Ring-Closing Metathesis

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Homodinuclear Ruthenium Catalysts for Dimer Ring-Closing Metathesis**

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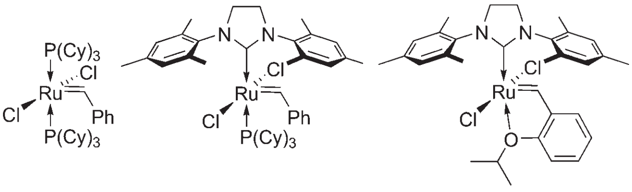
The development of practical olefin metathesis catalysts has led to significant advances in several areas of chemistry during the last decade.[1] For example, the olefin metathesis reaction has found utility in areas ranging from natural product synthesis[2] to polymer[3] and supramolecular chemistry.[4] Olefin metathesis is also now widely used in the pharmaceutical industry[5] and in materials sciences,[6] among other areas. The exceptional reactivity and functional-group tolerance of well-defined catalysts, such as the ruthenium catalysts **1**–**3** (Figure 1), have resulted in a plethora of novel synthetic pathways and strategies that were previously beyond the reach of organic chemists. Although not effortless by any means, the development of modified ruthenium olefin metathesis catalysts is fairly common and variations on the original Grubbs catalyst are many and varied:[7] the introduction of Arduengo-type N-heterocyclic carbene ligands[8] led to improved stability and increased reactivity, for example, while exchanging the phosphine ligand for an isopropoxy ligand (bound directly to the aromatic benzylidene) made the catalysts even more robust.[9]



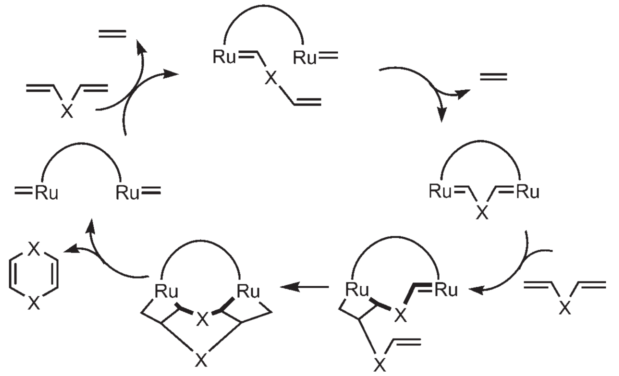
1 **2** **3**

Figure 1. Grubbs first- (**1**) and second-generation (**2**) catalysts and the second-generation Hoveyda–Grubbs catalyst (**3**).

There are three main modes for olefin metathesis: ring-closing metathesis (RCM), ring-opening metathesis polymerization (ROMP), and cross metathesis or acyclic diene metathesis (CM and ADMET). Whereas ROMP utilizes strained cyclic alkenes as a feedstock to produce polymers, RCM and ADMET reactions make use of dienes as starting materials. The product ratio between the intramolecular (RCM) and the intermolecular (ADMET) reaction is dependent on both concentration and effective molarity parameters. Thus, if the concentration of the diene is equal to the effective molarity then, by definition, the rate of the intermolecular reaction will equal the rate of the intramolecular reaction. This means that cyclizations are preferred at low concentrations and that the use of dienes with very low effective molarities will prevent ring closure.[10]

Cyclic dimers are appealing synthetic targets. For example, steroid cyclodimers have been studied as model biological systems and for their molecular recognition in enzymatic processes.[11a] In addition, many cyclodimers display remarkable properties in supramolecular and self-assembly systems.[11] We hypothesized that the development of a *double centered* olefin metathesis catalyst could combine the power of effective molarity and olefin metathesis to produce an alternative mode for the olefin metathesis reaction—a directed type of metathesis that would prefer to produce cyclodimers rather than oligomers or cyclic monomers.

Scheme 1 highlights the main intermediates involved in the process of generating dimeric rings from dienes in a process we have called "dimer ring-closing metathesis" (DRCM). For this strategy to be successful, the rate-determining step must be the disruption of the metallacyclobutane intermediate, in other words there must be enough time for the second double bond to bind to the adjacent ruthenium center before the first metallacyclobutane breaks



Scheme 1. Possible DRCM mechanism (first ruthenacyclobutane intermediates not shown for clarity).

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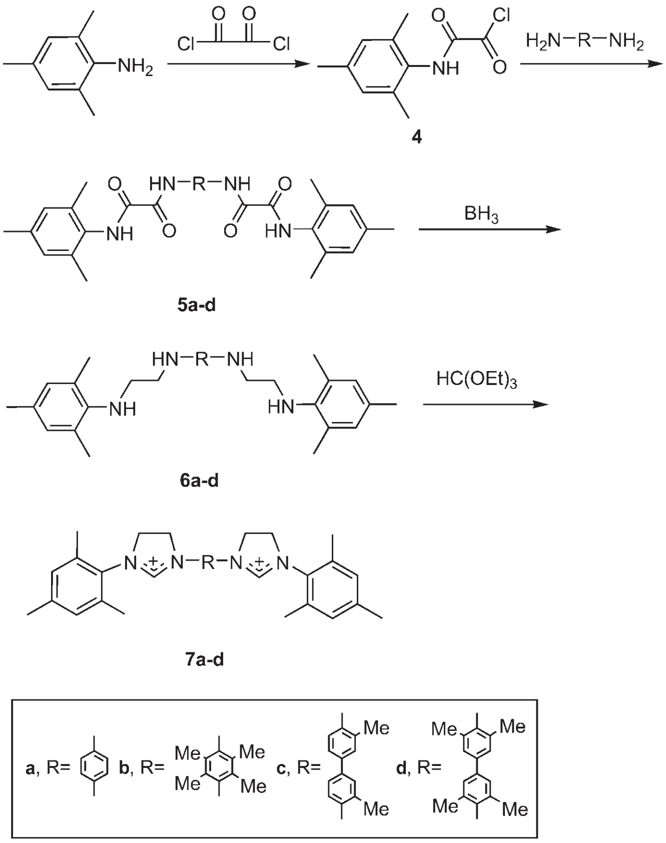
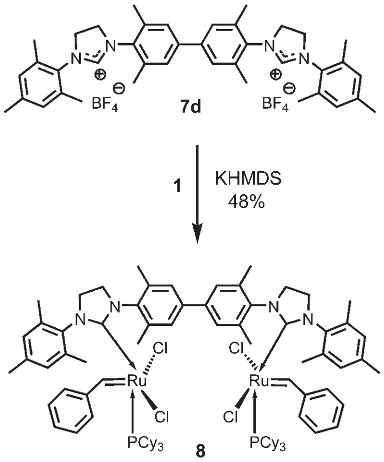
up; if this does not occur each side of the bimetallic catalyst would carry out the reaction independently. Many theoretical studies support the disruption of the ruthenacyclobutane as the rate-determining step,[12] although most authors have emphasized that simpler models may not simulate the complicated intermediates obtained under real metathesis conditions correctly. Nonetheless, for the reaction to be viable, we must assure that the highest effective molarity possible is achieved for the critical dimer ring-closing step.

We therefore set out to synthesize homo-bimetallic ruthenium-type catalysts to test our proposal and study their properties. The first step in the production of these catalysts involves the synthesis of bis-N-heterocyclic carbene (NHC) precursors. Although a few bis-NHC compounds are known in the literature,[13] most of them are used to ligate a single metal atom. We are also unaware of any attempts to obtain tailored distances between the NHC atoms by a modular spacer approach. A recent communication has reported the use of a dimeric linker for the production of oligomeric self-supported catalysts.[14]

The bis-NHC ligand precursors **7** were readily synthesized, as shown in Scheme 2. The length of the bis-aniline spacer is critical since it determines the final distance between the ruthenium atoms in the catalyst. The second step in this synthesis involves deprotonation of **7** to generate bis-carbenes and the exchange of a labile tricyclohexylphosphine ligand in two molecules of **1**. After several unsuccessful attempts to generate the bis-carbenes by typical procedures used for their monomeric counterparts, the addition of potassium hexamethyldisilazide to compound **7d**, followed by addition of catalyst **1** in situ, produced the desired diruthenium catalyst **8** in fair yields (Scheme 3). Significantly, the shorter spacers in **7a** and **7b** did not allow the pure diruthenium catalyst to be obtained by this methodology. We believe that significant steric constraints due to the large tricyclohexylphosphine ligand prevent the formation of the bis-metallic catalyst and lead to mainly mono-insertion.



Scheme 2. Synthesis of bis-NHC precursors.



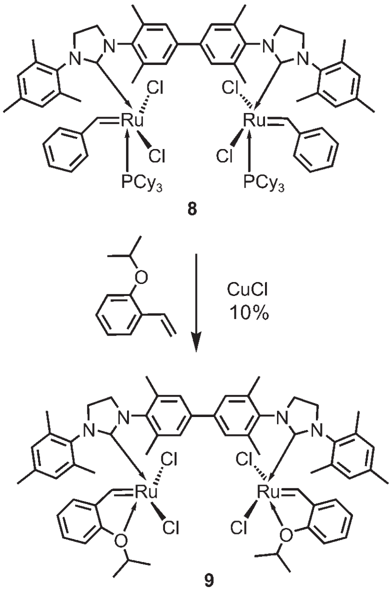
Scheme 3. Synthesis of bis-NHC catalyst **8**.

Catalyst **8** was characterized by NMR spectroscopy and FAB mass spectrometry but proved to be relatively unstable and decomposed after some hours in solution (both in CD_2Cl_2 and [D_8]toluene), in contrast to monomeric catalysts of this type. The detection of benzaldehyde as one of the decomposition compounds indicates the involvement of water in this process.[15] The addition of isopropoxystyrene and copper(I) chloride to improve the stability of the catalyst led to the formation of the isopropoxy chelated bis-catalyst **9**, albeit in low yields due to the instability of **8** (Scheme 4).

The attachment of the chelating isopropoxybenzylidene moiety greatly improved the catalyst stability (no discernible decomposition after standing in air for one week in deuterated dichloromethane solution). Diruthenium catalysts **8** and **9** may appear in the NMR spectrum as a mixture of rotamers due to restricted rotation around the Ru–NHC carbon bond.[16] Indeed, catalyst **8** shows three benzylidene signals due to "out-out" and "out-in" rotamers, while catalyst **9** also displays three benzylidene signals at low temperatures that coalesce into a single signal when the solution is warmed to room temperature. As observed for the monomeric Grubbs catalyst, the introduction of isopropoxybenzylidene ligands allows for faster rotation around the Ru–NHC carbon bond. We will report further details of the NMR dynamics of these, and similar, systems in a future paper.[17]

To our great satisfaction compound **9** also afforded single crystals that allowed its structure to be solved by X-ray diffraction (Figure 2).[18]

To probe the preliminary metathesis activity of the catalysts we realized typical RCM reactions with diethyl



Scheme 4. Synthesis of isopropoxy chelated diruthenium catalyst **9**.

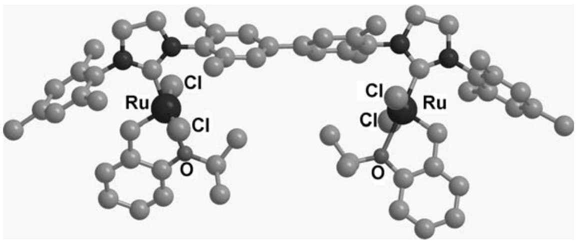
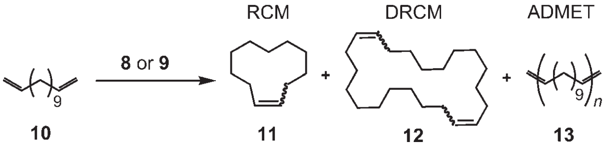


Figure 2. X-ray crystal structure of catalyst **9**.

diallylmalonate and observed that **8** and **9** show similar reactivity to the commercial Grubbs catalysts **1**–**3**. We then decided to test the metathesis reaction with 1,12-tridecadiene (**10**) to see whether our bis-catalyst could "catch" both ends of the diene (Scheme 5). Two main factors influenced the choice of a 13-membered diene as the preferred substrate to test the DRCM protocol: first, molecular modeling predicted this diene to have the right length to attach to both metal centers, and second, the formation of an unfavorable 11-membered ring should hinder ring-closing metathesis. The reaction progress was followed by GC-MS (using decaline as internal standard); the results are summarized in Figure 3.



Scheme 5. Metathesis reactions of **10**.

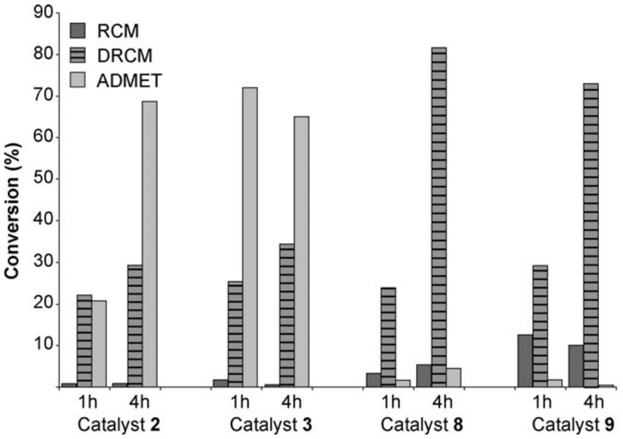
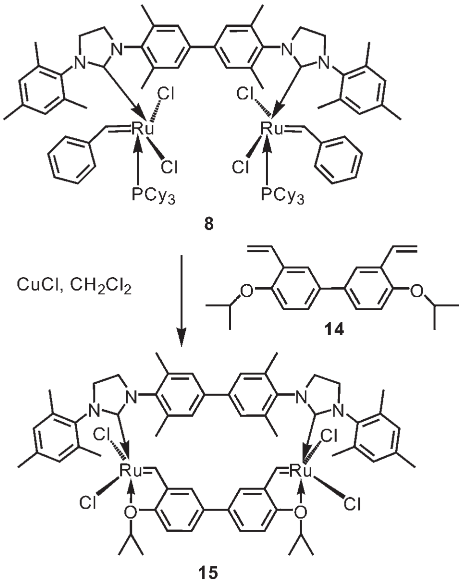


Figure 3. Metathesis of **10** by catalysts **2**, **3**, **8**, and **9**. Average of two measurements. [**10**] = 10 mм; catalyst loading: 5 mol%. DRCM conversion is calculated as the sum of cyclic dimers.[19] ADMET conversion is calculated by difference.

As predicted, in this case the diruthenium catalysts **8** and **9** showed a propensity to preferentially afford DRCM products[19] in comparison to the monomeric catalysts **2** and **3**. Furthermore, the use of diruthenium catalysts prevented the formation of ADMET products almost completely. Thus, a larger ratio of cyclic dimer to oligomer product is observed when the distance between the sp^2 centers is appropriate (the distance between the two Ru centers in **9** in the solid state is 10.2 Å).[20]

To support the assumption that both ruthenium atoms are metathetically active simultaneously, we attached diolefin **14** to catalyst **8**. Compound **14** was synthesized, and compound **15** was isolated after a typical benzylidene exchange procedure involving **8** (Scheme 6) and characterized by NMR spectroscopy and FAB mass spectrometry. The proposed structure for **15** confirms our hypothesis that both ruthenium centers can participate in the DRCM reaction.

In summary, we have demonstrated that by spacing two reactive catalytic centers at the correct distance, effective molarities may help dictate the course of the reaction and



Scheme 6. Synthesis of compound **15**.

produce specific compounds. By using the DRCM protocol, we have successfully inhibited oligomerization and promoted cyclodimerization when the diene starting materials are of the appropriate length. We are currently continuing our work on using these bis-NHC spacers with other metals to try to promote diverse dimer ring-closing reactions, as well as changing the length and rigidity of the spacer to improve the selectivity and scope of DRCM reactions.

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[18] $C_{60}H_{70}Cl_4N_4O_2Ru_2$ (excluding disordered CH_2Cl_2 solvent), monoclinic, space group $C2/c$, $a = 31.0017(4)$, $b = 17.4982(3)$, $c = 24.4562(5)$ Å, $\beta = 91.0662(5)°$, $V = 13264.6(4)$ Å^3, $T = 110$ K, $\rho_x = 1.225\ \text{g cm}^{-3}$. After subtracting the contribution of the disordered solvent from the diffraction data, $R1 = 0.086$ for 6897 reflections with $I > 2\sigma(I)$, and $R1 = 0.13$ and $wR = 0.23$ for all 11561 unique data. CCDC 679217 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[19] Rings of several sizes were observed as a consequence of isomerization (see the Supporting Information). For more information on isomerization of long-chain olefins during metathesis, see: F. C. Courchay, J. C. Sworen, I. Ghiviriga, K. A. Abboud, K. B. Wagener, *Organometallics* **2006**, *25*, 6074 – 6086.

[20] Similar results were obtained with other substrates, although the largest difference with the monomeric catalysts was observed with substrate **10** (see the Supporting Information).