

## Nonproductive Events in Ring-Closing Metathesis Using Ruthenium Catalysts

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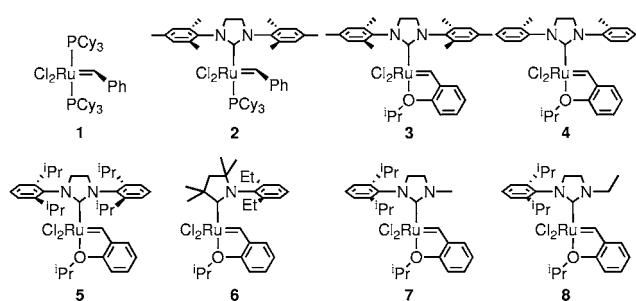
Received April 6, 2010; E-mail: rhg@caltech.edu

The widespread application of olefin metathesis in various fields of chemical synthesis has fueled the continued search for transition metal catalysts that exhibit high reactivity, selectivity, and stability.<sup>1</sup> Studies have described the effect on reactivity upon modifying every ligand of ruthenium-based catalysts. Generally, activity is reported as yield or turnover number (TON) for the reaction of a substrate of interest, which does not account for nonproductive metathesis events.

The role of nonproductive metathesis in the cross metathesis (CM) of terminal olefins has been studied in detail for early hetero- and homogeneous molybdenum and tungsten catalysts.<sup>2</sup> In general, the rate of degenerate metathesis greatly exceeds that of the productive metathesis reactions and evidence suggests the chain-carrying intermediate is a metal alkylidene (M=CHR), not a methyldiene (M=CH<sub>2</sub>). Thus, the TON determined from the amount of product formed is less than the total number of metathesis events that the catalyst has accomplished. An efficient catalyst must perform many turnovers and be selective for productive pathways. Although degenerate reactions do not result in a net change in concentration of the catalyst or the substrate, they can provide additional opportunities for catalyst decomposition and, therefore, can decrease efficiency. Recently, Hoveyda and Schrock reported that degenerate processes in asymmetric ring-closing metathesis (RCM) reactions are both prevalent and key to achieving high levels of enantioselectivity.<sup>3</sup>

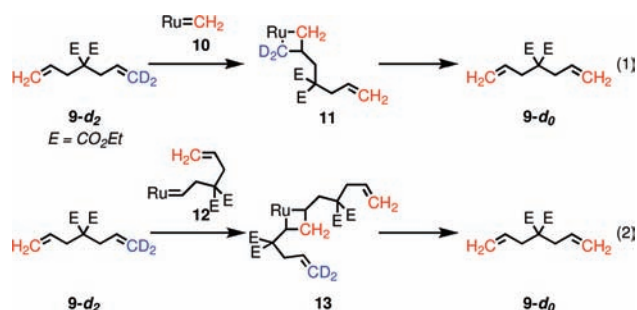
While measuring conversion of substrate is a common and straightforward method of assessing catalyst activity in olefin metathesis, and other catalytic reactions, degenerate metathesis reactions must also be assayed to provide a more complete picture of catalyst efficiency. No data on the rates of degenerate processes are available for modern ruthenium-based catalysts (Chart 1<sup>4</sup>), or for RCM reactions. Herein we report studies aimed at understanding the relative rates of degenerate and productive metathesis reactions.

### Chart 1. Ruthenium-Based Olefin Metathesis Catalysts



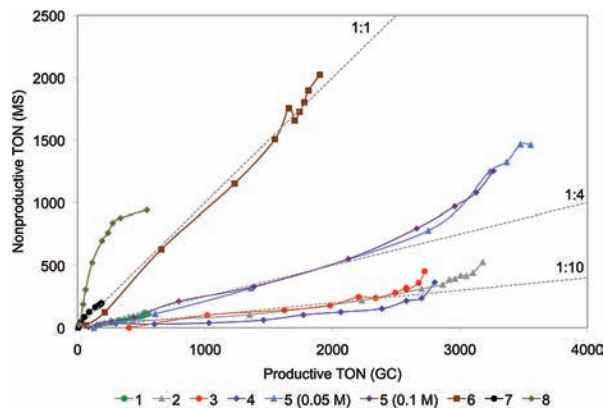
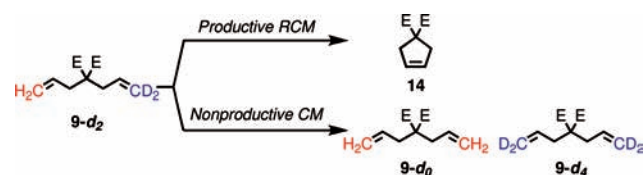
Diethyl diallylmalonate (**9**) and allylmethylmalonate (**15**) have become benchmark substrates for evaluation of olefin metathesis catalysts in RCM.<sup>5</sup> Besides the productive pathway, there are at least two potential nonproductive pathways. The first begins with a ruthenium methyldiene (**10**) and forms a  $\beta$ -substituted metallacycle (**11**); breakdown of this intermediate regenerates the starting material but exchanges the methylene termini (eq 1). Alternatively,

methylene exchange could take place via an  $\alpha,\alpha$ -disubstituted metallacycle (**13**) by coordination of a substrate molecule to ruthenium alkylidene **12** (eq 2).



To investigate these productive and nonproductive pathways, diethyl *d*<sub>2</sub>-diethylallylmalonate (**9-d**<sub>2</sub>) was prepared and subjected to catalysts **1–8**. The conversion to cyclopentene **14** was monitored by GC, while degenerate metathesis reactions were monitored by the appearance of **9-d**<sub>0</sub> and **9-d**<sub>4</sub> by TOF-MS (Scheme 1).<sup>6,7</sup>

### Scheme 1. Assay for Nonproductive RCM of **9**



**Figure 1.** Plot of nonproductive versus productive conversion for the RCM reactions shown in Scheme 1. Reaction conditions were 50 °C in toluene (1 mL) with substrate (0.1 mmol) and catalyst (**1** – 1000 ppm, **2**, **3**, **4**, **5** – 250 ppm, **6** – 500 ppm, **7** – 5000 ppm, **8** – 1000 ppm).

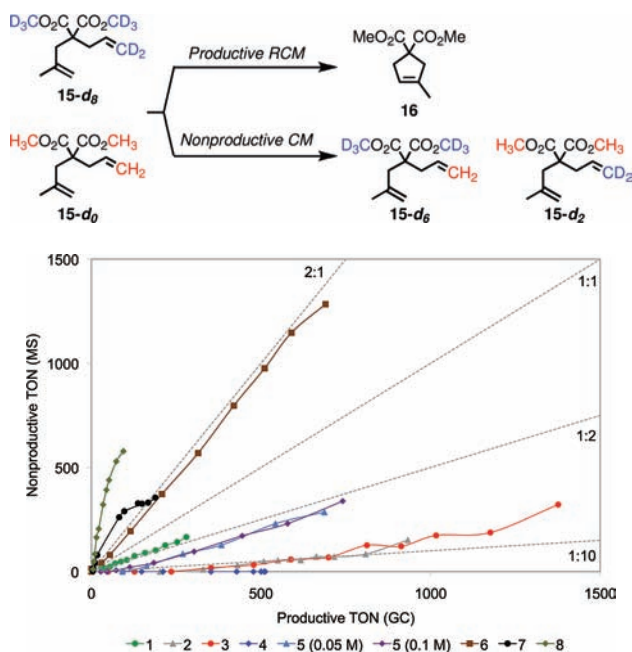
Figure 1 shows the degenerate TON versus productive TON. Surprisingly, significant levels of degenerate events were detected with many catalysts. NHC-bearing catalysts **2–4** display degenerate/

productive ratios of approximately 1:10, while that for **5**, which is a catalyst containing the bulky 2,6-diisopropylphenyl (DIPP) substituent, is closer to 1:4. Cyclic alkylaminocarbene (CAAC)-containing catalyst **6** catalyzes a nearly equal number of degenerate and productive metathesis events, as do *N*-alkyl catalysts **7–8**.

Catalyst **5** was evaluated at two concentrations, and no change in the ratio of degenerate to productive metathesis events was detected; this is highly suggestive that nonproductive metathesis events are catalyzed by a methylenide species (eq 1), as the alternative mechanism (eq 2) is second order in substrate and would be expected to have some concentration dependence.

To evaluate the significance of degenerate metathesis in the RCM of a more challenging substrate, deuterated dimethyl allylmethylmalonate **15-d<sub>8</sub>** was prepared. A mixture of this isotopomer and the per-protio compound (**15-d<sub>0</sub>**) was prepared and subjected to catalysts **1–8** (Scheme 2). Nonproductive metathesis was measured via TOF-MS by monitoring the appearance of **15-d<sub>6</sub>** and **15-d<sub>2</sub>**. Again, NHC catalysts **2–4** perform the fewest degenerate events; in fact almost none were detected with **4** (Figure 2). Bulky NHC-bearing complex **5** and diphosphine catalyst **1** perform around one degenerate event for every two productive turnovers. Catalysts **6–8**, however, perform two or more nonproductive reactions for every productive RCM event. As in the RCM of **9**, no concentration dependence on the ratio of degenerate to productive turnovers was detected with catalyst **5**.

#### Scheme 2. Assay for Nonproductive RCM of **15**

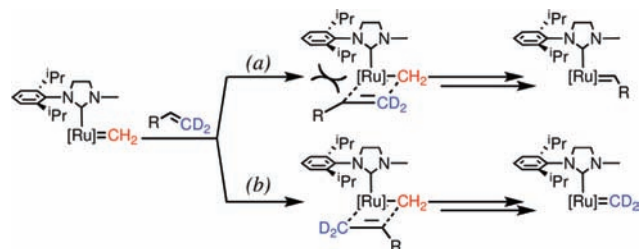


**Figure 2.** Plot of nonproductive TON versus productive TON for the RCM reactions shown in Scheme 2. Reaction conditions were 50 °C in toluene (1 mL) with substrate (0.1 mmol) and catalyst (**1** – 1000 ppm, **2, 3, 4, 5** – 250 ppm, **6** – 500 ppm, **7** – 5000 ppm, **8** – 1000 ppm).

From these two data sets, it is plausible to propose that sterics is the overriding determinant of the relative rates of degenerate to productive events. Specifically, a catalyst bearing an unsymmetric carbene ligand with significantly different-sized groups will favor degenerate metathesis pathways (e.g.,  $\text{CMe}_2$  vs *N*-2,6-Et<sub>2</sub>Ph in **6**, *N*-Me vs *N*-2,6-*i*Pr<sub>2</sub>Ph in **7**, *N*-Et vs *N*-2,4,6-Me<sub>3</sub>Ph in **8**). Scheme 3 illustrates this model beginning with the methylenide derived from catalyst **7**. Coordination of a terminal olefin can proceed with two possible regiochemistries: the first generates an  $\alpha$ -substituted metallacycle (path a) and results in the formation of an alkylidene that ultimately leads

to a productive turnover event; the second generates a  $\beta$ -substituted metallacycle (path b), which exchanges the olefin termini but does not generate a molecule of product. The nonproductive pathway is especially facile with catalysts **6–8** due to the absence of any significant steric interactions between the ligand and the approaching olefin en route to the  $\beta$ -substituted metallacycle. Catalysts with symmetric and bulky groups (e.g., *N*-2,6-*i*Pr<sub>2</sub>Ph on both sides of **5**) would experience similar interactions along path a but increased steric repulsion along path b, resulting in fewer nonproductive events and thus higher overall efficiency.

#### Scheme 3. Steric Model for Ligand Effect on Nonproductive Metathesis



Herein we have described the study of nonproductive reactions in ring-closing metathesis using ruthenium catalysts. The number of nonproductive events in relatively simple substrates is strikingly high but comparable with early work on heterogeneous systems. The steric model proposed can be applied to other important metathesis processes where selectivity is important.

**Acknowledgment.** The NIH (K99GM084302 to I.C.S., 5R01GM-31332 to R.H.G.) for generous financial support, Hosea Nelson and Brian M. Stoltz (Caltech) for assistance with and use of their TOF-MS instrument, and Scott Virgil (Caltech Center for Catalysis and Chemical Synthesis) for assistance with automation and analytical equipment.

**Supporting Information Available:** Experimental procedures and details of quantitative analysis. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- Note that exchanges of olefin termini that do not result in a change in isotopic composition are also occurring. For a complete discussion of how degenerate TONs were calculated see the Supporting Information. Isotope effects are beyond the scope of the current discussion.
- For a discussion on the reversibility of the RCM reaction, see the Supporting Information.

JA1029045