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Ring-Rearrangement Metathesis of Cyclopropenes: Synthesis of Heterocycles

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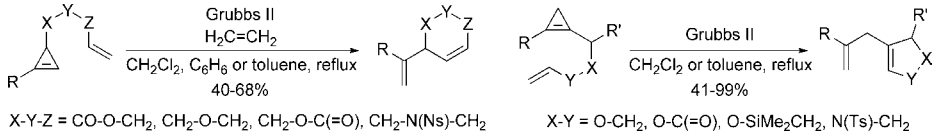
ABSTRACT

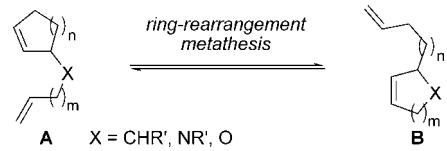


Cyclopropenes substituted by an unsaturated side chain have been successfully involved in ring-rearrangement metatheses leading to heterocyclic compounds, thereby expanding the synthetic potential of metathesis reactions with this class of highly strained cycloalkenes.

Ring-rearrangement metathesis (RRM) involves the sequential combination of ring-opening metathesis (ROM) and ring-closing metathesis (RCM). According to this process, an equilibrium can be established between cycloalkene derivatives **A**, bearing an unsaturated side chain, and unsaturated carbo- or heterocycles **B** in the presence of a metathesis initiator (Scheme 1).[1−7]

The position of this equilibrium is affected by thermodynamic parameters and notably by the difference of ring strain between the two unsaturated rings in compounds **A** and **B**, as well as their substitution pattern. Kinetic effects can also affect the rates of formation of the possible metallacyclobutane intermediates depending on the steric and electronic environment of the reacting metal carbene and its olefinic

Scheme 1. Ring-Rearrangement Metathesis



(1) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634–6640.

(2) For examples of RRM involving ROM of cyclobutenes, see: (a) White, B. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2003**, *125*, 14901–14904. (b) Nicolaou, K. C.; Vega, J. A.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4441–4445. (c) Fürstner, A.; Aïssa, C. *J. Am. Chem. Soc.* **2006**, *128*, 6306–6307. (d) Mori, M.; Wakamatsu, H.; Tonogaki, K.; Fujita, R.; Kitamura, T.; Sato, Y. *J. Org. Chem.* **2005**, *70*, 1066–1069.

(3) For RRM with ROM of bicyclic alkenes, see: (a) Stragies, R.; Blechert, S. *Synlett* **1998**, 169–170. (b) Maechling, S.; Norman, S. E.; McKendrick, J. E.; Basra, S.; Köppner, K.; Blechert, S. *Tetrahedron Lett.* **2006**, *47*, 189–192. (c) Hagiwara, H.; Katsumi, T.; Endou, S.; Hoshi, T.; Suzuki, T. *Tetrahedron* **2002**, *58*, 6651–6654. (d) Holtsclaw, J.; Koreeda, M. *Org. Lett.* **2004**, *6*, 3719–3722. (e) Büchert, M.; Meinke, S.; Prenzel, A. H.; G, P.; Deppermann, N.; Maison, W. *Org. Lett.* **2006**, *8*, 5553–5556. For applications to natural product synthesis, see: (f) Chandler, C. L.; Phillips, A. J. *Org. Lett.* **2005**, *7*, 3493–3495. (g) Henderson, J. A.; Phillips, A. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 8499–8501. (h) Barbe, G.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 13873–13875.

(4) Weatherhead, G. S.; Ford, J. G.; Alexanian, E. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 1828–1829.

(5) For the synthesis of nitrogen heterocycles by RRM with ROM of medium-size cycloalkenes, see: (a) Stragies, R.; Blechert, S. *Tetrahedron* **1999**, *55*, 8179–8188. (b) Voigtmann, U.; Blechert, S. *Synthesis* **2000**, 893–898. (c) Ovaa, H.; Stragies, R.; van der Marel, G. A.; van Boom, J. H.; Blechert, S. *Chem. Commun.* **2000**, 1501–1502. (d) Voigtmann, U.; Blechert, S. *Org. Lett.* **2000**, *2*, 3971–3974. (e) Stragies, R.; Blechert, S. *J. Am. Chem. Soc.* **2000**, *122*, 9584–9591. (f) Buschmann, N.; Rückert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325–4329. (g) Ovaa, H.; Stapper, C.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H.; Blechert, S. *Tetrahedron* **2002**, *58*, 7503–7518. (h) Neidhöfer, J.; Blechert, S. *Synthesis* **2004**, 3047–3054. (i) Zhao, Z.; Song, L.; Mariano, P. S. *Tetrahedron* **2005**, *61*, 8888–8894. (j) Holub, N.; Neidhöfer, J.; Blechert, S. *Org. Lett.* **2005**, *7*, 1227–1229. (k) Böhrsch, V.; Neidhöfer, J.; Blechert, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 1302–1305. (l) Böhrsch, V.; Blechert, S. *Chem. Commun.* **2006**, 1968–1970.

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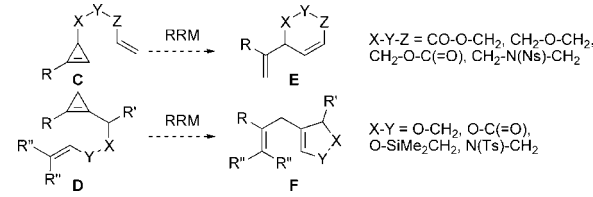
partner. RRM has been applied to the preparation of highly substituted carbocycles and heterocycles and has been used as a key step in several total syntheses of natural products.[1−7] In RRM, the endocyclic olefin involved in the ROM can be a medium sized cycloalkene;[1,5,6] however, bicyclic alkenes[1,3,4] and cyclobutenes[1,2,5] exhibit a higher reactivity owing to their ring strain. Surprisingly, to our knowledge, the highly strained cyclopropenes[8] have not been involved in RRM. It is known that Mo- or Ru-alkylidenes can initiate the ROM polymerization of a few 3,3-disubstituted cyclopropenes.[9] Though the hindered 3,3-diphenyl-cyclopropene was found to be unreactive in ROM−cross-metathesis (CM),[10] cyclopropenone ketals have been identified as useful partners in such processes.[11,12] The terminal olefin generated by ROM−CM of cyclopropenone ketals did not react further, but after hydrolysis of the ketal, the resulting divinyl ketone could be involved in a subsequent CM. This methodology has been applied to the synthesis of natural products.[12] Recently, enantio- and diastereoselective ROM−CM of 3,3-disubstituted cyclopropenes were also reported as a useful tool for the stereocontrolled formation of quaternary centers.[13] Despite these reports, the behavior of a wider variety of cyclopropenes, bearing tri- or tetrasubstituted endocyclic olefins, in metathesis reactions is a rather unexplored field. Recent progress in the synthesis of cyclopropene derivatives[14] encouraged us to examine RRM involving such compounds as a route to heterocycles, and we would like to report herein our results.

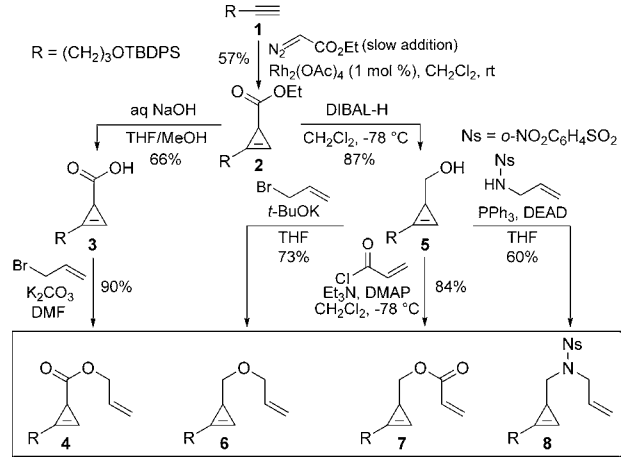
For this study, substituted cyclopropenes **C**, possessing a trisubstituted cyclic olefin, as well as derivatives of cyclopropenylcarbinyl alcohols or amines **D** were considered as substrates. Owing to the release of ring strain, it was anticipated that their RRM would be favorable and should allow access to heterocycles **E** and **F**, respectively (Scheme 2).

Scheme 2. RRM of Substituted Cyclopropenes



Several cyclopropenes **C** were synthesized from the cyclopropenecarboxylic ester **2**, easily prepared by rhodium-catalyzed cyclopropenation of the terminal alkyne **1** with ethyl diazoacetate (57%).[15] Saponification of ester **2** led to acid **3** (66%) which was alkylated with allyl bromide to afford allyl ester **4** (90%). Alternatively, reduction of ester **2** generated the primary alcohol **5** (87%) which was converted to allyl ether **6** (73%) or condensed with acryloyl chloride to deliver acrylate **7** (84%). Alcohol **5** was also engaged in a Mitsunobu reaction with *N*-allyl-2-nitrobenzenesulfonamide leading to sulfonamide **8** (60%) (Scheme 3).

Scheme 3. Preparation of Cyclopropenes **C**



Cyclopropenes **D** (with R″ = H) were prepared from the trihalocyclopropanes **9a** and **9b**.[16,17] Treatment with *n*-BuLi (2 equiv) generated the corresponding lithiated cyclopropenes **10a** and **10b**, and subsequent addition of benzyloxyacetaldehyde or 3-*tert*-butyldimethylsilyloxy-butanal afforded cyclopropenylcarbinols **11a** (85%), **11b** (62%) and **12a** (84%), **12b** (73%), respectively. Several derivatives were then synthesized by alkylation with allyl bromide [**13a** (92%), **13b** (77%), **14a** (86%), and **14b** (74%)], acylation with acryloyl chloride [**15a** (89%), **15b** (74%)], or silylation with allyldimethylsilyl chloride [**16a** and **16b** (unpurified)]. Alternatively, **10a** and **10b** were

(6) For the synthesis of oxygen heterocycles by RRM with ROM of medium-size cycloalkenes, see: (a) Harrity, J. P. A.; Visser, M. S.; Gleason, J. D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 1488−1489. (b) Johannes, C. W.; Visser, M. S.; Weatherhead, G. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 8340–8347. (c) Adams, J. A.; Ford, J. G.; Stamatos, P. J.; Hoveyda, A. H. *J. Org. Chem.* **1999**, *64*, 9690−9696. (d) Burke, S. D.; Quinn, K. J.; Chen, V. J. *J. Org. Chem.* **1998**, *63*, 8626–8627.

(7) RRM can be combined with other metathesis processes in a domino fashion (RCM or CM), see: (a) Hart, A. C.; Phillips, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 1094–1095. (b) Arjona, O.; Csákÿ, A. G.; Murcia, M. C.; Plumet, J. *Tetrahedron Lett.* **2000**, *41*, 9777–9779. (c) Arjona, O.; Csákÿ, A. G.; Medel, R.; Plumet, J. *J. Org. Chem.* **2002**, *67*, 1380–1383. (d) Funel, J.-A.; Prunet, J. *Synlett* **2005**, 235–238.

(8) For reviews, see. (a) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117–3179. (b) Rubin, M.; Rubina, M.; Gevorgyan, V. *Synlett* **2007**, 1221–1245. (c) Fox, J. M.; Yan, N. *Curr. Org. Chem.* **2005**, *9*, 719–732. (d) Baird, M. S. *Top. Curr. Chem.* **1988**, *144*, 137–209.

(9) (a) Buchmeiser, M. R. *Chem. Rev.* **2000**, *100*, 1565−1604. (b) Biewalski, C. W.; Grubbs, R. H. *Prog. Polym. Sci.* **2007**, *32*, 1–29. (c) Singh, R.; Czekelius, C.; Schrock, R. R. *Macromolecules* **2006**, *39*, 1316–1317. (d) Singh, R.; Schrock, R. *Macromolecules* **2008**, *41*, 2990–2993. (e) Binder, W. H.; Kurzhals, S.; Pulamagatta, B.; Decker, U.; Pawar, G. M.; Wang, D.; Kühnel, C.; Buchmeiser, M. R. *Macromolecules* **2008**, *41*, 8405–8412.

(10) Tallarico, J. A.; Randall, M. L.; Snapper, M. L. *Tetrahedron* **1997**, *53*, 16511–16520.

(11) Michaut, M.; Parrain, J.-L.; Santelli, M. *Chem. Commun.* **1998**, 2567–2568.

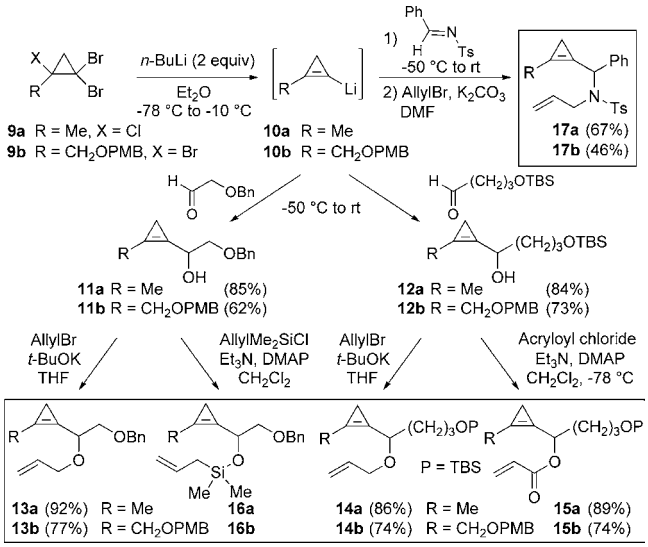
(12) (a) Statsuk, A. V.; Liu, D.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 9546–9547. (b) Marjanovic, J.; Kozmin, S. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8854–8857. (c) Matsumoto, K.; Kozmin, S. A. *Adv. Synth. Catal.* **2008**, *350*, 557–560.

(13) (a) Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2007**, *129*, 3824–3825. (b) Hoveyda, A. H.; Lombardi, P. J.; O'Brien, R. V.; Zhugralin, A. R. *J. Am. Chem. Soc.* **2009**, *131*, 8378–8379.

(14) Marek, I.; Simaan, S.; Masarwa, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7364–7376.

condensed with *N*-tosylbenzaldimine, and subsequent allylation of the intermediate secondary sulfonamides provided **17a** (67%) and **17b** (46%) (Scheme 4).

Scheme 4. Preparation of Cyclopropenes **D**



The RRM of the substituted cyclopropenes **C** was then investigated. When allyl ester **4** was treated with Grubbs second-generation catalyst [Grubbs II (2.5 mol %), CH_2Cl_2, reflux] under an atmosphere of ethylene, no conversion occurred. Under more forcing conditions (toluene, reflux), only 1,4-diene **18** resulting from ROM−CM of the cyclopropene with ethylene was isolated (43%). RCM of the latter compound could be achieved subsequently, provided that Ti(O*i*-Pr)$_4$ was used as an additive, and led to the desired β,γ-unsaturated δ-lactone **19** (64%).[18] The RRM of the allylic ether **6** occurred under milder conditions (CH_2Cl_2, reflux), but the yield of dihydropyran **20** could be significantly improved under an ethylene atmosphere (57% vs 40%). Acrylate **7** exhibited a lower reactivity since no conversion was observed in refluxing CH_2Cl_2, even in the presence of ethylene. More forcing conditions were required to achieve the RRM of this substrate (ethylene, C_6H_6, reflux) leading to the α,β-unsaturated lactone **21** (64%). Under similar conditions, the RRM of sulfonamide **8** delivered tetrahydropyridine **22** along with a minor regioisomer **22′** which was detected by NMR in this case (**22**:**22′** = 87:13, 68%) (Table 1).

The RRM of cyclopropenes **D** (with R″ = H) was then investigated. Treatment of allyl ethers **13a**, **13b**, **14a**, and **14b** with Grubbs II [(2.5 mol %), CH_2Cl_2, reflux] led in high yields to the corresponding dihydrofurans **23a** (87%), **23b** (83%), **24a** (82%), and **24b** (92%), respectively, and it is noteworthy that the presence of ethylene was not required. RRM of acrylates **15a** and **15b** turned out to be more difficult as Grubbs II failed to initiate the reaction in refluxing CH_2Cl_2. Fortunately, the use of toluene led to lactones **25a** (41%) and **25b** (50%), albeit in modest yields, but switching to Grela's catalyst[19] significantly improved the yield in **25a** (66%). The preparation of other classes of heterocycles was also investigated. Thus, allyldimethylsilyl ethers **16a** and **16b** underwent efficient RRM, and the corresponding sensitive cyclic siloxanes were immediately treated with MeLi to provide the allylic silanes **26a** (73%) and **26b** (62%). Finally, RRM of sulfonamides **17a** and **17b** proceeded smoothly and afforded pyrrolines **27a** (99%) and **27b** (70%) (Table 2).

Table 1. RRM of Cyclopropenes **C**

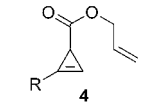
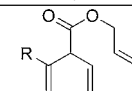
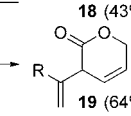
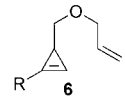
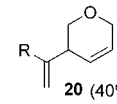
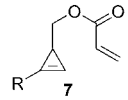
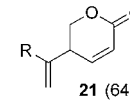
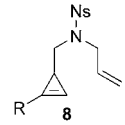
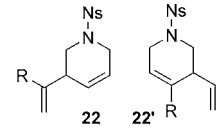
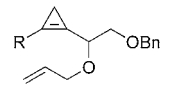
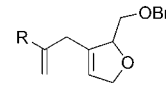
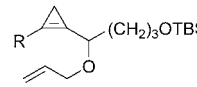
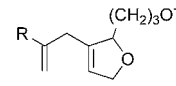
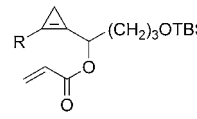
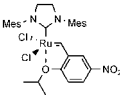
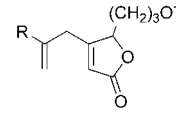
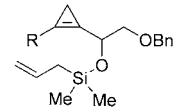
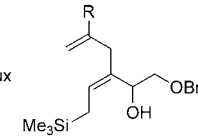
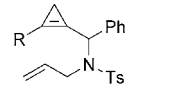
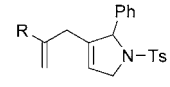
substrates	conditions	products
 **4**	Grubbs II (2.5 mol %) $H_2C{=}CH_2$ (1 atm) toluene (c = 0.02 M), reflux	 **18** (43%)
R = $(CH_2)_3$OTBDPS	Ti(O*i*-Pr)$_4$ (30 mol %) Grubbs II (2.5 mol %) C_6H_6 (c = 0.01 M), reflux	 **19** (64%)
 **6**	Grubbs II (2.5 mol %) CH_2Cl_2 (c = 0.1 M), reflux [a]without $H_2C{=}CH_2$ [b]$H_2C{=}CH_2$ (1 atm)	 **20** (40%[a], 57%[b])
 **7**	Grubbs II (2.5 mol %) $H_2C{=}CH_2$ (1 atm) C_6H_6 (c = 0.01 M), reflux	 **21** (64%)
 **8**	Grubbs II (2.5 mol %) $H_2C{=}CH_2$ (1 atm) C_6H_6 (c = 0.01 M), reflux	 **22** **22'** **22**:**22'** = 87:13 (68%)

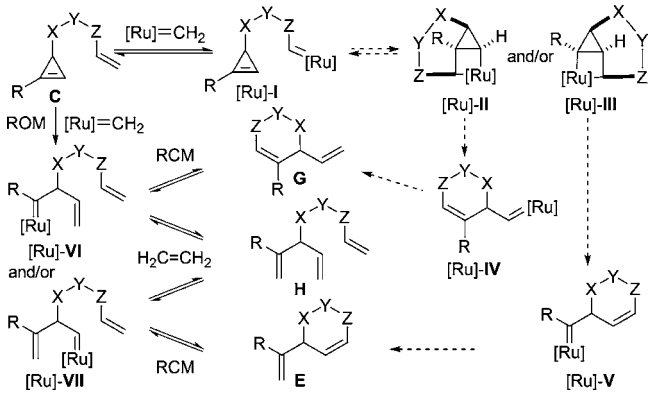
Table 2. RRM of Cyclopropenes **D**

substrates	conditions	products
 **13a** R = Me **13b** R = CH_2OPMB	Grubbs II (2.5 mol %) CH_2Cl_2 (c = 0.1 M), reflux	 **23a** R = Me (87%) **23b** R = CH_2OPMB (83%)
 **14a** R = Me **14b** R = CH_2OPMB	Grubbs II (2.5 mol %) CH_2Cl_2 (c = 0.1 M), reflux	 **24a** R = Me (82%) **24b** R = CH_2OPMB (92%)
 **15a** R = Me **15b** R = CH_2OPMB	Catalyst (2.5 mol %) toluene (c = 0.1 M), reflux [a]Grubbs II, [b]Grela's cat. 	 **25a** R = Me (41%[a], 65%[b]) **25b** R = CH_2OPMB (50%[a])
 **16a** R = Me **16b** R = CH_2OPMB	1) Grubbs II (2.5 mol %) CH_2Cl_2 (c = 0.1 M), reflux 2) MeLi, THF, 0 °C to rt	 **26a** R = Me (73%) **26b** R = CH_2OPMB (62%)
 **17a** R = Me **17b** R = CH_2OPMB	Grubbs II (2.5 mol %) CH_2Cl_2 (c = 0.1 M), reflux	 **27a** R = Me (99%) **27b** R = CH_2OPMB (70%)

These results indicate that cyclopropenes are valuable partners in usual RRM and that their reactivity can be controlled in spite of their high strain.

As there are two olefins in cyclopropenes **C** and **D**, different mechanistic pathways may intervene. For cyclopropenes **C**, initiation at the less congested exocyclic terminal alkene leading to alkylidene ruthenium complex [Ru]−**I** may be kinetically favored, but subsequent RCM−ROM would imply the formation of the highly strained tricyclic metallacyclobutanes [Ru]−**II** and/or [Ru]−**III**, to reach intermediates [Ru]−**IV** or [Ru]−**V**, which is rather unlikely. Thus, ROM should preferentially occur first and generate ruthenium carbenes [Ru]−**VI** and/or [Ru]−**VII**, the latter species being presumably favored for steric reasons. This would explain why heterocycles **E** (and not **G**) are preferentially formed. Also noteworthy is that the presence of ethylene is beneficial, if not necessary, for RRM of cyclopropenes **C**, presumably because equilibria are shifted toward trienes **H**. Thus, the success of the RRM process would depend on the ability of trienes **H** to undergo efficient RCM to heterocycles **E** (Scheme 5).

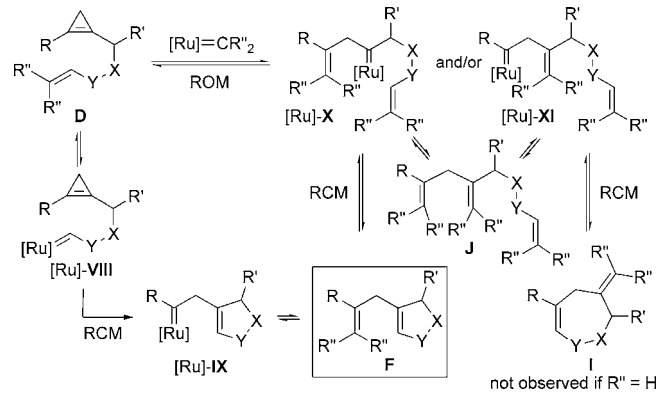
Scheme 5. RRM of Cyclopropenes **C**



The RRM of cyclopropenes **D** (Scheme 6), which is easier than for cyclopropenes **C** and does not necessitate ethylene, is likely to be initiated at the kinetically favored less hindered exocyclic alkene (R″ = H) leading to carbene [Ru]−**VIII**. After RCM−ROM, the resulting [Ru]−**IX** would propagate the catalytic cycle by reaction with the substrate to afford heterocycles **F**. The possibility that ROM occurred simultaneously cannot be ruled out especially for acrylates **15a**,**b** since initiation at an electron-deficient exocyclic alkene may be less favorable. ROM would then generate carbenes [Ru]−**X** and/or [Ru]−**XI**, and their subsequent RCM would lead to regioisomeric mixtures of heterocycles **F** and **I**; however, the latter compounds were not detected with substrates **13**−**17** (R″ = H). Thus, RCM of [Ru]−**XI**, if formed, may be slower than its conversion into triene **J** (by reaction with the terminal olefin in **D** when R″ = H), and the smaller ring-size heterocycles **F** would be produced even if both pathways operate (Scheme 6).

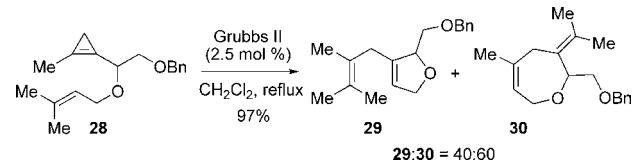
On the basis of the pathway described above, we reasoned that it should be possible to divert the RRM toward the

Scheme 6. RRM of Cyclopropenes **D**



formation of larger ring-size heterocycles **I** from substrates **D** bearing a trisubstituted exocyclic alkene (R″ ≠ H). Thus, prenyl ether **28** was synthesized by alkylation of **11a** with prenyl bromide (85%). As anticipated, the RRM produced a mixture of the five-membered ring **29** and the seven-membered ring **30** in a 40/60 ratio (97%) confirming the influence of an initial ROM event of the cyclopropene on the regioselectivity of the RRM of substrates **D** (Scheme 7).

Scheme 7. RRM of a Cyclopropenylcarbinyl Prenyl Ether



In conclusion, we have significantly expanded the synthetic potential of metathesis reactions with cyclopropenes by demonstrating that such substrates can be successfully involved in RRM to provide a variety of heterocyclic compounds.

Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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