Selective Ring-Opening Cross-Metathesis. Short Syntheses of Multifidene and Viridiene

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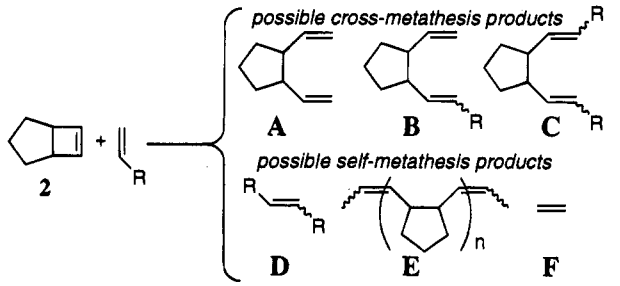
With the development of structurally defined, metathesis-competent alkylidene complexes,[1] advances in metathesis-based synthesis have been numerous.[2] For example, ring-closing metathesis has become a proven way of generating various heterocycles and cycloalkenes and has provided several applications toward natural product synthesis.[3] In contrast, while the value of ring-opening cross-metathesis for small molecule synthesis has been recognized, the selectivity and efficiency of the process is not yet of high synthetic utility.[4] Considering this shortcoming, we report herein a ring-opening cross-metathesis reaction between cyclobutene-containing substrates and terminal olefins in the presence of $(Cy_3P)_2Cl_2Ru{=}CHCH{=}CPh_2$ (**1**)[5] that selectively affords 1,5-diene-containing molecules.[6] The utility of the reaction is exemplified by concise total syntheses of the brown algae pheromones multifidene[7] and viridiene.[8]

At the onset of this project our expectation was that the cross-metathesis of two substituted olefins would produce several cross- and self-metathesis products with little selectivity (*cf.* Scheme 1). In view of this potential complication, we initially employed symmetrical olefins to reduce the number of undesired side products. Unfortunately, this combination yields only high molecular weight material derived from the polymerization of the cyclobutene substrate.[9] *However, when a terminal olefin is used in place of the symmetrical alkene, only the monomeric cross-metathesis product* ***B*** *(Scheme 1) is produced. Other*

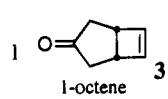
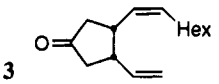
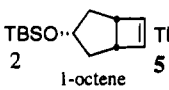
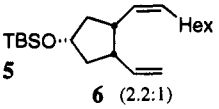
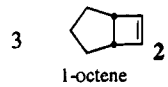
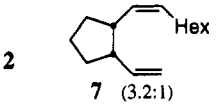
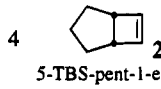
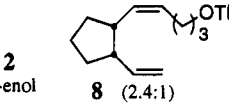
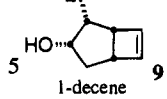
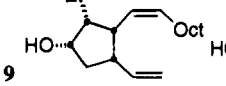
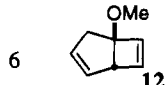
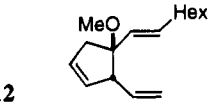
Scheme 1



cross- and self-metathesis products, ***C*** *and* ***D****, are observed only after all the cyclobutene substrate is consumed.*

As a hedge against competing self-metathesis of the cyclobutenes, the terminal olefins were initially employed in excess (8−15 equiv); however, subsequent reactions were run with as little as 1.5 equiv of terminal olefin with minimal diminution in reaction efficiency. Optimal yields are obtained when a mixture of the cyclobutene substrate and terminal olefin is added slowly to a CH_2Cl_2 or benzene solution of **1** (1 mol %, entries 1−5, Table 1, 10 mol %, entry 6).[10] Although GC and NMR yields are 80−95%, isolated yields after silica gel chromatography vary, depending on the volatility and reactivity of the 1,5-diene products (45−75%). Generally, the cis configuration of the newly formed product olefin is favored. The exception is substrate **12** (entry 6), which contains an angular methoxy group. In this case, the major product's alkenyl group, located on the more hindered side of the cyclopentyl ring, is of the trans configuration.

Table 1. Ring-Opening Cross-Metatheses[a]

Entry	Olefins	Products[b] (cis:trans)	Yield[c]
1	 1-octene	 **4** (2.3:1)	63% (96%)
2	 1-octene	 **6** (2.2:1)	69% (80%)
3	 1-octene	 **7** (3.2:1)	68% (89%)
4	 5-TBS-pent-1-enol	 **8** (2.4:1)	46% (95%)
5	 1-decene	 **10** (2.3:1) **11** (1.7:1)	56% **10:11**/1.3:1
6	 1-octene	 **13** (1:8.8) **14** (2.2:1)	66% (81%) **13:14**/4.1:1

[a] Cyclobutene substrates were prepared by photolyzing functionalized cycloheptadienes or cycloheptatriene.[20] [b] Only major product(s) are shown. [c] Isolated yields. GC yields corrected for FID response factors relative to dodecane are shown in parentheses.

To demonstrate further the utility of the ring-opening metathesis, efficient syntheses of the marine brown algae signaling molecules,[11] multifidene and viridiene were carried out. As

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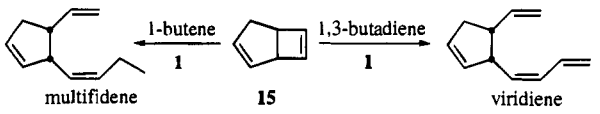
summarized in Scheme 2, bicyclo[3.2.0]hepta-2,6-diene (**15**), obtained through the photolysis of cycloheptatriene,[12] was slowly added to **1** (1 mol %) in benzene under a 1-butene atmosphere. Multifidene was produced in a 31% yield along with three other known multifidene isomers (70% total yield). Similarly, **15** was slowly added to **1** (1 mol %) under a 1,3-butadiene atmosphere to produce viridiene in 30% yield.[13] Both of these syntheses represent improvements over the previously reported routes.[14]

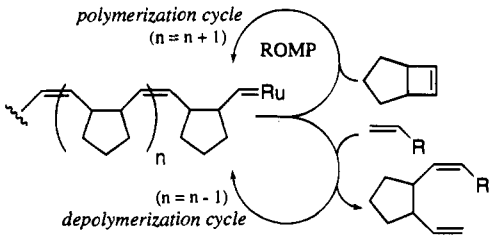
Scheme 2



Two mechanistic scenarios might be suggested for the selectivity observed in these transformations:

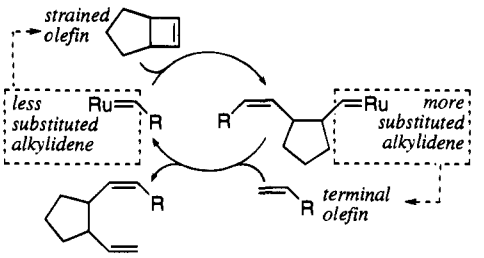
(1) As shown in Scheme 3, the cyclobutene substrate may first undergo a ring-opening metathesis polymerization (ROMP), which is then followed by a depolymerization of the living polymer by the remaining terminal olefin to produce selectively the observed monomer.[15] An attractive feature of this scenario is that the terminal olefin's initial lack of self-metathesis is explained by the sequestering of the ruthenium alkylidene on the terminus of the living polymer. However, in the context of this mechanistic sequence, it is noteworthy that treatment of preformed living polymer (made from **2**) with 1-octene affords the desired monomer **7**, albeit in low yield (15%).

Scheme 3

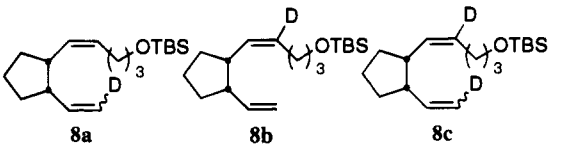


(2) Alternatively, various ruthenium alkylidenes formed along the catalytic cycle may differ in their olefin reactivity (Scheme 4).[16] It is possible that the more substituted ruthenium alkylidene, resulting from metathesis of the cyclobutene substrate, preferentially reacts with the less hindered terminal alkene.[17] In contrast, the less hindered alkylidene, derived from reaction with the terminal olefin, could be less sensitive to steric factors and react selectively with the strained cyclobutene. Such patterns in alkylidene reactivity may then account for the selective formation of a single cross-metathesis product.

Scheme 4



To help distinguish between the above two mechanistic hypotheses, a deuterium crossover experiment was carried out.[18] If the depolymerization process (1) is operative, a single terminal olefin would be expected to be entirely incorporated into each product molecule. On the other hand, if the second mechanism is active, the terminal olefin portion of the product should be scrambled. Ring-opening cross-metathesis of **2** with an equal mixture of CH_2=$CH(CH_2)_3OTBS$ and $CH(D)$=$CD(CH_2)_3OTBS$ generated a substantial amount of monodeuterated products (**8**: (**8a** + **8b**):**8c** ≈ 2.8:4.2:1). Since the labeling of the recovered terminal olefins was not altered, the results support mechanism 2 (Scheme 4).[19]



8a **8b** **8c**

As illustrated by the syntheses of multifidene, viridiene, and the examples in Table 1, ring-opening cross-metatheses catalyzed by **1** provide rapid access to 1,5-diene-containing systems. Terminal olefins add selectively to cyclobutene substrates with little or no other cross- or self-metathesis byproducts. Studies designed to provide a better understanding of alkylidene reactivity and selectivity issues are in progress.

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Supporting Information Available: Experimental procedures and spectrographic data for new compounds (19 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(10) In a representative procedure, the cyclobutene substrate (1.5 mmol), terminal olefin (3.0 mmol), and dodecane internal standard (0.23 mmol) in CH_2Cl_2 (2.5 mL) are added to **1** (0.015 mmol) in CH_2Cl_2 (7.5 mL) over 2 h under an Ar atmosphere. When the reaction is complete (judged by GC), the reaction mixture is filtered through silica (1 cm) and then purified by chromatography to yield the corresponding 1,5-diene. New compounds are characterized by IR, MS, (^{1}H,^{13}C) NMR spectroscopy, and elemental analysis.

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(14) Previous syntheses required 9–11 steps to produced viridiene or multifidene in approximately 3–8% overall yield. See references cited in footnote 13 for details.

(15) For related depolymerization reactions, see: (a) Wagener, K. B.; Puts, R. D. *Polym. Prepr.* **1991**, *32*, 379–380. (b) Marmo, J. C.; Wagener, K. B. *Macromolecules* **1993**, *26*, 2137–2138.

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(18) Casey, C. P.; Tuinstra, H. E. *J. Am. Chem. Soc.* **1978**, *100*, 2270–2272.

(19) As pointed out by a referee, it is not proven that a single terminal olefin is entirely incorporated into each product molecule in the depolymerization pathway. However, deuterium crossover results, low yield of product in the depolymerization experiment, and lack of oligomeric byproducts in the cross-metathesis all disfavor mechanism 1.

(20) (a) Chapman, O. L.; Pasto, D. J.; Borden, G. W.; Griswold, A. A. *J. Am. Chem. Soc.* **1962**, *84*, 1220–1224. (b) Schuster, D. I.; Kim, C. W. *J. Am. Chem. Soc.* **1974**, *96*, 7437–7444.