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The First Examples of Ring-Closing Olefin Metathesis of Vinyl Chlorides

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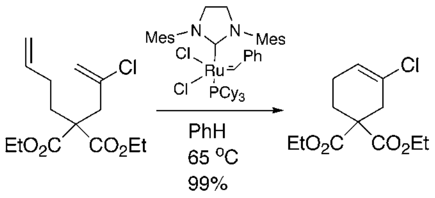
ABSTRACT



Ring-closing metathesis (RCM) of olefinic vinyl chlorides can be effected by using the second generation Grubbs catalyst (10 mol %, PhH, 65 °C) to produce a variety of carbocyclic and heterocyclic five-, six-, and seven-membered rings in excellent yields.

With the advent of functional group-compatible, well-behaved transition-metal alkylidene catalysts over the past decade, olefin metathesis has rapidly become one of the most important and widely used methods in organic synthesis.[1] In particular, ring-closing olefin metathesis (RCM) has been extensively explored as an annulation strategy. This methodology has been applied to construction of a variety of carbocyclic and heterocyclic ring systems including macrocycles. Moreover, RCM chemistry has been used as a pivotal step in several total syntheses of complex natural products. Although a number of permutations of metathesis have been described, relatively few examples have been reported involving participation of heteroatom-substituted olefins. To date, enol ethers of various types have been the most widely utilized partners in such RCM reactions.[2,3] Nitrogen-substituted olefins such as enamides have also been used successfully, but to a lesser degree.[4] There are still some unanswered mechanistic questions regarding these RCM reactions. For example, it is unclear how crucial it is that the transition metal catalyst first react with the nonheteroatom-substituted olefin to avoid formation of a stable Fischer-type carbene.[2,5] However, there are some documented instances where ruthenium Fischer carbene species can in fact initiate RCM processes.[6]

In a recent publication, Grubbs and co-workers reported that cross-coupling metathesis of vinyl halides with olefins could not be effected.[2] Despite these negative results, we decided to investigate the possibility of doing RCM reactions with vinyl halides since it seemed reasonable that the intramolecularity of the process might offer a viable mechanistic pathway. We also recognized the value of the metathesis products for subsequent transition-metal-mediated couplings, as well as other reactions. Initial exploratory studies were carried out with the vinyl chloride substrates shown in

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[1] For recent reviews of olefin metathesis see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (d) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037. (e) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.

[2] Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc*. **2000**, *122*, 3783.

[3] See, for example: Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565. Rainier, J. D.; Allwein, S. P. *J. Org. Chem.* **1998**, *63*, 5310. Sturino, C. F.; Wong, J. C. Y. *Tetrahedron Lett.* **1998**, *39*, 9623. Rainier, J. D.; Cox, J. M.; Allwein, S. P. *Tetrahedron Lett.* **2001**, *42*, 179. Okada, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 8023. Arisawa, M.; Theeraladanon, C.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **2001**, *42*, 8029. van Otterlo, W. A. L.; Ngidi, E. L.; Coyanis, E. M.; de Koning, C. B. *Tetrahedron Lett.* **2003**, *44*, 311. Whitehead, A.; Moore, J. D.; Hanson, P. R. *Tetrahedron Lett.* **2003**, *44*, 4275.

[4] Kinderman, S. S.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Org. Lett.* **2001**, *3*, 2045.

[5] For a discussion see: Geissert, A. J.; Snyder, L.; Markham, J.; Diver, S. T. *Org. Lett.* **2003**, *5*, 1793 and references cited.

[6] Louie, J.; Grubbs, R. H. *Organometallics* **2002**, *21*, 2153.

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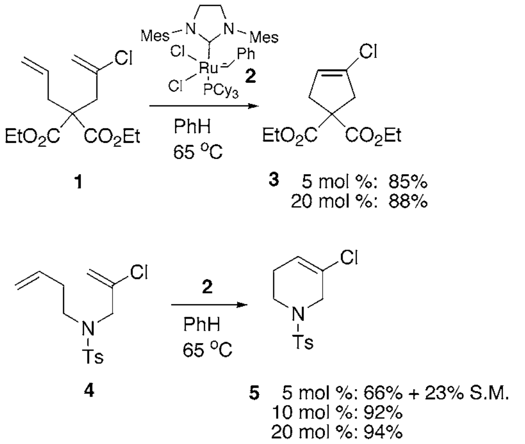
Scheme 1. Exploratory RCM Reactions of Vinyl Chlorides



1

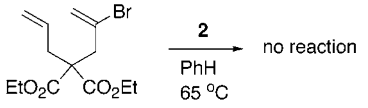
3 5 mol %: 85%
20 mol %: 88%

4

5 5 mol %: 66% + 23% S.M.
10 mol %: 92%
20 mol %: 94%

Scheme 1. We were pleased to find that the RCM reactions do indeed occur successfully in benzene at 65 °C using the second generation Grubbs catalyst **2**. With substrate **1**, the cyclization can be effected with 5 mol % of the catalyst to afford the five-membered ring product **3** in good yield. Increasing the catalyst loading to 20 mol % increased the yield only slightly. It was found that by using 5 mol % of the metathesis catalyst with substrate **4** the desired six-membered-ring RCM product **5** was obtained but a substantial amount of starting material remained. However, with 10 mol % of **2**, vinyl chloride **5** is formed in high yield. Increasing the amount of catalyst to 20 mol % produces only a marginal increase in product yield. Therefore, subsequent RCM reactions were performed by using 10 mol % of catalyst **2** (vide infra).[7,8]

We have also examined the possibility of utilizing a vinyl bromide in this process. Upon exposure of substrate **6** to the reaction conditions, which were developed for the vinyl chlorides, no reaction was observed (eq 1). It is possible here that the vinyl bromide functionality in **6** reacts with the Grubbs catalyst faster than the terminal alkene, producing an unreactive Fischer-type carbene.

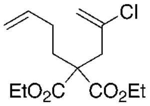
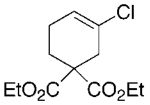
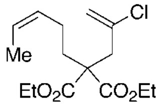
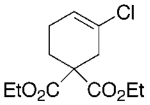
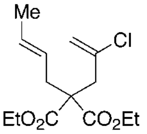
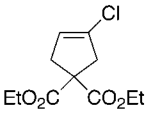
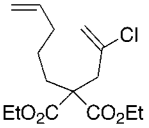
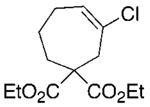
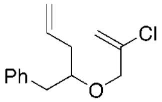
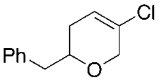
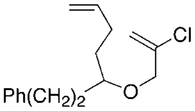
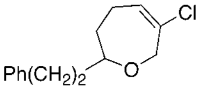
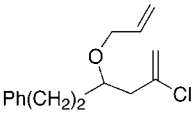
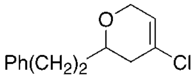
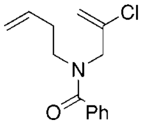
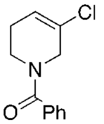


6

(1)

The scope of the vinyl chloride RCM reaction has been explored with several additional substrates, and some of the results are listed in Table 1. As can be seen, it is possible to use the methodology to prepare a wide variety of five-, six-, and seven-membered vinyl chloride-containing carbocyclic and heterocyclic compounds in high yields. In addition, using a 1,2-disubstituted olefin rather than a terminal one does not seem to cause problems with the cyclization (cf. entries **b** and **c**).

Table 1. Ring-Closing Metathesis Reactions of Representative Vinyl Chlorides[7]

entry	vinyl chloride	cyclization product	isolated yield (%)
a			99
b			98
c			96
d			92
e			84
f			88
g			90
h			90

We have also briefly investigated the possibility of forming larger rings by this process. Thus, exposure of vinyl chloride **7** to our optimized RCM conditions led to a complex mixture rather than the desired eight-membered ring **8** (eq 2). Moreover, all attempts to form a twelve-membered vinyl chloride ring also failed.

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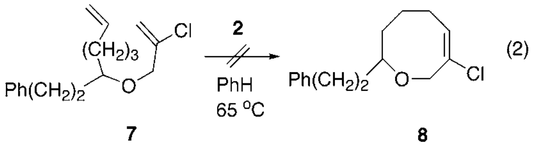
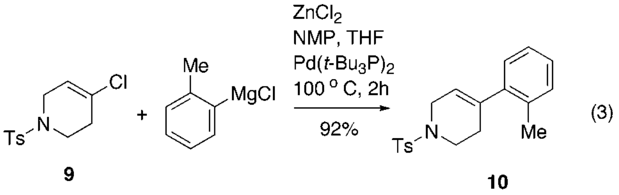
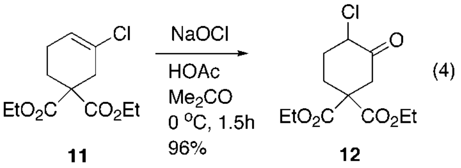
(7) **General experimental procedure for RCM of vinyl chlorides:** A 100-mL flask equipped with a condenser was flame dried in vacuo. The vinyl chloride substrate (0.24 mmol) in dry benzene (60 mL) was added and the solution was deaerated by bubbling argon through the mixture for 2 h. Second-generation Grubbs catalyst **2** (10 mol %) in 2 mL of dry benzene was added through the condenser and the argon bubbling was continued for an additional 30 min. The mixture was heated and stirred at 65 °C for 4−10 h until TLC showed the reaction was complete. The solvent was removed in vacuo and the residue was purified by silica gel chromatography to afford the desired metathesis product.

(8) At room temperature no metathesis occurs, and at 50 °C the reaction is very slow.



The metathesis products constructed by this methodology have considerable potential for a wide range of further transformations. Until recently, palladium-mediated couplings of vinyl chlorides in most cases were not synthetically useful processes.[9] However, this situation has changed with the recent important discovery of Fu and co-workers that using tri-*tert*-butylphosphine as the metal ligand allows one to efficiently utilize vinyl chlorides in Suzuki−Miyaura[10a] and Negishi[10b] couplings. Thus, cyclization product **9** could be arylated to afford **10** in high yield by using this methodology (eq 3). In addition, it is also possible to convert vinyl chlorides to the corresponding α-haloketones under mild conditions.[11] For example, using our recently reported procedure,[11] metathesis product **11** could be transformed to α-chloroketone **12** in excellent yield using sodium hypochlorite in a 5:2 mixture of acetone/acetic acid (eq 4).





In conclusion, we have shown that vinyl chlorides participate in RCM reactions with use of the second generation Grubbs ruthenium catalyst **2** to afford cyclized products in high yields. The process can be used to produce a diverse series of five- to seven-membered carbocyclic and heterocyclic systems. We are currently investigating further variations of this methodology, as well as applications to natural product total synthesis.

Acknowledgment. We are grateful to the National Institutes of Health (GM-32299) for financial support of this research.

Supporting Information Available: Copies of proton and carbon NMR spectra of metathesis products and compound **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] For recent reviews see: Miyaura, N., Ed. *Top. Curr. Chem.* **2002**, *219*.

[10] (a) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (b) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719.

[11] VanBrunt, M. P.; Ambenge, R. O.; Weinreb, S. M. *J. Org. Chem.* **2003**, *68*, 3323 and references cited therein.