J|A|C|S COMMUNICATIONS

Published on Web 10/11/2010

Efficient Ring-Closing Metathesis of Alkenyl Bromides: The Importance of Protecting the Catalyst during the Olefin Approach

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Abstract: We present the first productive ring-closing metathesis reaction that leads to the construction of cyclic alkenyl bromides. Efficient catalysis employing commercially available Grubbs II catalyst is possible through appropriate modification of the starting bromoalkene moiety.

The advent of alkylidene-based ruthenium metathesis catalysts featuring high functional group tolerance greatly contributed to the affirmation of alkene metathesis as one of the most important tools to manipulate a C−C double bond.[1] In particular RCM (ring-closing metathesis) has been widely explored and applied in the synthesis of complex natural products.[2] Less developed, but highly desirable, are versions of this reaction in which one of the two olefins bears heteroatom substituents. To date, a number of dienes containing enol ethers and enamines have been studied,[3] but good results in RCM were only obtained with high catalyst loadings and the applicability is restricted to a limited number of substrates. The synthesis of cyclic alkenyl halides, which could subsequently undergo an array of coupling reactions, represents another appealing version of the RCM reaction. Pioneering work in this field has been reported by the Weinreb group,[4a,b] who have shown that cyclic chloroalkenes could indeed be generated, albeit high catalyst loadings were again necessary for acceptable reactivity (10 mol %). This methodology has more recently been employed by Grubbs and Stoltz et al. in the successful synthesis of a specific natural compound.[4c,d] Unfortunately, the more useful alkenyl bromide substrates are known to be completely inactive with both Schrock-type as well as first- and second-generation Grubbs-type catalysts.[5,6]

In this report, we describe our effort toward the synthesis of carbo- and heterocyclic five-, six-, and seven-membered alkenyl halides via the RCM reaction of the corresponding dienes. Specifically, we show how appropriate protection of the starting alkenyl halide group not only leads to efficient RCM of alkenyl chlorides but also enables the unprecedented and highly efficient construction of cyclic bromoalkenes.

Initial exploratory studies were carried out with malonate-derived alkenyl bromide **1**. As previously reported,[4a,5] both **GI** (Grubbs I) and **GII** (Grubbs II) were completely ineffective for the RCM of **1** as were **HovII** (Hoveyda-Grubbs II) and **BleII** (Blechert II).[7] To possibly gain insight into what prevents catalytic turnover with **1**, we mixed equimolar amounts of **1** and **GII** in C_6D_6 and compared results with a mixture of **GII** and the analogous substrate (**2**) that lacks the second terminal olefin unit (Figure 1). Rather unexpectedly, NMR spectroscopy of this latter mixture did not show appreciable amounts of decomposition of **GII** (and of **2**) over a period of 2 days, whereas substrate **1** was able to completely destroy the precatalyst. During the course of the reaction, a color change to red-brown was observed with concomitant formation of a white precipitate which when analyzed turned out to be clean SIMes·HBr.[8,9] Another byproduct identified in solution and in nearly stoichiometric quantity (>90% against an internal standard) after the reaction was styrene. While the overall mechanism by which **GII** decomposes is speculative at this point, the generation of styrene (and the lack of reactivity between **2** and **GII**) strongly points to a reaction scenario where initial cross metathesis of the unsubstituted olefin in **1** with the benzylidene moiety of **GII** preceeds decomposition of the catalyst.[10] This in turn would mean that the alkenyl bromide unit only reacts irreversibly with the active ruthenium species when it is forced into close proximity to the metal center.[11]

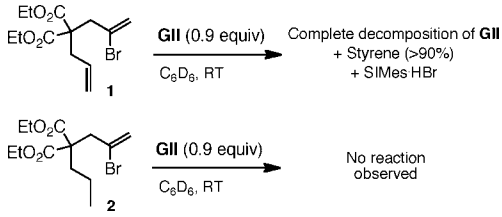
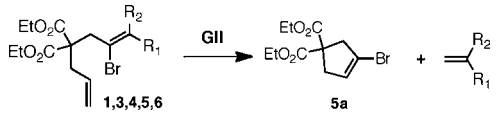


Figure 1. Stoichiometric reactivity of model substrates **1** and **2**.

Table 1. Influence of Olefin Substitution on Catalytic Activity[a]



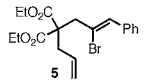
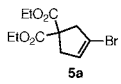
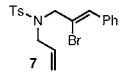
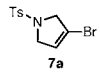
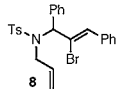
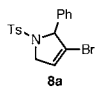
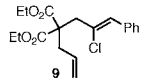
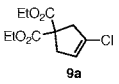
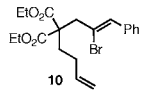
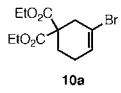
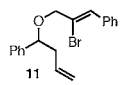
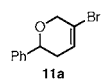
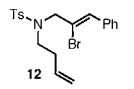
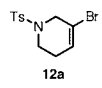
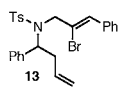
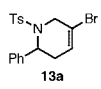
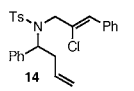
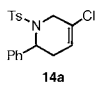
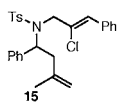
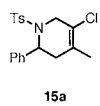
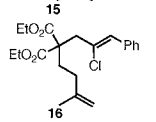
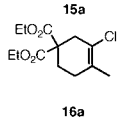
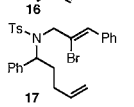
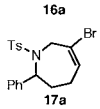
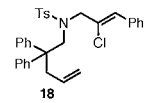
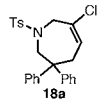
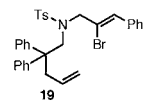
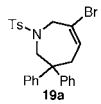
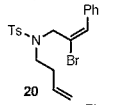
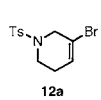
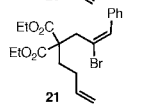
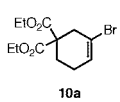
entry	R_1	R_2	mol % GII[b]	solvent	T (°C)	t (h)	yield (%)[c]
1 (**1**)	H	H	2	benzene	60	24	0
2 (**3**)	Me	Me	2	benzene	60	24	0
3 (**4**)	Me	H	2	benzene	60	24	70
4 (**5**)	Ph	H	2	benzene	60	0.5	>98 (90)
5 (**6**)	H	Ph	2	benzene	60	24	0

[a] All the reactions were performed with a 0.1 M substrate concentration. The substrate was added via syringe to a solution of catalyst preheated in an oil bath for 2 min. [b] For a screening of different solvents and catalysts, see the Supporting Information. [c] Yields based on NMR analysis. Isolated yield in parentheses.

Given these unexpectedly insightful stoichiometric studies, we reasoned that, by simply introducing one or two substituents to the terminal position of the bromoalkene, we could reduce its ability to destroy the catalyst and be able to catalytically generate cyclic bromoalkenes via RCM.[12,13]

As a first attempt, we tested a substrate featuring a geminal dimethyl substitution (Table 1, entry 2) that proved to be unreactive in RCM, most probably due to the low propensity of a tetrasubstituted olefin to approach the metal center and bind to it. In contrast, the introduction of a single substituent *Z* to the bromine atom turned out to be highly beneficial. In the presence of a methyl group (Table 1, entry 3) formation of a substantial amount of product was observed from NMR analysis;[14] when a substrate featuring a *Z*-configured terminal phenyl group was employed, full conversion

Table 2. RCM Reactions Generating Cyclic Alkenyl Bromides and Chlorides

entry[a]	substrate[b]	product	**GII** (mol %)	solvent	t (h)	yield (%)[c]
1	 **5**	 **5a**	2	Benzene	0.5	90
2	 **7**	 **7a**	2	Benzene	1.5	64
3	 **8**	 **8a**	2	Benzene	1.5	76
4	 **9**	 **9a**	2	Benzene	0.5	96
5	 **10**	 **10a**	2 0.5 0.1	Benzene Benzene Benzene	0.5 2 2	96 92 75
6	 **11**	 **11a**	2	Benzene	0.5	94
7	 **12**	 **12a**	2	Benzene	1.5	95
8	 **13**	 **13a**	2	Benzene	2	95
9	 **14**	 **14a**	2	Benzene	2	97
10	 **15**	 **15a**	5	CH_2Cl_2[d]	4	81
11	 **16**	 **16a**	5	CH_2Cl_2[d]	14	92
12	 **17**	 **17a**	5	CH_2Cl_2[d]	24	0[d]
13	 **18**	 **18a**	5	CH_2Cl_2[d]	3	76
14	 **19**	 **19a**	5	CH_2Cl_2[d]	3	67
15	 **20**	 **12a**	2	Benzene	5	Trace
16	 **21**	 **10a**	2	Benzene	5	Trace

[a] All the reactions were performed using 0.16 mmol of substrate with a 0.1 M substrate concentration except entries 11−13 (0.01 M). [b] Shelf lives of all compounds at −25 °C are at least 6 months without decomposition. [c] Isolated yield after column chromatography. [d] Reactions performed in benzene gave slightly lower yields. The main product of the reaction was compound **13a**.

was observed and product **5a** was obtained in 90% isolated yield using 2 mol % of **GII** (Table 1, entry 4). Mechanistically most relevant and in line with the idea of correctly protecting the alkenyl bromide during its approach to the metal, incorporation of a terminal phenyl group *E* to the halide (Table 1, entry 5) did not lead to any product formation under otherwise identical reaction conditions.[15]

The scope of the reaction was then explored with a wider range of bromoalkene derivatives, and the results are summarized in Table 2. Overall, five-membered and especially six-membered rings were generated in good to excellent isolated yields within short reaction times. Indeed, less than 2 mol % of **GII** seem to suffice for efficient ring closing as evidenced from data collected for substrate **10** (Table 2, entry 5). Vastly improved results as compared to data in the literature[4a] were obtained when applying the same concept to the construction of representative cyclic alkenyl chlorides **9a** and **14a** (Table 2, entries 4 and 9). Likewise, the synthesis of six-membered tetrasubstituted cyclic chloroalkenes **15a** and **16a** proceeded with remarkable ease and in high yield when employing a higher catalyst loading (Table 2, entries 10 and 11).[16] Unfortunately, an attempt to generate the analogous tetrasubstituted cyclic alkenyl bromide gave only trace amounts of product. For the synthesis of seven-membered rings (substrates **17**−**19**), the disposition of the substituents proved to be important and efficient catalysis was only possible with substrates **18** and **19**, where a stronger Thorp−Ingold effect is to be expected (Table 2, entries 13 and 14).[17] Indeed, when trying to ring-close substrate **17**, relatively clean conversion (50% isolated yield) to the six-membered product **13a** was observed, meaning that an unusually efficient olefin isomerization step occurs before the expected metathetical ring closure.[18]

The last two entries in Table 2 (15 and 16) again underline the importance of correctly substituting the starting alkenyl bromide and the strikingly different reactivity of the resulting diene, as both *E*-configured olefins **19** and **20** did not generate the desired RCM products.[19]

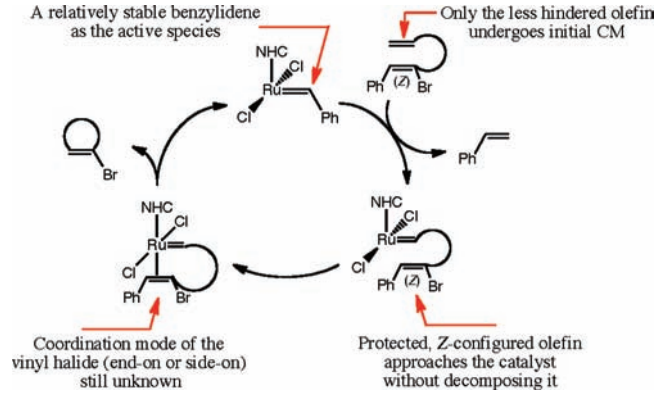


Figure 2. Proposed catalytic cycle for the RCM of bromoalkenes.

In conclusion, we have developed a catalytic method (Figure 2) to access cyclic alkenyl bromides via the ruthenium-catalyzed ring-closing metathesis reaction using synthetically useful catalyst loadings of **GII** (Grubbs II). The starting diene compounds are easily accessible and should make the present protocol attractive as a methodology for the construction of more elaborate molecular structures.

The concept of sterically protecting double bonds that would otherwise irreversibly react and deactivate metathesis-active catalysts should not be applicable to only alkenyl halides, and studies aimed at developing this idea further are currently underway.

Acknowledgment. We thank the Alfred Werner Foundation (R.D.), the Swiss National Foundation (L.W.), the Roche Research Foundation (E.D.), and the University of Zurich (M.G., E.D.) for financial support.

Supporting Information Available: Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(1) (a) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: Weinheim, Germany, 2003 and references therein. (b) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243. (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490. (d) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. (e) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (f) Fürstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, f.; Theil, O. R. *Chem.—Eur. J.* **2001**, *7*, 323.

(2) For selected recent applications in synthesis, see: (a) Pfeiffer, M. W. B.; Phillips, A. J. *J. Am. Chem. Soc.* **2005**, *127*, 5334. (b) Enquist, J. E.; Stoltz, B. M. *Nature* **2008**, *453*, 122. (c) Shu, C.; Zeng, X.; Hao, M.; Wei, X.; Yee, N. K.; Busacca, C. A.; Han, Z.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2008**, *10*, 1303. (d) Fürstner, A.; Bouchez, L. C.; Morency, L.; Funel, J.; Liepins, V.; Porée, F.; Gilmour, R.; Laurich, D.; Beaufils, F.; Tamiya, M. *Chem.—Eur. J.* **2009**, *15*, 3983. (e) Monfette, S.; Eyholzer, M.; Roberge, D. M.; Fogg, D. E. *Chem.—Eur. J.* **2010**, *16*, 11720.

(3) For a review on metathesis of heteroatom-substituted olefins, see: Van de Weghe, P.; Bisseret, P.; Blanchard, N.; Eustache, J. *J. Organomet. Chem.* **2006**, *691*, 5078.

(4) (a) Chao, W.; Weinreb, S. M. *Org. Lett.* **2003**, *5*, 2505. (b) Chao, W.; Meketa, M. L.; Weinreb, S. M. *Synthesis* **2004**, *12*, 2058. (c) White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810. (d) White, D. E.; Stewart, I. C.; Seashore-Lodlow, B. A.; Grubbs, R. H.; Stoltz, B. M. *Tetrahedron* **2010**, *66*, 4668. This paper indeed indicates that related structures to the one reported in ref 4c cannot be obtained via RCM of the corresponding alkenyl chloride substrates.

(5) For Grubbs II (**GII**), see ref 4 and b. For Schrock and Grubbs I (**GI**), see: Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310.

(6) For recent efforts to use alkenyl halides in CM, see: (a) Sashuk, V.; Samojlowicz, C.; Szadkowska, A.; Grela, K. *Chem. Commun.* **2008**, 2468. (b) Macnaughtan, M. L.; Gary, J. B.; Gerlach, D. L.; Johnson, M. J. A.; Kampf, J. W. *Organometallics* **2009**, *28*, 2880.

(7) See the Supporting Information for details.

(8) The identity of the counterion (Br^- or Cl^-) was established through comparison of the ^1H NMR signal of the imidazolinium proton with authentic samples of SIMes·HCl and SIMes·HBr recorded in $CDCl_3$ at the same concentration. See the Supporting Information for spectra.

(9) To our knowledge, this is the first example where a second-generation ruthenium catalyst decomposes via formal loss of the NHC ligand. For other decomposition pathways, see: (a) Samojlowicz, C.; Bieniek, M.; Grela, K. *Chem. Rev.* **2009**, *109*, 3708. (b) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746, and references cited.

(10) It is commonly assumed that alkenyl halides react very rapidly with the ruthenium center, giving rise to Fischer-type carbene moieties; see discussion in ref 4a and: Macnaughtan, M. L.; Johnson, M. J. A.; Kampf, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 7708.

(11) In a separate experiment, we made sure that compound **2** does not react with an equimolar amount of tricyclohexylphosphine. This excludes a reaction scenario where the phosphine liberated from **GII** during the initial CM of **1** attacks the bromoalkene via elimination of HBr.

(12) Terminal substitution has been successfully used in the past to minimize unwanted secondary metathesis activity during RCM. For the first example, see: (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324. For more recent, selected examples where the geometry of a terminal phenyl or methyl group affects reaction yields, see: (b) Kirkland, T. A.; Lynn, D. M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 9904. (c) Rölle, T.; Grubbs, R. H. *Chem. Commun.* **2002**, 1070. (d) Stenne, B.; Timperio, J.; Savoie, J.; Dudding, T.; Collins, S. K. *Org. Lett.* **2010**, *12*, 2032.

(13) This strategy would also generate, after each catalytic cycle, a propagating species more stable than a methylidene. For a discussion regarding the advantages of a stable propagating species in solution, see ref 12b.

(14) The main byproduct was unreacted starting material.

(15) Screening of reaction conditions (solvents, precatalysts etc.) can be found in the Supporting Information.

(16) Reference 4d reports a 24% yield of **16a** starting from the non-phenylated malonate derivative of **16** when employing 5 mol % of an optimized second-generation ruthenium precatalyst.

(17) In these cases, the approach of the alkenyl bromide seems to be more difficult resulting in lower activity. For an early example on the Thorpe−Ingold effect in RCM, see: Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746.

(18) Probably, a correct and swift approach of the bromoalkene is not possible in this case. For earlier studies that show how olefin isomerization can occur before RCM, see: (a) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204. (b) Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865, and references cited therein.

(19) While compound **6** did not show any apparent reactivity, substrates **20** and **21** partially decomposed with concomitant formation of trace amounts of product (< 10%). A detailed investigation on catalyst and substrate decomposition pathways is underway.

JA108253F