

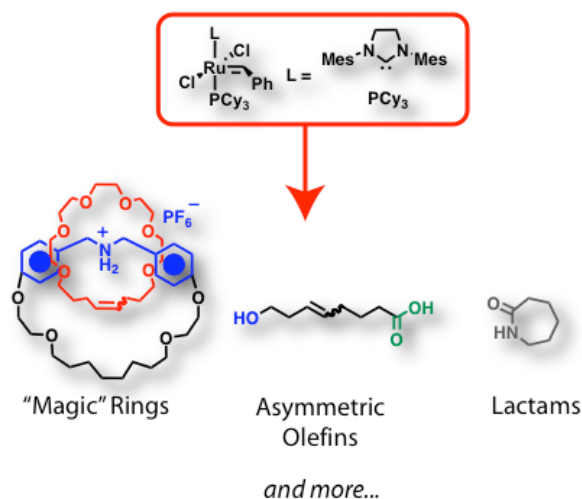
Mobility of Olefin Metathesis in Templated Synthesis

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ABSTRACT



Abstract. Olefin metathesis, a versatile carbon-carbon bond forming and breaking reaction, has recently found widespread use in the templated synthesis of entropically constrained and topologically interesting structures such as catenanes, rotaxanes, and macrocycles, as well as other many other synthetic targets such as asymmetric olefins, ADMET trimers, and lactams. This article examines several strategies to reach difficult synthetic targets using templated olefin metathesis.

In Nature, both regioselectivity and stereoselectivity of chemical transformations are influenced and controlled by templates that manipulate molecules through noncovalent interactions, molecular recognition, and self-assembly.¹ The high-fidelity replication of information rich sequences by DNA and RNA are hallmark examples of biochemical templated synthesis that operate under an umbrella of complexity unprecedented in synthetic laboratories. Nonetheless, synthetic chemists are increasingly motivated by Nature, and the reliance on templates during difficult chemical transformations is on the rise.

With the advancement of template-directed synthetic protocols, olefin metathesis² has quickly emerged as a powerful tool for the covalent bond forming step(s) required during many templated reactions. What makes olefin cross metathesis (CM) and ring-closing metathesis (RCM) particularly suited for template-directed synthesis is the dynamic³ nature of these reactions, whereby the covalent bond making and breaking steps are reversible,

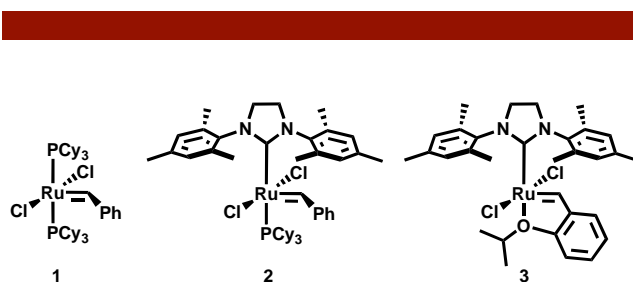


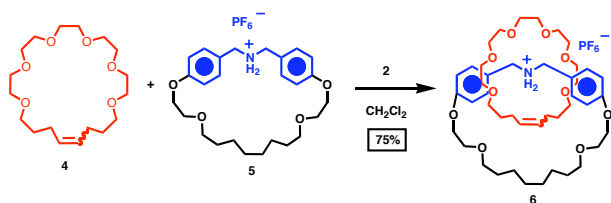
Figure 1. Ruthenium-alkylidene initiators commonly employed in template-directed synthesis.

providing for an internal error checking mechanism similar to Nature's synthetic machinery. Aside from being dynamic covalent reactions, olefin CM and RCM using ruthenium alkylidene catalysts (Figure 1) are tolerant of a

wide array of functional groups, allowing for easy noncovalent manipulation of pre-organized and thermodynamically stable templates prior to the covalent bond forming step(s).

An excellent illustration of both the dynamic and tolerant nature of olefin CM is the so-called “magic ring” formation developed by Grubbs, Stoddart, and coworkers.^{5c} In these systems, a preorganized template was formed through supramolecular⁴ assistance provided by the interaction between dibenzylammonium cations and crown ether macro-rings or precursors to crown ether macro-rings. The mechanism for these “magic” transformations can be illustrated by the catenane formation example (Scheme 1) which presumably proceeds through a ring-opening metathesis of **4** to form a linear oligoether species, which then threads through **5** to form a [2]-pseudorotaxane after which a ring-closing metathesis reaction occurs to form catenane **6**. Similar approaches were used for the synthesis of rotaxanes,^{5a} catenanes,^{5c} and an otherwise inaccessible “molecular bundle,”^{5b} under thermodynamic control.

Scheme 1. “Magic Ring” Catenation by Grubbs and Stoddart



Mechanically interlocked structures, such as the “magic” catenane **6** shown in Scheme 1, provide not only for aesthetically pleasing molecular structures that are interesting from a historical and philosophical viewpoint,⁶ but have also been tested^{7a} as memory and logic elements in electronic devices. An example^{7b} has emerged from the Stoddart group in which rotaxanes have been used as the key element in a memory device with a density of 10¹¹ bit/cm², a density predicted for commercial devices in 2020. As the successful utility of interlocked molecules continues to be demonstrated in materials science, the need for straightforward synthetic approaches to these structures will increase, and templated olefin metathesis approaches are at the forefront of many of these efforts.

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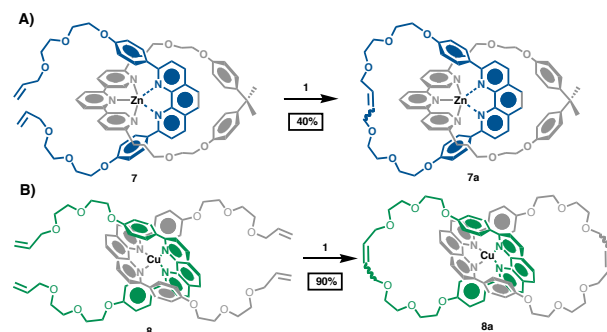
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Supramolecular interactions other than electrostatic and hydrogen bonding interactions have been used in similar examples of template-assisted catenane synthesis. Namely, metal complexes based on a number of transition metal complexes involving Zn^{8d} (Scheme 2A), Rh,^{8b} Ru,^{8c} and Cu^{8a} (Scheme 2B) to name a few, have mediated several successful catenane syntheses. In some cases, a linear species bearing two terminal olefins is threaded through a preformed macrocycle and held in place by a coordination bond. Subsequently, RCM forms the second ring, producing an interlocked [2]-catenane, such as **7a** shown in Scheme 2A. Alternatively, two linear segments can be brought together using metal-ligand interactions, and a two-fold RCM reaction can be used to form both rings at once. A [2]-catenane **8a** produced in this fashion is shown in Scheme 2B.

Several other topologically interesting and otherwise hard to reach structures have been synthesized by templated RCM and templated CM. The van Koten group has utilized a templated metathesis approach to synthesize huge macrocycles based on Pt NCN pincer-type complexes.⁹ In one elegant example, three different linear segments each consisting of di-olefins are combined with a trifurcate Pt template, and the metathesis of all three segments proceeds around the template in one-pot to produce a large macrocycle **9a** in 67% yield (Scheme 3). It is important to note that the synthesis of such macrocycles from multiple components *without* a template has thus far not been possible. Likewise, similar macrocycles have been

Scheme 2. Two Approaches to Catenanes Mediated by Metal-ligand Interactions^a



^aA) RCM around a preformed ring and B) RCM of two connected linear segments.

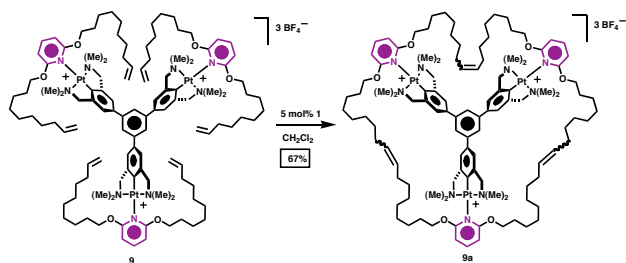
(6) *Molecular Catenanes, Rotaxanes, and Knots*; Sauvage, J.-P., Dietrich-Buchecker, C., Eds.; Wiley-VCH: Weinheim, 1999.

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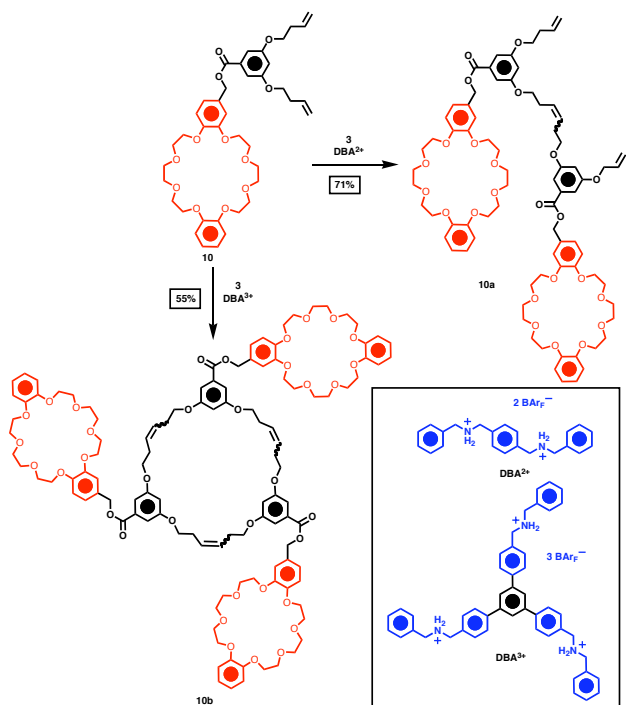
Scheme 3. Templated Multimacrocycle Synthesis



produced by templated CM and RCM mediated by metal-ligand based calixarenes,^{10b} and porphyrins.^{10a, c-d}

Another unique element that is often seen in Nature's templated syntheses is the ability to achieve different transformations on the same substrate under different environments, i.e. by utilizing different templates. To be able to alter reactivity in this way in conventional chemical laboratories would open up endless possibilities for dynamic and combinatorial approaches to diverse libraries of compounds. A proof-of-principle example has recently emerged in the literature demonstrating that by varying the template used during an olefin metathesis reaction, one mechanism can be favored over the other, creating two different products from the same starting material and the same catalyst (Scheme 4). This example

Scheme 4. Enabling CM or ADMET With Different Templates



is based on pseudorotaxane interactions between dibenzylammonium cations and dibenzo[24]crown-8 (DB24C8) macrorings. As shown in Scheme 4, if a dimer, **DBA²⁺**, is used as the template for metathesis with the di-olefin containing DB24C8 monomer **10**, then the CM mechanism is predominately enabled, producing mainly a dimer (**10a**) (70% yield) of monomer **10**, and largely disabling the production of higher order products which would be expected if acyclic diene metathesis (ADMET) would be the dominant mechanism.^{11a} On the other hand, if the trifurcate template, **DBA³⁺**, is used, then ADMET is enabled and the cyclic trimer **10b** is formed in 50% yield.^{11b} Neither exclusively dimer or trimer is formed with monomer **10** under metathesis conditions in the *absence* of a template. These results can be explained largely on the basis of effective concentrations. When only the dimer template, **DBA²⁺**, is used under dilute (10 mM) conditions, the effective concentration is only sufficient to allow for the formation of a corresponding dimer based on the pre-organization of two monomers on a dimeric template. When the trimer template, **DBA³⁺**, is used, however, three olefin bearing monomers are in close enough proximity to react *via* ADMET, producing a cyclic trimer replicated from the trimeric template.

Multivalency^{5c} and binding cooperativity¹² may have also promoted olefin metathesis of the DB24C8 monomers (**10**) situated on either dimer or trimer template. In both cases, binding cooperativity has been observed for the binding of multiple DB24C8 rings with **DBA²⁺** templates (i.e. $K_{a1} < K_{a2}$ or $K_{a1} < K_{a2} < K_{a3}$). Future studies will hopefully highlight an example where binding cooperativity is not required for switching mechanisms of olefin metathesis as well as probe the relationship between olefin reactivity and the association strength (and even association and dissociation kinetics) of the preorganized template.

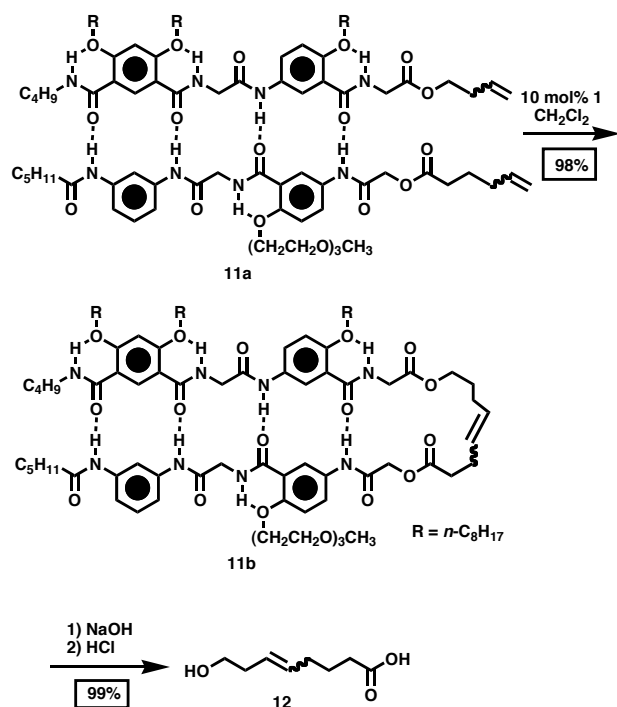
Influencing regioselectivity and, most importantly, sequence are also important goals among synthetic chemists. Nature's approach to synthesizing sequence-specific biopolymers is based exclusively on templated synthesis. A few biomimetic examples have recently emerged in the literature based on templated olefin metathesis. Gong and coworkers successfully synthesized a heterodimer from CM on a sacrificial template that aligned two olefin containing monomers **11a** in the desired geometry (Scheme 5) sufficient for hetero-CM.¹³

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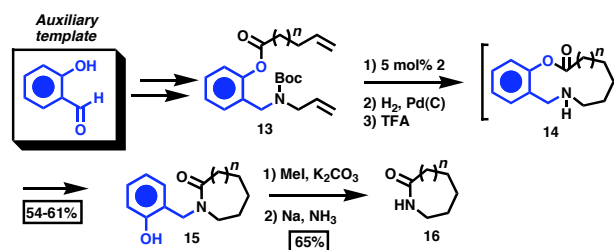
Scheme 5. Templated Synthesis of a Heterodimer



In this case, complementary oligoamide strands bearing terminal olefins were designed to form a heterodimeric hydrogen bonded duplex that situated the two olefin arms on the same side of the duplex. Using initiator **1**, CM covalently connects the two strands. Upon hydrolysis of the ester linkages, a heterodimeric product **11b** is obtained in high overall yield. *Without* a template, two unwanted homodimeric products mixed with the desired heterodimeric product are formed.

While most examples of templated olefin metathesis fall under the umbrella of supramolecular chemistry involving self-assembly and molecular recognition with various noncovalent interactions, templated CM and RCM have become prolific among medicinal and total synthetic laboratories. A clever approach¹⁴ taken by Maarseveen and coworkers utilizes a covalently bound sacrificial template to efficiently synthesize medium-sized lactams (Scheme 6). Salicylaldehyde is used as an auxiliary, sacrificial template for the synthesis of lactams. Salicylaldehyde serves two roles as a template: (i) it promotes the RCM reaction between the amine and the aryl ester olefinic containing arms by keeping the olefins in close proximity to one another, and (ii) it provides the correct spatial positioning of the secondary amine and the carbonyl functional group during the transannular ring-contraction reaction. After ring contraction, the benzyl protecting group is removed, and the desired lactam is obtained (Scheme 6).

Scheme 6. Templated Synthesis of Lactams



Other approaches have utilized a similar internal template that is part of the desired synthetic final target and is *not* sacrificed after use. For example, γ -lactones have been used¹⁵ as templates for RCM in the enantioselective synthesis of medium-sized carbocycles fused to butyrolactones, a functional motif common to many natural products.¹⁶ Similarly, macrocyclic helical peptides have been used as templates for RCM between the *i* and *i*+4 amino acid residues within the helix. In this case, the helix is the template, and the resulting templated product is more stable than the helical precursor.^{17a} The Arora group has optimized this approach by replacing one of the hydrogen bonds between *i* and *i*+4 residues in small alpha helices with a covalent bond formed by templated RCM to produce “hydrogen-bond surrogate helices.”^{17b} This approach has been applied in medicinal chemistry, as the surrogate helices produced by templated metathesis are more stable and are hence more successful at regulating protein-protein interactions.^{17c}

In conclusion, templated olefin metathesis provides straightforward routes to many otherwise inaccessible molecular structures such as catenanes, rotaxanes, and multi-macrocycles, heterodimers, and natural product moieties. Olefin metathesis is particularly suited for templated synthesis because of its reversibility, which permits templates to engage in error checking mechanisms throughout the bond forming or breaking steps. Much like enzymes in biochemistry, templates can readily engage or disengage different metathetical pathways depending on the pre-organization of substrates around a template. It is likely that in the near future, we will see many more examples of how reaction yield, reaction rates, and various forms of selectivity can be controlled through templated olefin metathesis.

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