Effect of a proximal oxygen substituent on the efficacy of ruthenium-catalyzed cross-metathesis and RCM

Tarun K. Maishal, Dilip K. Sinha-Mahapatra, Kavita Paranjape and Amitabha Sarkar*

Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune 411008, India

Abstract—Ruthenium-catalyzed cross-metathesis of various derivatives of 1,2-dihydroxy-3-butene reveals that cyclic acetals are best suited as substrates compared to acyclic diethers or diacetates, while RCM is relatively insensitive to the presence of allylic or homoallylic hydroxy or acetoxy groups. © 2002 Elsevier Science Ltd. All rights reserved.

While remarkable functional group tolerance of Grubbs' ruthenium catalyst[1] [Cl_2{(c-C_6H_{11})$_3$P}$_2$-Ru=CHPh, **1**] for alkene metathesis[2] has been widely hailed and extensively utilized in recent times—so much so that ring-closing metathesis[3] (RCM) and cross-metathesis[4] (CM) readily invaded even carbohydrate and peptide chemistry[5]—the precise nature of activation or deactivation of metathesis by neighboring oxygen-bearing functions (hydroxy or alkoxy groups) are yet to be rationalized in terms of a consistent pattern.

It is usually believed that an allylic alcohol adversely affects metathesis involving the adjacent double bond presumably by strong coordination with the catalyst thereby arresting the cycle, and there are several reported instances of such difficulty.[6a,b] Even when the allylic OH group is protected as an ether, there could be interference by such groups to the detriment of catalytic efficiency.[6] A remotely placed hydroxyl function or a tertiary alcohol usually does not affect the course of this reaction.[7] On the other hand, several recent reports not only describe efficient metathesis despite the presence of an allylic alcohol,[8] some results suggest that this function could even assist the process.[9] A collection of representative data from the literature indicates that more than one structural factor may be responsible for such apparently conflicting situations (see Table 1).
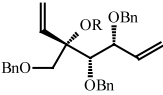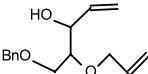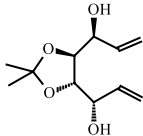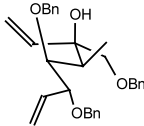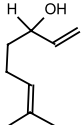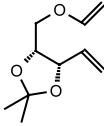
In this context, we are prompted to disclose the results of our experiments with simple four-carbon substrates, all of which contain allylic and homoallylic oxygen functions, which were subjected to cross-metathesis or RCM conditions. We find that while the reactions are sensitive to the nature of the oxygen functionality and its placement in the molecule, a straightforward correlation still remains elusive.

The substrates used in this study are derivatives of 3-buten-1,2-diol obtained readily from 1,2-epoxy-3-butene.[10] The first three substrates (**2a**–**c**) were 1,3-dioxolane derivatives differing only in the precursor ketone. Th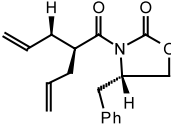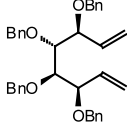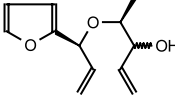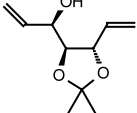e reaction time was held constant at 8 h for all entries included in Scheme 1, so that the relative ease of metathesis for different substrates could be assessed. They afforded self-metathesis products on refluxing with 5 mol% of catalyst **1** in dichloromethane in good yields (70–80%) indicating that cyclic acetal derivatives are good substrates for metathesis. On the other hand, the acyclic derivatives, esters or ethers derived from 3-buten-1,2-diol, are poor cross-metathesis substrates. When the hydroxyl groups were protected as methyl ethers (**2d**), the reaction was even less efficient than when one of them was protected as an acetate (**2e**) or both were protected as acetates (**2f**).[11] A cyclic carbonate **2g** was not a good substrate either. This is intriguing, since allyl acetate (**2h**) and homoallyl acetate (**2i**) are excellent substrates for self-metathesis affording products in 91 and 73% isolated yields, respectively. These results imply that two vicinal oxygen functions on a flexible four-carbon chain coordinate to the catalytic species more strongly than one and impede the catalytic process. The reaction works for carbohydrates probably because the oxygen functions are present on the periphery of rings and have definite but inflexible orientations—also the reaction site is usually further removed.

---

* Corresponding author. Fax: +91 20 589 3153/589 3355; e-mail: sarkar@ems.ncl.res.in

Table 1.

RCM procedes with allylic OH	Ref.	Allylic OR deters RCM	Ref.
	8a		6f
	8a		6e
	5b		6h
	9		6h
	8e		6e
	8d		
	8c		

Consistent with its observed ease of self-metathesis reaction, the substrate **2a** underwent facile cross-metathesis with several partners (**4a–e**) (Scheme 2). Allyltrimethylsilane (**4e**) is the least prone to self-metathesis, while a simple hydrocarbon like 1-octene (**4d**) undergoes self-metathesis at a very high rate. The relative ratios of substrates (**2a:4a–e**) were decided on the basis of this difference of reactivity. Indeed the cross-metathesis worked well and desired products were isolated in acceptable yields.

To study the effect of the oxygen function in allylic or homoallylic positions on RCM, we prepared two regioisomeric compounds (**2j** and **2k**) from epoxybutene (Scheme 3). In one sequence, the epoxide was opened with allyl alcohol which attacks the allylic carbon of the epoxide with high selectivity to afford substrate **2j**. To obtain the other regioisomer, the epoxide was first converted to the diol. The cyclic tin derivative permitted attack by allyl bromide selectively at the primary carbon

to afford substrate **2k**. Both **2j** and **2k** were converted to the corresponding acetates, **2l** and **2m**, by standard procedure.

The compounds **2j** and **2k** proved to be excellent substrates for RCM (Scheme 4). However, cyclic products were obtained in even better yield and in shorter time periods when hydroxyl functions were protected as acetates (**2l** and **2m**). These results tend to suggest that a neighboring hydroxyl or acetoxy group is much better tolerated in RCM than in cross-metathesis.
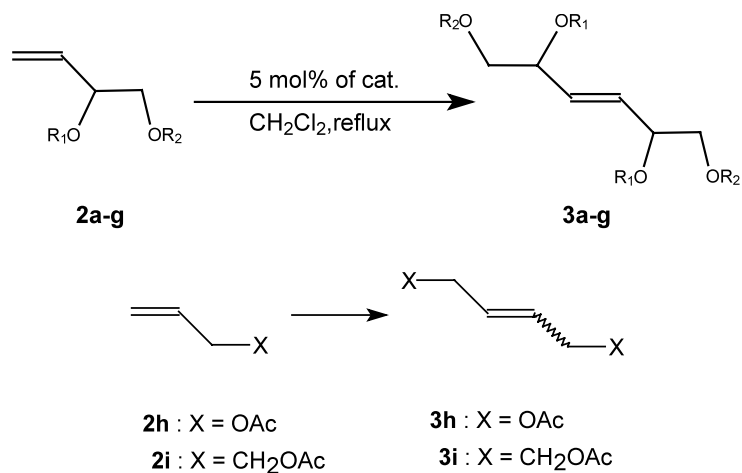
	R$_1$	R$_2$	Yield (%)
2a	-C(CH$_3$)$_2$-		83
2b	-C(CH$_3$)(C$_2$H$_5$)-		81
2c	-C(CH$_2$)$_5$-		80
2d	-CH$_3$	-CH$_3$	7
2e	-CH$_3$	-COCH$_3$	18
2f	-COCH$_3$	-COCH$_3$	27
2g	-(CO)-		0

Scheme 1.
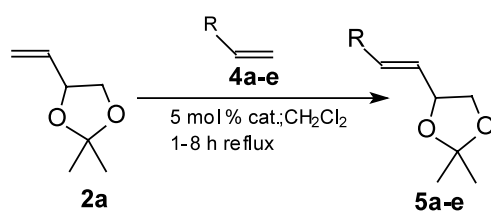
4	R	Mol Ratio (2:4)	Time(h)	Yield (%)
4a	- C$_6$H$_5$	3:1	1	75
4b	-CH$_2$:CHPh	3:1	2	64
4c	-(CH$_2$)$_5$CH$_3$	2:1	6	68
4c	-(CH$_2$)$_5$CH$_3$	1:2	6	36
4d	-(CH$_2$)$_7$CH$_3$	2:1	6	72
4e	-CH$_2$SiMe$_3$	1:3	8	63

Scheme 2.
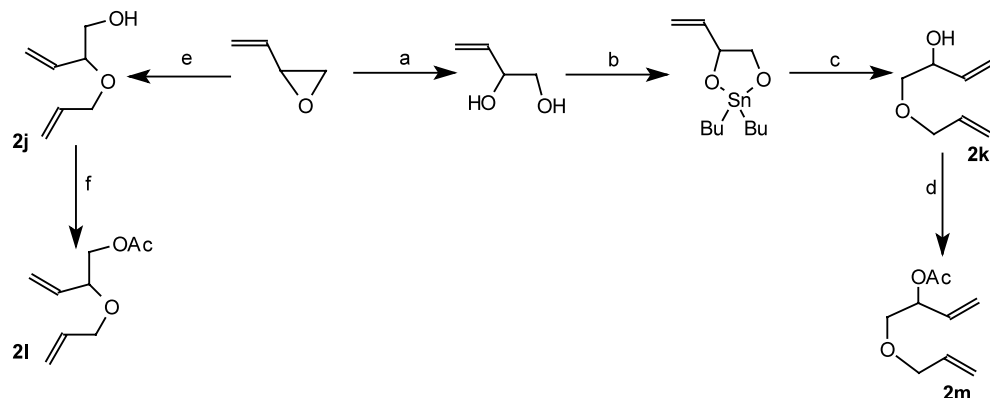
Scheme 3. *Reagents and conditions*: (a) H_2O, heat; (b) dibutyltin oxide, MeOH, rt; (c) allyl bromide, DCM, heat; (d) Ac_2O, Py, DCM, rt; (e) allyl alcohol, K-10 clay, heat; (f) Ac_2O, Py, DCM, rt.
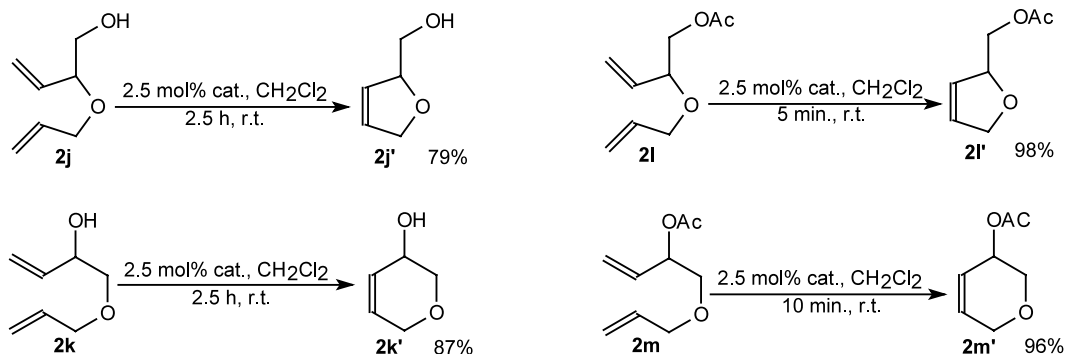
Scheme 4.

References

1. Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
2. (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29; (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043; (c) Pariya, C.; Jayaprakash, K. N.; Sarkar, A. *Coord. Chem. Rev.* **1998**, *168*, 1–48; (d) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450; (e) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036–2056; (f) Grubbs, R. H.; Pine, S. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 5, Chapter 9.3.
3. (a) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–388; (b) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792; (c) Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833–1836; (d) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446–552.
4. (a) 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; (b) O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Miura, K.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 1091–1094; (c) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751–1753; (d) Dominique, R.; Das, S. K.; Roy, R. *Chem. Commun.* **1998**, 2437–2438; (e) O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, *39*, 7427–7430; (f) Cossy, J.; BouzBouz, S.; Hoveyda, A. H. *J. Organomet. Chem.* **2001**, *624*, 327–332.
5. For a recent review, see: (a) Roy, R.; Das, S. K. *Chem. Commun.* **2000**, 519–529. For carbohydrates and peptides, see: (b) Kapferer, P.; Sarabia, F.; Vasella, A. *Helv. Chim. Acta* **1999**, *82*, 645; (c) Ovaa, H.; Leeuwenburgh, M. A.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1998**, *39*, 3025–3028; (d) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606–9614; (e) Clark, T. D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1995**, *117*, 12364–12365.
6. (a) Gurjar, M. K.; Yakambram, P. *Tetrahedron Lett* **2001**, *42*, 3633–3636; (b) Paquette, L. A.; Efremov, I. *J. Am. Chem. Soc.* **2001**, *123*, 4492–4501; (c) Hu, Y.-J.; Dominique, R.; Das, S. K.; Roy, R. *Can. J. Chem.* **2000**, *78*, 838–845; (d) Bourgeois, D.; Pancrazi, A.; Ricard, L.; Prunet, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 726–728; (e) Ackermann, L.; Tom, D. E.; Fürstner, A. *Tetrahedron* **2000**, *56*, 2195–2202; (f) Sellier, O.; Van de Weghe, P.; Eustache, J. *Tetrahedron Lett.* **1999**, *40*, 5859–5860; (g) Holt, D. J.; Braker, W. D.; Jenkins, P. R.; Davies, D. L.; Garratt, S.; Fawcett, J.; Russell, D. R.; Ghosh, S. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3298; (h) Sturino, C. F.; Wong, J. C. Y. *Tetrahedron Lett.* **1998**, *39*, 9623–9626.
7. (a) Maity, B. C.; Swamy, V. M.; Sarkar, A. *Tetrahedron Lett.* **2001**, *42*, 4373–4376; (b) Bassindale, M. J.; Edwards, A. S.; Hamley, P.; Adams, H.; Harrity, J. P. A. *Chem. Commun.* **2000**, 1035–1036; (c) Lautens, M.; Hughes, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 129–131.
8. (a) Davoille, R. J.; Rutherford, D. T.; Christie, S. D. R. *Tetrahedron Lett.* **2000**, *41*, 1255–1259; (b) Krikstolaityte, S.; Hammer, K.; Undheim, K. *Tetrahedron Lett.* **1998**,

39, 7595–7598; (c) Ovaa, H.; Codee, J. D. C.; Lastdrager, B.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1998**, *39*, 7987–7990; (d) Schmidt, B.; Sattelkau, T. *Tetrahedron* **1997**, *53*, 12991; (e) Crimmins, M. T.; King, B. W. *J. Org. Chem.* **1996**, *61*, 4192–4193.

9. Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123–1125.
10. The Eastman Chemical Company, USA, is thanked for the generous gift of epoxybutene. All yields refer to isolated yield of chromatographically purified compounds. All compounds were characterized by their proton and carbon NMR data as well as mass spectra. The cross-metathesis products consisted of >90% *trans* isomers (based on proton NMR spectra recorded at 200 MHz).
11. Oguri, H.; Sasaki, S.; Oishi, T.; Hirama, M. *Tetrahedron Lett.* **1999**, *40*, 5405–5408.