Regio- and Stereoselective Ring-Opening Cross-Metathesis. Rapid Entry into Functionalized Bicyclo[6.3.0] Ring Systems

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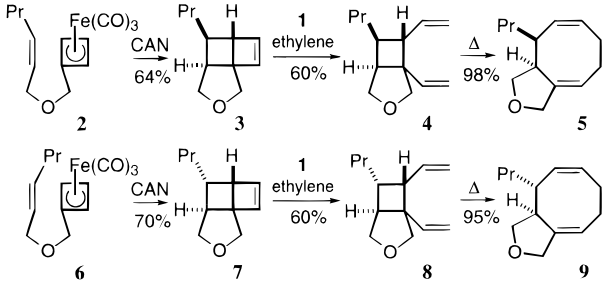
Selectivity issues remain an important challenge in the development of new and synthetically useful olefin metatheses.[1] This is particularly relevant with *inter*molecular metatheses, where, unlike the related *intra*molecular variants, geometric constraints play little or no role in affecting the reaction outcome. Nevertheless, recent studies in these and other laboratories have shown that with proper consideration of steric and electronic factors, selective intermolecular metatheses between differing alkenes are indeed possible.[2] Issues concerning regio- and stereochemical control in some of these processes, however, are largely unexplored. Accordingly, we report herein the first regio- and stereoselective ring-opening cross-metathesis of cyclobutene-containing substrates; the utility of the transformation is illustrated through a rapid and stereospecific synthesis of bicyclo[6.3.0] ring systems.

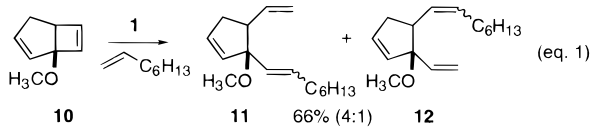
To exploit our recently reported preparation of functionalized cyclobutene-containing systems,[3] we examined the ring-opening cross-metathesis of compounds **3** and **7** (Scheme 1). We find that a $Cl_2(Cy_3P)_2Ru{=}CHPh$ (**1**)[4] catalyzed cross-metathesis of cycloadducts **3** or **7** with ethylene followed by a Cope rearrangement[5] provides a concise entry into bicyclo[6.3.0] ring systems (*i.e.,* **3** → **5** and **7** → **9**).

Considering the functionality observed in natural products that possess the bicyclo[6.3.0] architecture,[6] employing a substituted alkene in the ring-opening cross-metathesis will be of greater value. Using an unsymmetrically substituted olefin, however, introduces new regio- and stereochemical control questions. As indicated in our initial report,[2a] some selectivity

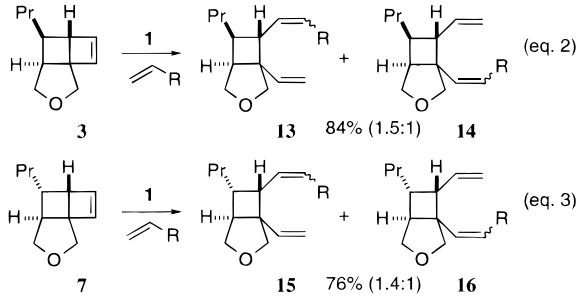
Scheme 1



is observed in the ring-opening cross-metathesis of cyclobutene **10**, where regioisomers **11** (1:9 *Z*:*E*) and **12** (2:1 *Z*:*E*) are formed in a 4:1 ratio (eq 1). In light of these and related observations, we were optimistic that compounds **3** and **7** would display similar or greater levels of control.



Contrary to our expectations, cross-metathesis of cyclobutenes **3** or **7** with a terminal olefin (TBS protected 4-penten-1-ol) provides ring-opened products with little regiocontrol (eqs 2 and 3). Variations in solvent polarity, reaction temperature, and terminal olefin electronics unfortunately did not lead to improvements of selectivity in this transformation.



Reconsideration of the steric factors influencing the cross-metathesis regioselectivity in **10** suggested that the conformation of the methoxy group may play a role in dictating the reaction outcome. To test this possibility, substrates containing substituents that occupy the analogous region about the reactive cyclobutene moiety in **3** and **7** were prepared. As illustrated in Table 1, cycloadducts with a methyl (**17**) or hydroxyl group (**19**) projecting from the *exo*-face of the cyclobutene provide reasonable levels of regioselectivity. Moreover, the newly-formed olefins in the major regioisomers were exclusively of the *E*-olefin geometry (>20:1; entries 1 and 2).

The critical nature of the substituent geometry relative to the reacting cyclobutene becomes evident with the ring-opening cross-metatheses of the corresponding diastereomers, **21** and

(1) For recent representative examples, see: (a) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634−6640. (b) Fujimura, O.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 2499−2500. (c) Visser, M. S.; Heron, N. M.; Didiuk, M. T.; Sagal, J. F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 4291−4298. (d) Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y.; Patzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251−7264. (e) Pandit, U. K.; Borer, B. C.; Bieraugel, H. *Pure Appl. Chem.* **1996**, *68*, 659−662. (f) Miller, S. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 5855−5856. (g) Martin, S. F.; Wagman, A. S. *Tetrahedron Lett.* **1995**, *36*, 1169−1170. (h) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108-2109. (i) Houri, A. F.; Xu, Z.; Cogan, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943−2944. (j) Schrock, R. R.; Lee, J.-K.; O'Dell, R.; Oskam, J. H. *Macromolecules* **1995**, *28*, 5933−5940. (k) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446−452, and references cited therein.

(2) (a) Randall, M. L.; Tallarico, J. A.; Snapper, M. L. *J. Am. Chem. Soc.* **1995**, *117*, 9610−9611. (b) Crowe, W. E.; Zhang, A. J. *J. Am. Chem. Soc.* **1993**, *115*, 10998−10999. (c) Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162−5163. (d) Clark, T. D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1995**, *117*, 12364−12365. (e) Bespalova, N. B.; Bovina, M. A.; Sergeeva, M. B.; Oppengeim, V. D.; Zaikin, V. G. *J. Mol. Catal.* **1994**, *90*, 21−27. (f) Schneider, M. F.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 411−412.

(3) Tallarico, J. A.; Randall, M. L.; Snapper, M. L. *J. Am. Chem. Soc.* **1996**, *118*, 9196−9197.

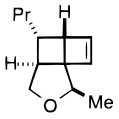
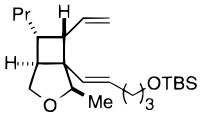
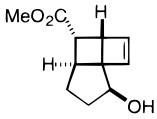
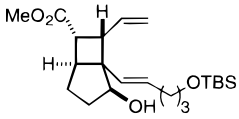
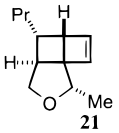
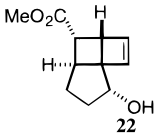
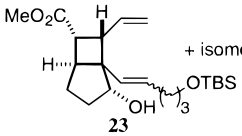
(4) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.

(5) For examples of preparing cyclooctadiene-containing systems through a Cope rearrangement, see: (a) Wehrli, R.; Bellus, D.; Hansen, H.; Schmid, H. *Chima* **1976**, *30*, 416. (b) Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 1. (c) Hammond, G. S.; Turro, N. J.; Fischer, A. *J. Am. Chem. Soc.* **1961**, *83*, 4674. (d) Berson, J. A.; Dervan, P. B.; Malherbe, R.; Jenkins, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 5937. (e) Wender, P. A.; Correia, C. R. D. *J. Am. Chem. Soc.* **1987**, *109*, 2523.

(6) For example, see: (a) Hanson, J. R. *Nat. Prod. Rep.* **1986**, *3*, 123−132. (b) Burke, J. W.; Doskotch, R. W.; Ni, C.-Z.; Clardy, J. *J. Am. Chem. Soc.* **1989**, *111*, 5831−5833. (c) Gadwood, R. C.; Lett, R. M.; Wissinger, J. E. *J. Am. Chem. Soc.* **1986**, *108*, 6343−6350. (d) Hashimoto, T.; Tori, M.; Taira, Z.; Asakawa, Y. *Tetrahedron Lett.* **1985**, *26*, 6473−6476. (e) Kato, N.; Wu, X.; Tanaka, S.; Takeshita, H. *Chem. Lett.* **1989**, 91−94. (f) Enoki, N.; Furusaki, A.; Suehiro, K. *Tetrahedron Lett.* **1983**, 4341−4342. (g) Adesomoju, A. A.; Okogun, J. I. *J. Nat. Prod.* **1984**, *47*, 308−311. (h) Wahlberg, I.; Eklund, A.-M.; Nishida, T.; Enzell, C. R. *Tetrahedron Lett.* **1983**, *24*, 843−846. (i) Prestwich, G. D.; Tempesta, M. S.; Turner, C. *Tetrahedron Lett.* **1984**, *25*, 1531−1532. (j) San Feliciano, A.; Barrero, A. F.; Medarde, B. M.; Miguel del Corral, J. M. *Tetrahedron Lett.* **1985**, 26, 2369−2372. (k) Huneck, S.; Baxter, G.; Cameron, A. F.; Connolly, J. D.; Rycroft, D. S. *Tetrahedron Lett.* **1983**, *24*, 3787−3788.

S0002-7863(96)03826-7 CCC: $14.00

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

entry	substrate	major product	yield[b] (regioisomer ratio)
1	 **17**	 **18**	72% (8:1)
2	 **19**	 **20**	60% (10:1)
3	 **21**	-	0%
4	 **22**	 **23**	57% (1.9:1)

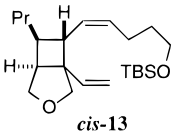
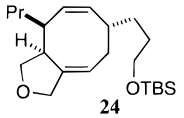
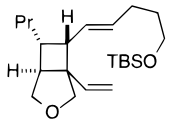
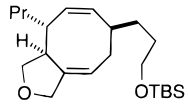
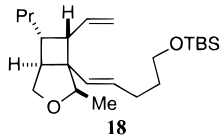
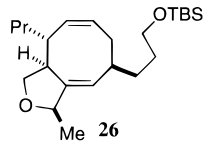
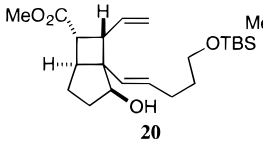
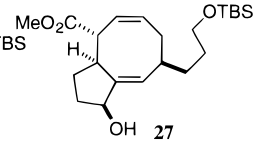
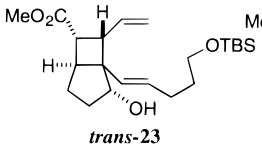
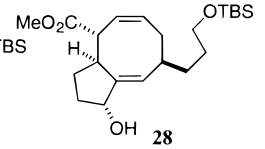
[a] Cross-metathesis of cyclobutene substrates with TBS-pent-4-en-1-ol. [b] Isolated yields after silica gel chromatography.

22. In both cases (entries 3 and 4, Table 1), little or no selectivity was observed. In fact, no ring-opening metathesis occurred (*i.e.*, <5%) when cyclobutene **21** was present in either a pure state or as a mixture with its diastereomer **17**. Treatment of **21** with stoichiometric amounts of ruthenium catalyst **1** indicates that cyclobutene **21** does react with the catalyst; however, the newly formed alkylidene does not undergo subsequent turnover with terminal olefins added to the reaction.[7] These observations emphasize the crucial role that substrate structure plays in the reactivity profile of ruthenium alkylidene-catalyzed olefin metatheses, an understanding that may prove pivotal in the development of new metathesis-based methods.

Notwithstanding these mechanistic issues, the utility of the regio- and stereoselective ring-opening process is illustrated with the conversion of the metathesis products into cyclooctadiene-containing systems. In the transformations depicted in Table 2, Cope rearrangements of the metathesis products proceed stereospecifically in good yield to furnish functionalized bicyclo-[6.3.0] ring systems in relatively few steps (*i.e.*, ≤6) from readily available materials.[8]

In summary, several key issues have been documented here. First, as illustrated in Scheme 1, ring-opening cross-metathesis between cyclobutene-containing substrates and ethylene proceeds readily and selectively. Second, local chirality plays a crucial role in determining the facility and selectivity with which ring-opening cross-metathesis of functionalized cyclobutenes take place (Table 1). Finally, the ring-opening cross-metathesis products of the cyclobutadiene cycloadducts undergo Cope rearrangements to provide an efficient and stereoselective route to bicyclo[6.3.0] ring systems (Table 2). Further mechanistic studies as well as applications toward natural product syntheses will be the subject of future reports from these laboratories.

Table 2. Cope Rearrangement on Ring-Opened Products[a]

entry	substrate	product[b]	yield[c]
1	 ***cis*-13**	 **24**	70%
2	 ***trans*-15**	 **25**	97%
3	 **18**	 **26**	90%
4	 **20**	 **27**	96%
5	 ***trans*-23**	 **28**	99%

[a] Typical conditions: Substrates heated (200 °C, 1 h) in benzene [0.01 M]. [b] Structural and stereochemical assignments were made through degradative and spectroscopic techniques. [c] Isolated yields after silica gel chromatography.

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Supporting Information Available: Experimental procedures and spectrographic data are provided for all new compounds (18 pages). See any current masthead page for ordering and Internet access instructions.

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(7) The new ruthenium alkylidenes resulting from the addition of complex **1** to cyclobutenes **7**, **17**, and **21** have been characterized by ^{1}H, ^{13}C, and ^{31}P NMR. Additional studies on the structure and reactivity of these complexes are presently underway.

(8) Pettit, R.; Henery, J. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 310.