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Selective Ring Opening Cross Metathesis of Cyclooctadiene and Trisubstituted Cycloolefins

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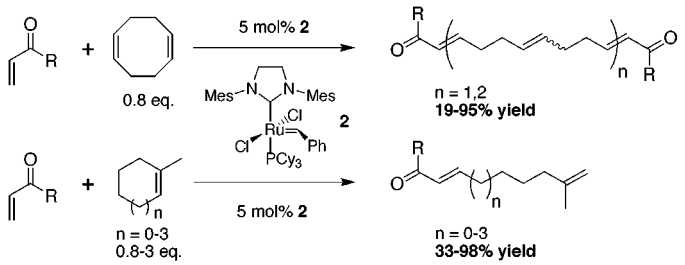
ABSTRACT



The selective ring opening cross metathesis of 1,5-cyclooctadiene and trisubstituted cycloolefins with acroyl species is described. The ring-opened products contain electronically differentiated olefins suitable for additional metathesis reactions. Trisubstituted cycloolefins open regioselectively, placing the acroyl cap on the less-substituted terminus.

The flexibility of the olefin metathesis reaction allows the efficient production of highly functionalized, unsaturated polymers and small molecules.[1] Many synthetically relevant applications that involve multiple metathesis transformations utilize the ruthenium catalysts **1** and **2** (Figure 1).[2] For example, the combination of ring opening metathesis polymerization (ROMP) and cross metathesis (CM) produces unique telechelic and multiple-block copolymers with novel properties.[3] For the synthesis of small molecules, ring opening−ring closing metathesis "tandem" sequences (ROM−RCM) allow the rapid construction of multiple ring systems, including those in natural products.[4,5] In all of these cases, the product of one metathesis event is directly available for

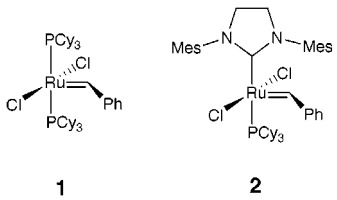


Figure 1. Ruthenium-based olefin metathesis catalysts.

(1) For recent reviews on ruthenium-catalyzed olefin metathesis, see: (a) Trnka, T. M., Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (c) Randall, M. L.; Snapper, M. L. *J. Mol. Catal. A-Chem.* **1998**, *133*, 29−40.

(2) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039−2041. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110. (c) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(3) (a) Chung, T. C.; Chasmawala, M. *Macromolecules* **1992**, *25*, 5137−5144. (b) Hillmyer, M. A.; Nguyen, S. T.; Grubbs, R. H. *Macromolecules* **1997**, *30*, 718−721. (c) Maughon, B. R.; Morita, T.; Bielawski, C. W.; Grubbs, R. H. *Macromolecules* **2000**, *33*, 1929−1935. (d) Bielawski, C. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2903−2906. (e) For a review on telechelic polymers, see: Goethals, E. J. *Telechelic Polymers: Synthesis and Applications*; CRC: Boca Raton, FL, 1989.

(4) For selected references on ROM−RCM, see: (a) Zuercher, W. J.; Scholl, M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 4291−4298. (b) Weatherhead, G. S.; Ford, J. G.; Alexanian, E. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 1828−1829. (c) Voigtmann, U.; Blechert, S. *Synthesis* **2000**, 893−898. (d) Voigtmann, U.; Blechert, S. *Org. Lett.* **2000**, *2*, 3971−3974.

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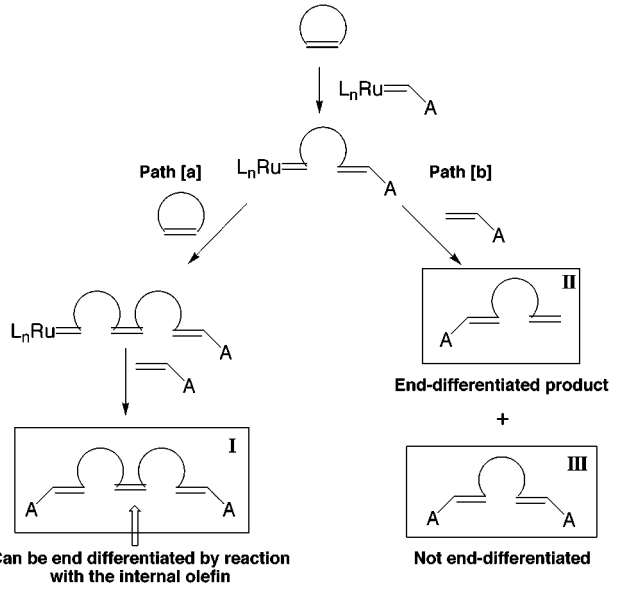
the next, which permits the rapid generation of complexity in a single reaction.[6]

An important variation on this theme is ring opening cross metathesis (ROCM, Scheme 1).[7−9] In this tandem sequence,

Scheme 1. Ring Opening Cross Metathesis (ROCM)



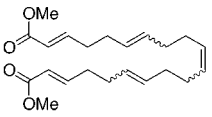
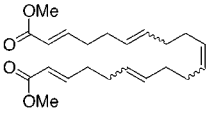
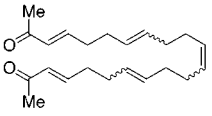
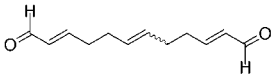
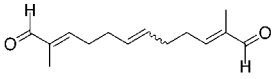
a cycloolefin is opened and other alkenes are crossed onto the newly formed termini. Ideally, the product olefins should be electronically or sterically orthogonal to allow subsequent elaboration in a straightforward manner. Two approaches to end-differentiation of alkenes are shown in Scheme 1 (paths [a] and [b]). After the initial ring opening event, the ruthenium-bound intermediate has two options: reaction with another cycloolefin (path [a]) or reaction with the cross partner (path [b]). In the first case, the ring opening of the cycloolefin is fast relative to the rate of cross metathesis. The resulting dimeric intermediate can then react with the cross partner to form symmetrically capped product **I**.[10] A subsequent cross metathesis reaction on the internal olefin produces 2 equiv of an end-differentiated product, thereby achieving ROCM selectivity in two steps.

The second case (path [b] in Scheme 1) allows end-differentiation in a single reaction. This path will be followed if the cross metathesis step is faster than the ring opening of another cycloolefin. Two products are possible from this cross metathesis: the desired end-differentiated product **II** and the symmetrically capped product **III**. Selectivity for product **II** is therefore highly dependent on the nature of both the substrates and the catalyst.

In particular, catalyst **2** is well-suited to these selective ROCM reactions as a result of its combination of tunable activity and expanded substrate scope. The ability of **2** to react with both electron-poor acrylates and electron-rich cycloolefins makes it ideal for electronic end-differentiation in ROCM. In this letter, we describe both stepwise and one-pot selective ROCM reactions using catalyst **2**.

Promising initial efforts toward ROCM along path [a] focused on the readily polymerizable substrate 1,5-cyclooctadiene (COD, Table 1).[11] High yields of ROCM dimers

Table 1. Ring Opening Cross Metathesis of Cyclooctadiene with Various Acroyl Species[a]

entry	substrates	products	isolated yield
1	COD + 		80%
2	COD + 		75%
3	COD + 		40%
4	COD + 		95%
5	COD + 		19%

[a] All reactions are performed in refluxing CH_2Cl_2, at 0.2 M concentration of cycloalkene and 5 mol % catalyst **2**. The relative stoichiometry is 1:1.2 cycloolefin/acroyl species, except for entry 5, in which methacrolein is used as solvent. All acroyl alkenes are predominantly *trans*. The stereochemistry of all other internal olefins is approximately 3−4:1 *E*:*Z* by 500 MHz ^{1}H NMR analysis.[14]

(5) For the synthesis of chromenes by ROM−RCM, see: (a) Harrity, J. P.; Visser, M. S.; Gleason, J. D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 1488−1489. (b) Harrity, J. P.; La, D. S.; Cefalo, D. R.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 2343−2351.

(6) For reviews on the applications of tandem metathesis sequences, see: (a) Schuster, M.; Blechert S. *Chem. Unserer Z.* **2001**, 35, 24−29. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013−3043. (c) Naota, T.; Takaya, H.; Murahashi, S. I. *Chem. Rev.* **1998**, *98*, 2599−2660 and references therein.

(7) For selected examples of regioselective ROCM, see: (a) Snapper, M. L.; Tallarico, J. A.; Randall, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1478−1479. (b) Tallarico, J. A.; Randall, M. L.; Snapper, M. L. *Tetrahedron* **1997**, *53*, 16511−16520. (c) Michaut, M.; Parrain, J.-L.; Santelli, M. *Chem. Commun.* **1998**, 2567−2568. (d) Arjona, O.; Csáky, A. G., Murcia, C.; Plumet, J.; Mula, M. B. *J. Organomet. Chem.* **2001**, *627*, 105−108. (e) Arjona, O.; Csáky, A. G.; Plumet, J. *Synthesis* **2000**, 857−861. (f) Katayama, H.; Urushima, H.; Nishioka, T.; Wada, C.; Nagao, M.; Ozawa, F. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 4513−4515. (g) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179. (h) Cuny, G. D.; Cao, J.; Hauske, J. R. *Tetrahedron Lett.* **1997**, *38*, 5237−5240.

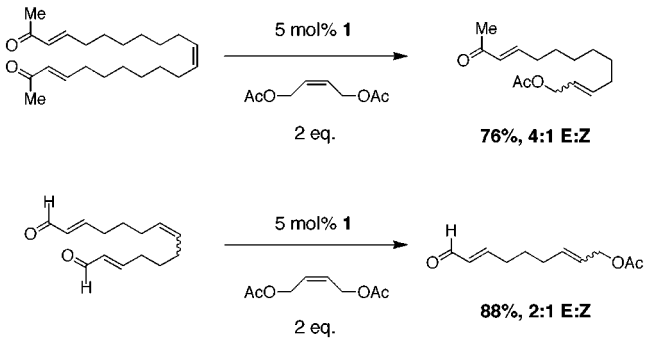
(8) For examples of selective ROCM with chiral alkylidenes, see: (a) La, D. S.; Ford, J. G.; Sattely, E. S.; Bonitatebus, P. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 11603−11604. (b) La, D. S.; Satteley, E. S.; Ford, J. G.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 7767−7778.

(9) For examples of the ROCM of low-strain cycloolefins, see: (a) Stüer, W.; Wolf, J.; Werner, H.; Schwab, P.; Schulz, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3421−3423. (b) Randl, S.; Connon, S. J.; Blechert, S. *Chem. Commun.* **2001**, 1796−1797.

analogous to **I** can be achieved under typical reaction conditions.[12] A comparison of entries 1 and 2 reveals that the presence of a β-methyl group has little effect on product structure; the same dimer is formed in both cases. A similar product, containing three internal olefins, predominates for methyl vinyl ketone (entry 3). In contrast, crotonaldehyde and methacrolein result in monomeric species containing only one internal olefin (entries 4 and 5). Apparently the cross metathesis of an α,β-unsaturated aldehyde can most efficiently compete with the ring opening of another cycloolefin.

The critical step in end-differentiation of the dimeric products lies in the selective manipulation of the internal, electron-rich olefins. As illustrated in Scheme 2, bisphosphine

Scheme 2. Selective Cross Metathesis of Internal Olefins[a]

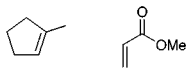
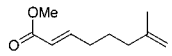
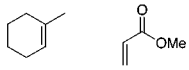
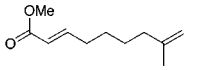
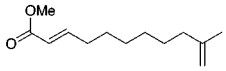
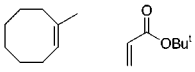
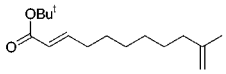
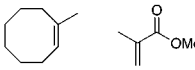
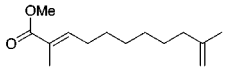
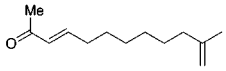
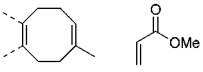
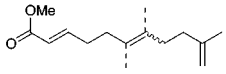
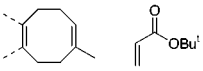
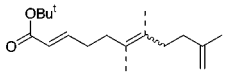


[a] Percent conversions and *E*:*Z* ratios were determined by ^{1}H NMR. *E*:*Z* ratios reflect the distribution of allylic acetate internal olefins. Acroyl olefins are predominantly *trans*.

catalyst **1** is ideal for this selective cross metathesis of the dimers at the desired positions.[11] The fact that **1** does not significantly react with acroyl species ensures that the acroyl cap remains untouched throughout this metathesis reaction.[13] Catalyst choice can therefore be important in the selective manipulation of ROCM products.

A more efficient route to selective ROCM would involve the generation of end-differentiated products in a single metathesis reaction (Scheme 1, path [b]). To suppress dimer formation (path [a]), cycloolefins with a reduced tendency to dimerize must be chosen. Trisubstituted cycloolefins fall into this category; their ring opening is sufficiently slow to suppress dimer formation (Table 2).[15] Formation of the symmetrical product **III** (Scheme 1) is also disfavored as a result of the kinetically slow cross metathesis of acroyl

Table 2. Ring Opening Cross Metathesis of Trisubstituted Cycloolefins with Acroyl Species[a]

entry	substrates	products	isolated yield
1[b]			33%
2[b]			0%
3[c]			83%
4[c]			98%
5[d]			67%
6[e]			57%
7[b,f]			66% (mixture)
8[b,f]			72% (mixture)

[a] All reactions are performed in refluxing CH_2Cl_2 at 0.02−1.2 M concentration of cycloalkene and 5 mol % catalyst **2**. Yields are reported as isolated yields. All α,β-unsaturated alkenes are predominantly *trans*, by ^{1}H NMR analysis. The stereochemistry of all other internal olefins is undetermined. [b] Relative stoichiometry is 3:1 cycloolefin:acrylate. [c] Relative stoichiometry is 1:2 cycloolefin:acroyl species. [d] Methyl methacrylate is used as solvent. [e] Relative stoichiometry is 1:1 cycloolefin:acroyl species. [f] The cyclodiene is a 4:1 mixture of 1,5- and 1,6-dimethylcyclooctadiene, resulting in both *E*,*Z* stereoisomers and methyl regioisomers.[19]

species onto geminally disubstituted olefins.[16] These two factors make trisubstituted cycloolefins ideal for alkene differentiation by ROCM.

For all observed cases in Table 2, the acrylate is crossed onto the less-substituted terminus, regardless of ring size, ring strain energy, or acroyl cross partner. A potential pathway that describes this regioselective ROCM is detailed in Scheme 3. The propagating methylidene opens the ring regioselectively, placing the sterically large metal fragment away from the methyl group on the olefin.[17] A subsequent

(10) Alternatively, **I** may form from the depolymerization of a ROMP oligomer that is rapidly formed during the ROCM of a readily polymerizable monomer.

(11) Cyclooctene generally results in lower yields, presumably as a result of its lower ring strain relative to cyclooctadiene. The methyl ketone dimer substrate in Scheme 2 can be produced in low yield from cyclooctene ROCM.

(12) If the stoichiometry of the acroyl species is reduced relative to COD, a range of multiple oligomers that contain 4−10 internal alkenes predominates in the product mixtures.

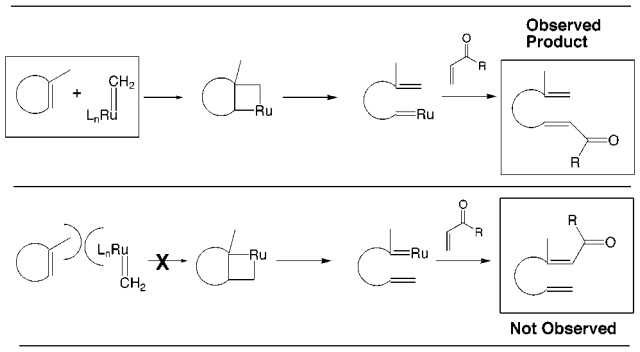
(13) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58−71.

(14) *E*:*Z* ratios were determined by comparison of chemical shift data to those of similar compounds reported in Hoye, T. R.; Suhadolnik, J. C. *Tetrahedron* **1986**, *42*, 2855−2862.

(15) For example, the ring opening metathesis polymerization of 1,5-dimethylcyclooctadiene is considerably slower than that of COD. See ref 3d.

(16) (a) Choi, T.-L.; Lee, C. W.; Chatterjee, A. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 10417−10418. (b) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783−3784. (c) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204−2207. (d) Ulman, M.; Belderrain, T. R.; Grubbs, R. H. *Tetrahedron Lett.* **2000**, *41*, 4689−4693.

Scheme 3. Selectivity Model for the ROCM of Trisubstituted Cycloolefins



cross metathesis with the acroyl species caps the product and regenerates the ruthenium methylidene.

Although regioselectivities are favorable, yields in trisubstituted ROCM appear dependent on the efficiency of ring opening. For example, five- and six-membered rings (Table 2, entries 1 and 2) show poor yields, presumably as a result of lower ring strain; higher strain cyclooctenes (entries 3−8) perform reasonably well. Much higher yields for geminally disubstituted acroyl species (entry 5) are observed in contrast to unsubstituted COD cases. Dimethylcyclooctadiene (entries 7 and 8) can also be opened, leading to products with three differentiated alkenes: acroyl, geminally disubstituted, and trisubstituted. Importantly, all of the products in Table 2 can also be further functionalized by a cross metathesis on the geminally disubstituted terminus using previously disclosed methodology.[18]

Substrate and catalyst control in regioselective ROCM make this reaction a potentially powerful means to rapidly and efficiently synthesize highly functionalized alkenes.

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Supporting Information Available: Characterization data for products reported in Tables 1 and 2 (^{1}H, ^{13}C NMR, HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

OL016918S

(17) This selectivity model is favored by analogy to similar steric preferences described in Stille, J. R.; Santarsiero, B. D.; Grubbs, R. H. *J. Org. Chem.* **1990**, *55*, 843−862.

(18) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751−1753.

(19) Dimethylcyclooctadiene is typically produced as a mixture of isomers that are not readily separated. See: (a) van Leeuwen, P. W. N. M.; Roobeek, C. F. *Tetrahedron* **1981**, *37*, 1973−1983. (b) Hammond, G. S.; Turro, N. J.; Liu, R. S. H. *J. Org. Chem.* **1963**, *28*, 3297−3303.