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Relay Ring-Closing Metathesis (RRCM): A Strategy for Directing Metal Movement Throughout Olefin Metathesis Sequences

Thomas R. Hoye,* Christopher S. Jeffrey, Manomi A. Tennakoon, Jizhou Wang, and Hongyu Zhao

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

Received June 18, 2004; E-mail: hoye@chem.umn.edu

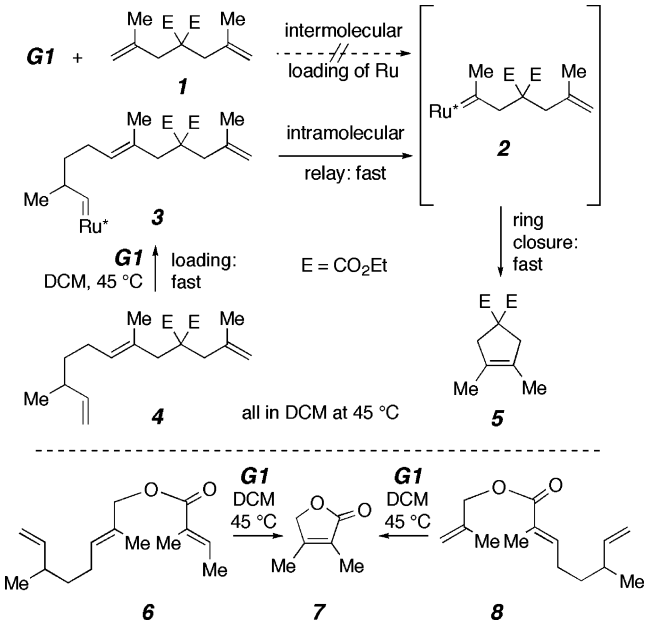
In the past decade, ring-closing metathesis (RCM) has been established as a powerful and generally applicable method for construction of carbocycles. However, even with the remarkable successes emanating from literally thousands of laboratories, the applicability of RCM is not universal. Limitations are most often encountered as users attempt to apply the technology to the construction of increasingly complex molecular targets. More specifically, RCM can fail when substrate alkenes are either sterically hindered or electronically deactivated.

To circumvent these types of problems, thereby increasing the scope of the RCM reaction, we have developed the concept of *relay* ring-closing metathesis (RRCM).[1] This involves the design of substrates that, in effect, permit one to dictate the sequence of metathesis events by choreographing the metal atom (Ru in the case of **G1**[2a] and **G2**[2b]) through the individual steps of the RCM cascade.[3] As we show here, relay RCM (RRCM) permits the cyclization of many types of otherwise recalcitrant alkene substrates. The results described here demonstrate how to rationally design modifications of imperfect RCM substrates so that subsequent RRCM solves a reactivity or selectivity problem. This constitutes a new type of substrate control, one in which use of a newly designed substrate steers the reaction pathway in a preferred direction.

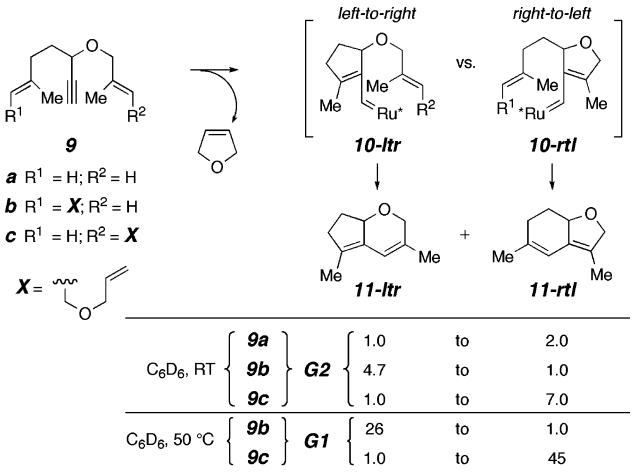
Our first example of RRCM[1a] involved the cyclization shown in Scheme 1.[4] Diene **1**, bearing two 1,1-disubstituted ethylene moieties, is known to be unreactive toward the first-generation Grubbs initiator **G1**[5], the ruthenium complex in hand at that time. **G1** is not sufficiently active to engage geminally substituted terminal alkenes.[6] In contrast, exposure of the modified relay substrate **4** to **G1** resulted in smooth cyclization to the cyclopentene derivative **5**.[7a] This and **7** are the only examples we know of tetrasubstituted alkenes formed by **G1**-mediated RCM of a simple α,ω-diene. Thus, introduction of the remote terminal alkene in **4** (readily derived from citronellene) opened a pathway to access **2** by way of **3**. A second example involved closure of either of the isomeric substrates **6** or **8** to the electron-deficient, tetrasubstituted alkene. Thus, one can access either of two independent pathways (no identical intermediates)[7b] from either end of a molecule. These results also demonstrate that cyclization both onto (during **6** to **7**) and into (during **8** to **7**) an electron-deficient alkene is viable.

Although these first successes clearly demonstrated the RRCM concept, the advent of the second-generation Grubbs initiator (**G2**) significantly increased the scope of the traditional RCM reaction (e.g., **1** can be closed to **5** with **G2**[8]). Nonetheless, that scope is finite. The results presented in Scheme 2 constitute definitive examples in which RRCM provides a level of control that is not available with traditional RCM. In addition, they demonstrate that catalyst-to-substrate matching can provide synergistic benefits.

Scheme 1



Scheme 2



Tandem enyne metathesis[9] substrates **9** (Scheme 2)[4] can cyclize with either a *left-to-right* or *right-to-left* endedness to give isomeric dienes **11-*ltr*** (via **10-*ltr***) or **11-*rtl*** (via **10-*rtl***). Closure of parent dienyne **9a** with **G2** provided the benchmark value of 1.0:2.0 for the ratio of products **11-*ltr*** to **11-*rtl***. The related relay substrates **9b** vs **9c** (now containing an allylic ether relay moiety) provided improved, but imperfect, selectivity. RRCM closure of each with **G2** gave 1.0:7.0 vs 4.7:1.0 ratios of **11-*ltr*** to **11-*rtl***, respectively. Thus, **G2** may not be highly discriminating of the two termini in **9b** or **9c**.[7c] If true, then the less reactive **G1** should be superior. Consistent with this analysis, relay substrate **9b**, when treated with **G1**, gave the bicyclic diene **11-*ltr*** very selectively (26:1.0).

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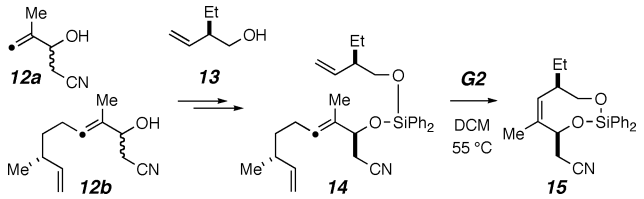
Scheme 3

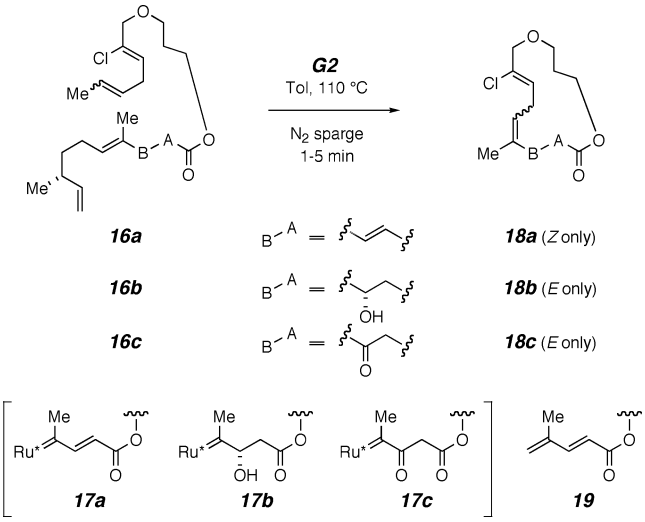


Moreover, analogous treatment of the isomeric **9c** (the "endomer" of **9b**) was highly complementary, giving **11-*rtl*** nearly exclusively (1.0:45).

RRCM also offers nonobvious advantages. In the course of preparing a nonracemic sample of **15** (Scheme 3),[4] the anticipated product of a silicon-tethered cross-metathesis of **12** with **13**, we observed that the lipase resolution of carbinol (±)-**12a** was not serviceable (40% ee). Recognizing the expendable nature of the remote alkene atom (• in **12**) *and all that it bears* during RRCM, we capitalized on the greater size difference of the groups flanking the carbinol center in (±)-**12b** to achieve a much more efficient lipase differentiation (≥90% ee). RRCM of **14** with **G2** then led to **15** in good (58%) isolated yield.[1b]

The RRCM reactions shown in Scheme 4[4] are instructive in different ways. Substrates **16a**−**c** are armed with a relay moiety, ready to pass the metal into an otherwise less accessible (electronically and/or sterically deactivated) site (cf. the atypical Ru-alkylidene intermediates **17a**−**c**). When each of the polyenes **16a**−**c**

Scheme 4



was subjected to **G2** in toluene at 110 °C (with continuous N_2 sparging), it was consumed within minutes.[7d] The cyclized product **18**, a 14-membered lactone, was formed as the exclusive [**18a** (*Z*-only) and **18b** (*E*-only)] or major product [**18c** (*E*-only) + ∼20% byproducts]. Importantly, a control experiment demonstrated that the independently prepared truncation product **19**, corresponding to substrate **16a**, did not give **18a** under the reaction conditions, ruling out its intermediacy in the conversion of **16a** to **18**. Ring closure originating from the opposite end of **16a**−**c** would likely suffer from low reactivity and/or regioselectivity issues inherent to the alkenes in the C═C(Me)ABCO$_2$R subunit. Finally, since most acyclic RCM substrates are synthesized by convergent strategies in modular fashion (e.g., **16a**−**c** were all easily assembled by straightforward esterification), it will usually be a relatively simple task for a researcher to modify the appropriate alkene to incorporate the relay extension even if commitment to the RRCM strategy is not made from the outset of a synthetic plan.

The specific examples of relay-driven ring closures presented here demonstrate a number of strategic advantages. Tetrasubstituted, electron-deficient alkenes were prepared using **G1** (Scheme 1), fully complementary control of directionality (endedness) was achieved (Scheme 2), nonobvious auxiliary benefits (enzyme specificity) from the incorporation of additional steric bulk were recognized (Scheme 3), mechanistic insight (not discussed) has emerged, ineffective substrates for traditional RCM closures were turned on (Schemes 1−4), and unorthodox alkenes could be used as initiation sites for ring closure (Scheme 4). From these examples, one can see that relay ring-closing metathesis is complementary to traditional RCM. It represents enabling technology for molecular construction at the strategic level. We predict that many applications will emerge as investigators contemplate their own uses of RRCM.

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Supporting Information Available: Spectral characterization data for compounds **4**, **5**, **6-8**, **9a-c**, **11-*ltr***, **11-*rtl***, **12a**,**b**, **14**, **15**, **16a**−**c**, and **18a**−**c**; reaction conditions for all RRCM reactions; yield data for all reactions; and a representative sequence of ^{1}H NMR spectra from monitoring tandem dienyne metathesis cyclization (**9b** to **11-*ltr*** + **11-*rtl***) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) (a) **G1** [$(Cy_3P)_2(Cl_2)$Ru═CHPh]: Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110. (b) **G2** [$(H_2IMes)(Cy_3P)$-(Cl_2)Ru═CHPh]: Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org Lett.* **1999**, *1*, 953−956.

(3) For recent reports where this strategy was used to an advantage in improving the efficiency (directionality) of metathesis cross-coupling and macrocylization reactions, respectively, see: (a) Hansen, E. C.; Lee, D. *Org. Lett.* **2004**, *6*, 2035−2038. (b) Wang, X.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2004**, *43*, 3601−3605. See also (c) Randl, S.; Gessler, S.; Wakamatsu, H.; Blechert, S. *Synlett* **2001**, 430−432. (d) She, J.; Crimmins, M. T. *Abstracts of Papers*, 226th National Meeting of the American Chemical Society, Sept 7−11, 2003, New York; American Chemical Society: Washington, DC, 2003; ORGN-193. (e) Robinson, J.; Piscopio, A. D. *Abstracts of Papers*, 226th National Meeting of the American Chemical Society, Sept 7−11, 2003, New York; American Chemical Society: Washington, DC, 2003; ORGN-118.

(4) For reaction conditions see Supporting Information.

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(7) (a) Trace amount (<2%) of the "truncation" byproduct **1** (E = CO_2Et) was observed, presumably arising from cross-metathesis of **2** with either **4** or ethylene. A control experiment in which **4** (E = CO_2Et) was doped with **1** (E = CO_2Me) gave none of **5** (E = CO_2Me), demonstrating that the truncated byproduct was not part of a productive pathway. (b) A control experiment showed that methallyl methacrylate was, as expected, unreactive and, therefore, not a common intermediate. (c) An alternative explanation is that a portion of **9b** or **9c** was being truncated to parent **9a**, thereby eroding selectivity. In situ NMR monitoring (see Supporting Information) suggested that this was not the case. (d) Without active removal of ethylene and propylene (N_2 sparging and vigorous reflux), truncation products such as **19** were frequently formed as terminal events.

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