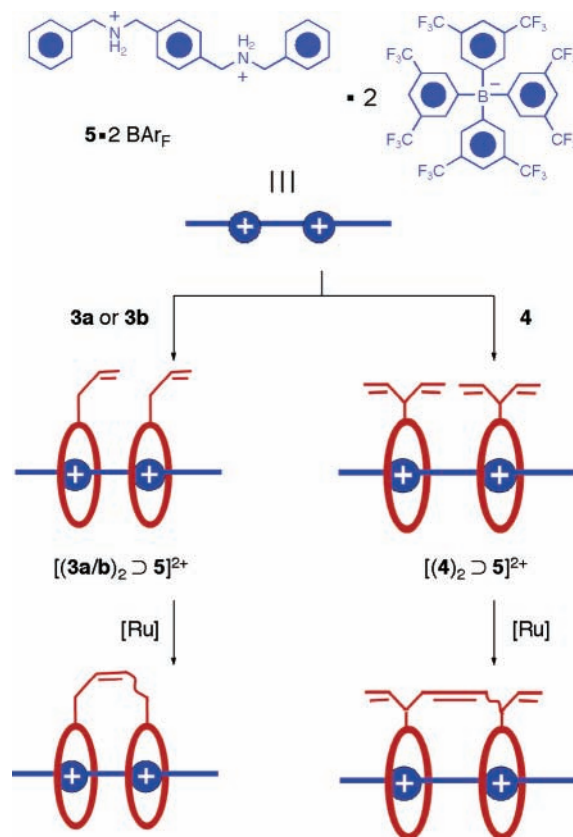
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(9) Other recognition motifs have also been employed in supramolecular assistance to covalent synthesis. For example, dimerization via an *N*-alkylation has been facilitated by hydrogen bonding interactions with a linear template ((a) Kelly, T. R.; Grider, G. J.; Zhao, C. *J. Am. Chem. Soc.* **1990**, 112, 8024–8034), and metal–ligand interactions have been used to promote transacylation reactions using a cyclic Zn–porphyrin-based template ((b) Walter, C. J.; Anderson, H. L.; Sanders, J. K. M. *J. Chem. Soc., Chem. Commun.* **1993**, 458–460).

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(11) Yang, X.; Gong, B. *Angew. Chem., Int. Ed.* **2005**, 44, 1352–1356.

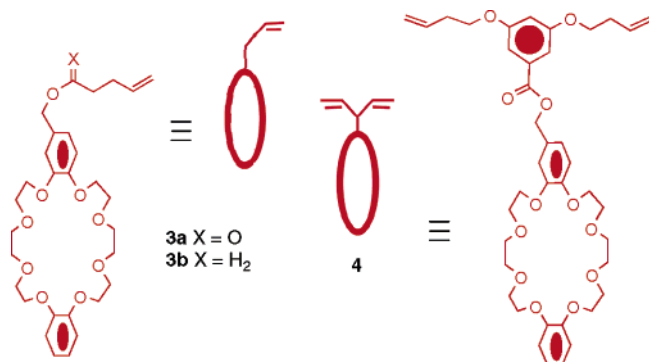
**Scheme 1.** Templated Dimerization of the DB24C8 Derivatives **3a/b** and **4**



Particularly relevant to the task we have in hand is the ability to use the thermodynamic control we associate with supramolecular<sup>12</sup> and dynamic covalent<sup>13</sup> chemistry (DCC), both practices in chemistry which rely upon the reversible noncovalent and covalent bond making and breaking processes as part of key proofreading and crucial error-checking mechanisms, to template the formation of a well-defined molecular compound during a reaction that, if it were performed under kinetic control, would afford a myriad of products. Thus, the thermodynamically controlled protocol depends, at the outset for its success, on the formation of ternary and higher complexes that are extremely stable prior to the catalyst (**1** and **2** in Figure 1) carrying out an olefin cross metathesis.

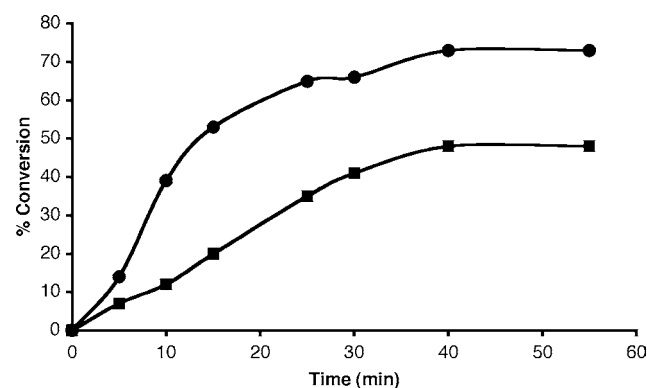
Our initial experiments were carried out (Scheme 1) with a DB24C8 derivative (**3a** or **3b** in Figure 1) to which a tether comprising a single terminal olefin was added and a dicationic template  $5 \cdot 2\text{BARF}$  containing two  $-\text{CH}_2\text{NH}_2^+-\text{CH}_2-$  centers (Figure 2). It has been demonstrated previously<sup>14</sup> that the two  $-\text{CH}_2\text{NH}_2^+-\text{CH}_2-$  centers present in  $5^{2+}$  (as its  $2\text{PF}_6^-$  salt) can each thread and bind a DB24C8. Since  $5 \cdot 2\text{PF}_6$  is insoluble in solvents such as  $\text{CHCl}_3$  and  $\text{CH}_2\text{Cl}_2$ , where the noncovalent bonding interactions between the two recognition partners is strongest, the  $\text{BARF}^-$  salt of  $5^{2+}$ , which is soluble in these solvents, was prepared for use in the preliminary experiments. The association constants,  $K_{a1}$  and

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**Figure 2.** Olefin-bearing crown derivatives **3a/3b** and **4**.

$K_{a2}$ , in  $\text{CH}_2\text{Cl}_2$  (at 298 K) for the complexation of  $5 \cdot 2\text{BAR}_\text{F}$  with **1** and then 2 equiv of DB24C8, forming first a 1:1 complex and then subsequently a 1:2 complex, were found<sup>15</sup> to be  $4.53 \times 10^6$  and  $7.17 \times 10^7 \text{ M}^{-1}$ , respectively. The relationship between  $K_{a1}$  and  $K_{a2}$  (i.e.,  $K_{a2}/K_{a1} > 0.25$ )<sup>16a</sup> implies that there is positive cooperativity<sup>16</sup> between the two binding sites. When a 5 mM solution of  $5 \cdot 2\text{BAR}_\text{F}$  in  $\text{CD}_2\text{Cl}_2$  is treated with 2 equiv of **3a**, the template is bound by this olefin-bearing DB24C8 derivative as determined (see Supporting Information) by  $^1\text{H}$  NMR spectroscopy. The  $^1\text{H}$  NMR spectrum reveals that both sites on the  $5^{2+}$  template are occupied (>95%) by crown ethers, namely, **3a**. After the formation of  $[(3a)_2 \supset 5]^{2+}$ , the catalyst **1** was added to the  $\text{CD}_2\text{Cl}_2$  solution, which was then heated to 40 °C; the formation of the dimer was followed by  $^1\text{H}$  NMR spectroscopy. The dimerization of  $[(3a)_2 \supset 5]^{2+}$  was established to be 73% complete within 40 min, whereas the dimerization of **3a** in the absence of the template  $5^{2+}$  resulted in only 48% conversion under identical reaction conditions in the same amount of time. The template affected (Figure 3) the rate of the reaction as well. In the presence of  $5^{2+}$ , the cross



**Figure 3.** Formation over time (using catalyst **1**) in  $\text{CD}_2\text{Cl}_2$  at 40 °C of the dimer from the monomer **3a** for the reaction in the presence (●) and absence (■) of the template  $5^{2+}$ , as determined from  $^1\text{H}$  NMR spectroscopy using the olefin resonances as a probe. The concentration of **3a** and  $5 \cdot 2\text{BAR}_\text{F}$  were both 0.1 mM.

metathesis of **3a** occurred faster than the reaction in the absence of the template.

The homodimerizations of the olefin-bearing DB24C8 derivatives **3a** and **3b** were studied<sup>17</sup> (Table 1) at a

**Table 1.** Conversion of Either **3a** or **3b**,<sup>a</sup> in the Presence and Absence of the Template  $5^{2+}$ , to the Expected Dimer as Determined by HPLC

component	catalyst	yield (%) of dimer
<b>3a</b>	10 mol % <b>1</b>	35
$[(3a)_2 \supset 5]^{2+}$	10 mol % <b>1</b>	72
<b>3a</b>	10 mol % <b>2</b>	6
$[(3a)_2 \supset 5]^{2+}$	10 mol % <b>2</b>	39
<b>3a</b>	20 mol % <b>2</b>	27
$[(3a)_2 \supset 5]^{2+}$	20 mol % <b>2</b>	56
<b>3b</b>	10 mol % <b>1</b>	35
$[(3b)_2 \supset 5]^{2+}$	10 mol % <b>1</b>	72
<b>3b</b>	25 mol % <b>2</b>	17
$[(3b)_2 \supset 5]^{2+}$	25 mol % <b>2</b>	78

<sup>a</sup> Concentration of crown ether = 1 mM.

concentration of 1 mM by HPLC. Each reaction was performed in the presence of both catalysts **1** and **2** separately for a period of 2 h at 40 °C. In the presence of 10 mol % **1**, the dimerization of either **3a** or **3b** in the absence of a template resulted in a 35% yield of the respective dimers in each case. However, under the same conditions,  $[(3a/b)_2 \supset 4]^{2+}$  reacted to afford a 72% yield of the respective dimer. Using catalyst **2** in the reactions of either **3a** or **3b** in the absence of the template resulted in much lower conversions to dimers. Templating the dimerization of the olefin-bearing DB24C8 derivatives using catalyst **2** produced higher yields of the dimers relative to the reactions without the added template. Notably, when  $[(3a)_2 \supset 5]^{2+}$  was treated with 25 mol % **2**, a 78% yield of the dimer was obtained, compared with only 17% for the reaction in the absence of the template.

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(15) Binding constants ( $K_a$ ) were determined by isothermal titration calorimetry. The details of the determinations are given in Supporting Information.

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(17) During the CM of **3a** and **3b** at this dilute concentration (1 mM) and in the absence of a template, olefin isomerization products were observed (for recent references regarding olefin isomerization, see: Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865–1880. Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* Submitted) in both the HPLC traces and the mass spectra ( $[M - 14]^+$ ) recorded on the reaction mixtures. The presence of the template during the reaction, however, minimizes the amount of isomerized products, while increasing the rate of dimerization relative to olefin isomerization.

To extend the concept of a template-directed olefin metathesis toward the formation of oligomers (Scheme 1), the DB24C8 derivative **4**, carrying an aromatic tether bearing two olefin-containing sidearms, was synthesized. While this monomer is expected to have the ability to form polymers by ADMET at higher concentrations, the templated reaction under more dilute conditions should yield only well-defined oligomers. When a 1 mM solution of crown **4** in  $\text{CH}_2\text{Cl}_2$  was exposed to the catalyst **1**, the dimer was formed (Table 2) in 56% yield. The concentration of terminal olefin

elevated to a yield of 76%. Similar trends were observed for the dimerization of **4** using the catalyst **2**.

In conclusion, a template presenting two  $\text{RCH}_2\text{NH}_2^+\text{CH}_2\text{R}$  recognition sites promotes the efficient formation in dichloromethane at low concentrations of dimeric DB24C8 derivatives by means of CM from olefin-bearing DB24C8 monomers in the presence of ruthenium–alkylidene catalysts. The CM experiments with both monoolefins **3a** and **3b** as monomers demonstrated that the rates as well as the yields of dimers in the catalyzed reactions are enhanced by the presence of the template **5**<sup>2+</sup>. When the diolefin **4** was used as the monomer instead of **3a** or **3b**, the same template was found to be effective in amplifying the production of the expected dimer at the expense of higher oligomers.<sup>18</sup> Currently, our efforts are being focused on developing templates capable of templating the formation of larger oligomers of well-defined constitutions and chain lengths by ADMET.

**Acknowledgment.** The authors thank the Office of Naval Research (ONR) for its support through the Multidisciplinary University Research Initiative (MURI) program, the Alexander von Humboldt Foundation for a Feodor Lynen postdoctoral fellowship to S.P.S., the Croucher Foundation (HKSAR) for a postdoctoral fellowship to K.C.-F.L., and the National Institutes of Health for a postdoctoral fellowship to A.N.

**Supporting Information Available:** Synthetic and template-directed catalytic procedures, in addition to spectroscopic and thermodynamic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(18) During the preparation of this manuscript, Constable and co-workers reported the templated formation of a dimer using metal–ligand interactions (as an alternative recognition motif) to mediate olefin cross metathesis; see: Constable, E. C.; Housecroft, C. E.; Lambert, J. N.; Malarek, D. A. *Chem. Commun.* **2005**, 3739–3741.

**Table 2.** Conversion of **4** in the Presence and Absence of the Template **5**<sup>2+</sup> to the Expected Dimer as Determined by HPLC

component	catalyst	yield (%) of dimer
<b>4</b>	10 mol % <b>1</b>	56 <sup>a</sup>
$[(\mathbf{4})_2 \supset \mathbf{5}]^{2+}$	10 mol % <b>1</b>	76 <sup>a</sup>
<b>4</b>	10 mol % <b>1</b>	34 <sup>b</sup>
$[(\mathbf{4})_2 \supset \mathbf{5}]^{2+}$	10 mol % <b>1</b>	72 <sup>b</sup>
<b>4</b>	20 mol % <b>2</b>	37 <sup>a</sup>
$[(\mathbf{4})_2 \supset \mathbf{5}]^{2+}$	20 mol % <b>2</b>	71 <sup>a</sup>

<sup>a</sup> Concentration of crown ether = 1 mM. <sup>b</sup> Concentration of crown ether = 0.5 mM.

functions in this case is twice that of the DB24C8 derivative since **4** contains two homoallyl functionalities. Thus, when the dimerization of **4** was performed where the concentration of the crown was decreased to 0.5 mM (and therefore 1 mM in olefin), the yields employing catalyst **1** were comparable to those for the dimerization of **3a** and **3b**. Higher oligomers were not observed as a result of the dilute concentration of the reactions. In the presence of **5**·2BAr<sub>F</sub>, the DB24C8 derivative **4** forms a 2:1 complex ( $[(\mathbf{4})_2 \supset \mathbf{5}]^{2+}$ ) with the template **5**. The productive CM for this complex at 1 mM in the template-directed reaction using the catalyst **1** was