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The Ring-Closing Metathesis of Vinyl Ethers with Grubbs' Catalyst for the Synthesis of Dihydropyrans

Claudio F. Sturino* and Jerome C. Y. Wong

Merck Frosst Centre for Therapeutic Research, P.O. Box 1005, Pointe Claire-Dorval, Québec, Canada, H9R 4P8

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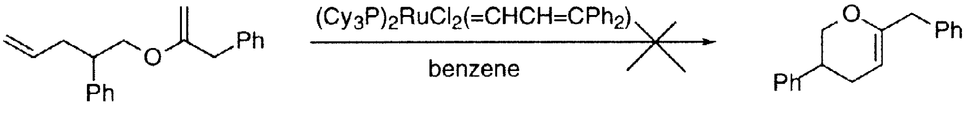
Abstract: A series of acyclic vinyl ethers have been prepared and treated with Grubbs' ruthenium catalyst ($(Cy_3P)_2RuCl_2{=}CHPh$). Contrary to previous findings, it has been shown that certain vinyl ethers are excellent substrates for the ring closing metathesis with ruthenium based catalysts. © 1998 Elsevier Science Ltd. All rights reserved.

There has been intense interest in recent years in the ring closing metathesis reactions of olefins.[1] This type of carbon-carbon bond formation has proven to be a powerful method for the synthesis of cyclic systems. Of the various catalysts reported that induce olefin ring-closing metathesis, Grubbs' ruthenium catalyst ($(Cy_3P)_2RuCl_2{=}CHPh$) has attracted a significant amount of interest due to its ease of handling and broad substrate applicability.[2] It has been reported by several groups, though, that vinyl ethers are poor substrates for the ruthenium based catalysts and that the more reactive Schrock[3] molybdenum catalyst is required. For example, as shown in equations 1 and 2 below, vinyl ethers **1** and **3** failed to provide any of the corresponding dihydropyrans **2** or **4** with ruthenium catalysts. However, the same substrates cleanly cyclized to the dihydropyrans when treated with Schrock's catalyst in 84 and 63% yields, respectively.[4,5] It has been suggested that the carbene resulting from the rapid reaction between the vinyl ether and the ruthenium catalyst is inert towards further metathesis.[6] During the course of a methathesis study which would allow for the preparation of various oxygenated systems, we have found that certain vinyl ethers do undergo ring closing metathesis with Grubbs' ruthenium catalyst to provide the corresponding dihydropyrans. Herein, we wish to report our initial findings on this reaction.



Equation 1

1 **2**

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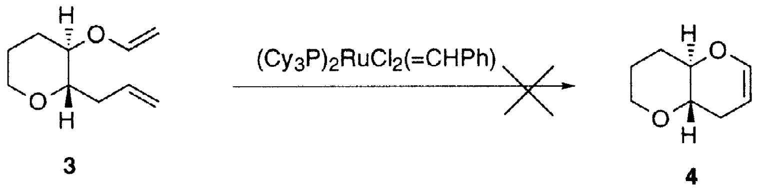
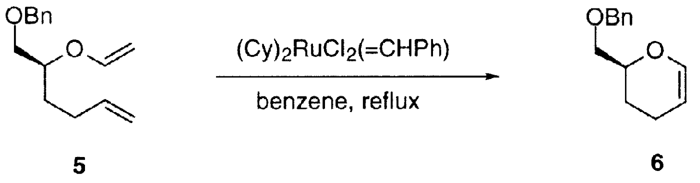


Equation 2

Our preliminary attempt at affecting a ring closing metathesis of a vinyl ether focused on diene **5** (see equation **3**, Table **1**). When **5** was treated with 5 mol% of Grubbs' ruthenium catalyst, we were pleased to find that, in contrast to the reported inactivity of vinyl ethers **1** and **3**, ring closing metathesis had indeed occurred to provide the corresponding dihydropyran **6** in 55% yield (Table **1**, entry 1). The ^{1}H nmr spectrum of **6** displayed the characteristic dihydropyran vinylic signals at δ 6.4 and 4.6 ppm and was found to be identical to that reported in the literature.[7] The ^{13}C nmr spectrum of **6** displayed two vinylic signals at δ 143.6 and 100.4 ppm, again in accord with the proposed structure. In an effort to improve the efficiency of this ring-closing process the reaction conditions were examined in some detail. Table **1** below summarizes the effects of varying the catalyst loading, reaction time and concentration on the yield of the dihydropyran. It was found that a high loading of Grubbs' catalyst (20 mol%) and short reaction times (0.5 hr) were necessary for efficient formation of the dihydropyran. Under these optimal conditions, a 69% yield of dihydropyran **6** was realized. Prolonged reaction times or higher reaction concentrations only served to decrease the yield of the desired dihydropyran (entries 4 and 5).

Table 1: Optimization of the Intramolecular Metathesis of Substrate 5

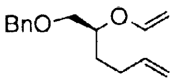
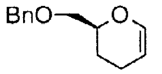
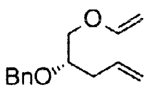
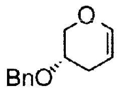
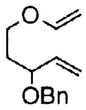
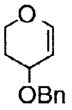
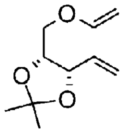
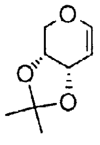
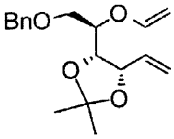
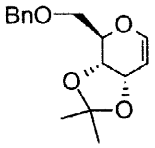
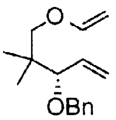
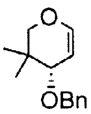


Equation 3

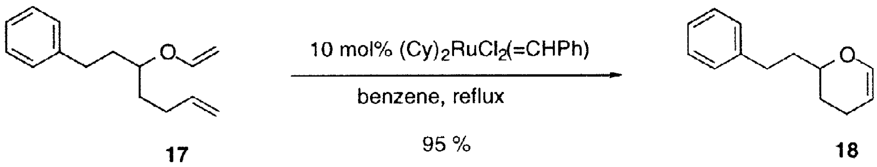
Entry	*Catalyst Loading*	*Reaction time (hr)*	*Concentration (M)*	*Yield (%)*
1	5 mole %	20	0.017	55
2	20 mole %	2	0.017	59
3	20 mole %	0.5	0.017	69
4	20 mole %	0.5	0.033	42
5	20 mole %	3	0.033	9

It is noteworthy to compare the success of **5** in the ring closing metathesis reaction using Grubbs' catalyst with the reported failure of substrates **1** and **3** (equations **1** and **2**). It maybe argued from these preliminary results that the metathesis of vinyl ethers with Grubbs' catalysts is sensitive to the particular substitution pattern present in the molecule. This point is illustrated by comparing the different reactivities between the apparently similar substrates **3** and **5**. In order to further examine the scope of this reaction a series of vinyl ethers were prepared and the metathesis results of these substrates are summarized in Table **2**.[8]

Table 2: Ring-Closing Metathesis of Vinyl Ethers

Entry	Substrate		*Product*		*Yield (%)*
1		5		6	69
2		7		8	45
3		9		10	0
4		11		12	0
5		13		14	0
6		15		16	45

Enol ether **7** (Table 1, entry 2) was subjected to the optimal ring closing metathesis reaction conditions to provide the corresponding enol ether **8** in 45% yield. However, in contrast to the success of the first two substrates examined, substrates **9**, **11** and **13** (Table **2**, entries **3**-**5**) completely failed to provide any of the desired cyclic material under a variety of different experimental conditions. These initial findings suggest that the presence of an allylic alkoxy substituent has a negative influence on the ring-closing reaction. An exception to this is found with substrate **15** (Table **1**, entry **6**) where a 45 % isolated yield of the cyclic ether was obtained. The increased reactivity of this diene likely arises from a Thorpe-Ingold effect of the gem-dimethyl substituents. It should be noted that all the substrates in Table 2 possess alkoxy substituents. In order to investigate the reactivity of a vinyl ether that lacked any alkoxy substitution, substrate **17** was prepared. Subsequent metathesis of 17 with 10 mol% Grubbs' catalyst resulted in a 95% isolated yield of the corresponding dihydropyran **18**. This result clearly establishes the ability of vinyl ethers to participate in a ring closing metathesis reaction with Grubbs' catalyst.



Equation 4

In summary, we have shown that certain vinyl ethers are excellent substrates for the ring closing metathesis reaction with ruthenium based catalysts. In these reactions, neighbouring alkoxy substituents appear to exert a negative influence on the metathesis process. We are currently exploring the structural requirements necessary to allow vinyl ethers to undergo ring closing metathesis reactions with ruthenium catalysts and these results will be disclosed in due course.

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