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Some Allylic Substituent Effects in Ring-Closing Metathesis Reactions: Allylic Alcohol Activation

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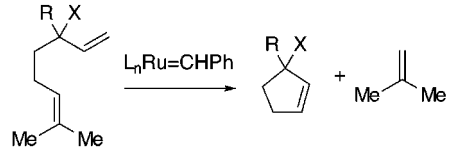
ABSTRACT

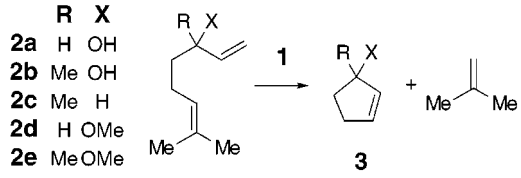


2	2a	2b	2c	2d	2e
R	H	Me	Me	H	Me
X	OH	OH	H	OMe	OMe
rel reactivity	60	12	8	1	~0

Dienes 2a–e were used to study allylic substituent effects in the ring-closing metathesis reaction (RCM). Both the steric and electronic character of the allylic substituents were found to influence alkene reactivities. Free allylic hydroxyl groups exert a large activating effect on the RCM reaction rates.

The power of ring-closing metathesis reactions of dienes is indisputable.[1] Systematic studies that add definition to the type of substrates that tolerate the cyclization conditions provide valuable information that can be used in planning the application of RCM reactions to more complex systems. Ulman and Grubbs reported a very instructive and fundamental kinetic study in which they determined the relative rates of initial reaction of a series of simple hydrocarbons with the Grubbs ruthenium benzylidene carbene, PhHC═Ru(PCy$_3$)$_2$Cl$_2$ (**1**).[2] These alkenes differed in the degree of substitution on the double bond and at the allylic and homoallylic centers.

We report here the ring-closing metathesis reactions of a series of substrates **2**, which differ in the nature and number of allylic substituents. The skeleton, which bears one mono- and one trisubstituted alkene, was chosen so that the initial metathesis event would occur only at the less substituted alkene.[2] The allylic carbon in these five substrates bears an array of methyl, hydroxy, and/or methoxy substituents.[3]



The first substrate we examined, linalool (**2b**), underwent RCM unexpectedly quickly at room temperature using just 5 mol % of **1** to give 1-methylcyclopent-2-en-1-ol (**3b**) very efficiently.[4] This was surprising for two reasons. It is known that *tert*-butylethylene, containing a *fully substituted* allylic center, is nearly inert to reaction with **1**,[2] and the ring-closing event involves reaction with a *trisubstituted* alkene, of which there are few reported examples.[5] We took advantage of the opportunity that this diene framework provided to probe the effect of various allylic substituents.

The substrates **2a**−**e** were prepared, where necessary, by conventional routes.[6] Various pairs were then subjected to

(1) (a) Grubbs R. H.; Chang S *Tetrahedron* **1998**, *54*, 4413−4450. (b) Schuster M.; Blechert S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037−2056.

(2) Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484−2489.

(3) For a study of the effect of various substituents (including hydroxymethyl) on the ring-opening polymerization by **1** of a series of 3-substituted cyclobutenes, see: Maughon, B. R.; Grubbs, R. H. *Macromolecules* **1997**, *30*, 3459−3469.

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competition experiments. Equimolar mixtures of, e.g., **2c** and **2d** were treated with 4−10 mol % of **1** in $CDCl_3$ at room temperature. Reaction progress was monitored directly by ^1H NMR spectroscopy. In no case were any intermediate alkylidene species detected, implying that the rate-limiting event in the reaction of each substrate was the metal exchange reaction between an external ruthenium alkylidene (either benzylidene or isopropylidene) and the terminal vinyl group in **2**. The results of the various pairwise competition experiments are indicated in Figure 1 and are summarized by the approximate relative reactivity values listed to the left of each structure.

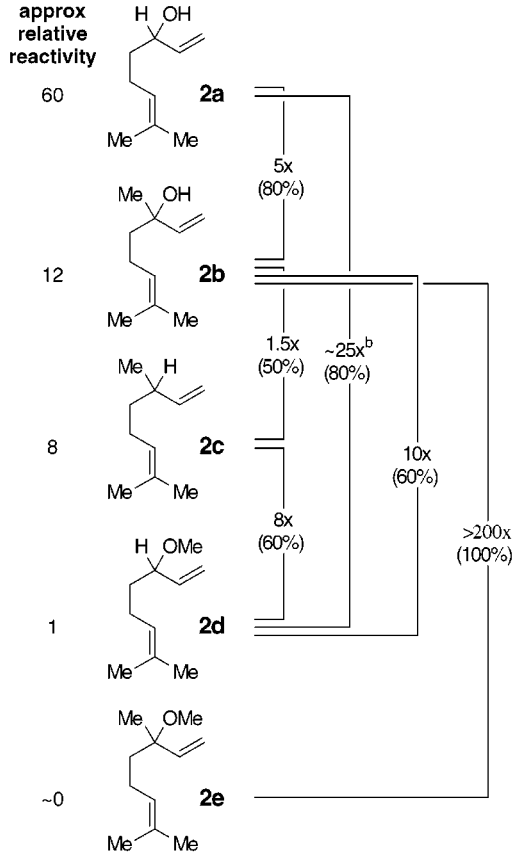


Figure 1. Results of RCM competition reactions between equimolar amounts (~0.02 M in each diene) of the bracketed pairs of substrates in $CDCl_3$ at room temperature in the presence of 4−10 mol % of **1**. #x represents the product ratio (determined by integration of appropriate ^1H NMR resonances) at the percent conversion of the more reactive substrate (as indicated in parentheses). In experiments involving the secondary alcohol **2a**, 90−100 mol % of **1** was used since carbene species are consumed by competitive methyl ketone formation (see text). There is a considerable error bar in the measurement marked b, since only a small amount of the cyclopent-2-en-1-ol methyl ether (**3d**) was present even at high conversion of **2a**.

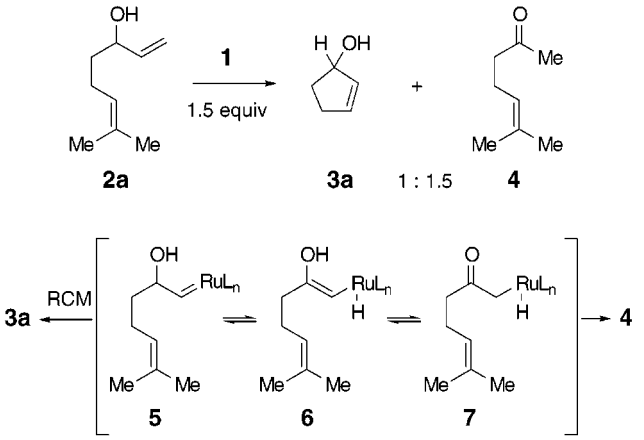
One early competition experiment convincingly demonstrated the fact that the allylic free hydroxyl group in linalool (**2b**) has a significant activating effect on the reaction rate. Namely, linalool methyl ether (**2e**) was unreactive in competition with **2b**; indeed, the ether was inert even when heated (~65 °C, $CDCl_3$) with **1**. Thus, the completely substituted allylic carbon in **2e** is sufficient to inhibit alkylidene formation. The lack of reaction within **2e** also supports the assertion that all RCM events in **2a**−**2d** are initiated at the monosubstituted alkene.

To rule out the possibility that the reactivity difference between **2b** and **2e** was primarily steric in nature, we competed linalool (**2b**) with citronellene (**2c**) in which the latter clearly has a less hindered vinyl group.[7] Nonetheless, the tertiary alcohol **2b** reacted faster than **2c**, again confirming the hydroxyl activating effect. There are several possible reasons for the large activating effect of the hydroxy group. For example, rapid and reversible ligand exchange at the ruthenium center of alkoxy for chloride [to give a species such as $(RO)Cl(Cy_3P)_2Ru{=}CHR'$] or of alcohol for phosphine [to give species such as either $Cl_2(Cy_3P)(ROH)Ru{=}CHR'$ or the anionic complex $[Cl_2(Cy_3P)(RO)Ru{=}CHR']^-[Cy_3PH]^+$] could promote reaction by preassociation. Similarly, hydrogen bonding between the hydroxy group and one of the chloride ligands could be the event that favors subsequent reaction between the alkene (in R) and carbene centers.

The outcome of the previously mentioned competition between **2c** and **2d** suggests that the inductive effect of the allylic ether reduces the reaction rate of the adjacent, less electron-rich alkene by nearly an order of magnitude.

Finally, we studied the RCM reaction of the secondary alcohol **2a**. As we recently noted in a different context,[8] an unexpected reaction pathway was uncovered. Namely, in addition to the ring-closed cyclopent-2-en-1-ol (**3a**), the methyl ketone **4** was formed in a 1:1.5 ratio (Scheme 1). It

Scheme 1



is clear that ruthenium carbene species are being consumed by this side reaction, since use of only 10 mol % of **1** results in low conversion of **2a** and all ^1H NMR resonances due to **1** disappear. We suggest[8] that the initial carbene **5** undergoes tautomerization to the enolyl ruthenium hydride species **6**, which can further undergo reductive elimination, either before or after tautomerization to the oxoalkyl ruthenium

hydride **7**, to produce the methyl ketone **4**. As a result of this consumption of ruthenium carbenes, we elected to use 90−100 mol % of **1** in our competition experiments involving **2a**. Nonetheless, it is clear that the unhindered secondary allylic alcohol **2a** is the most reactive RCM substrate among all of **2a**−**e**. However, the designed use of substrates containing the $RCH(OH)CH{=}CH_2$ substructure in productive RCM reactions is risky since only the most rapid ring closures would likely compete with the unwanted net fragmentation reaction like that involved in the **2a** to **4** transformation. One instance in which an RCM substrate containing a secondary allylic alcohol [i.e., $CH_2{=}CHCH(OH)$-$CH(R)CH_2CH{=}CH_2$] was successfully ring-closed (to a cyclopentene derivative) has been reported, but it is unknown at which alkene the RCM was initiated.[9]

In conclusion, allylic hydroxyl groups greatly accelerate the rate of carbene-exchange reaction between the adjacent vinyl group and external ruthenium alkylidenes. This enhancement is sufficient to overcome significant steric deactivation. The corresponding methyl ethers are reduced in reactivity relative to sterically similar methylated substrates. Secondary allylic alcohols are a liability in RCM reactions because of a net fragmentation reaction that consumes ruthenium alkylidene species.

Acknowledgment. We thank the National Institutes of Health (CA76497) for funding this investigation.

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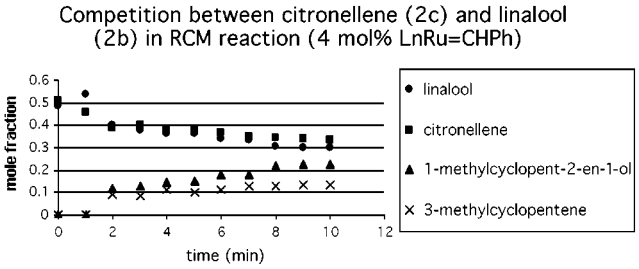
(4) Three RCM reactions involving tertiary allylic alcohols were reported recently: (a) Holt, D. J.; Barker, W. D.; Jenkins, P. R.; Davies, D. L.; Garratt, S.; Fawcett, J.; Russell, D. R.; Ghosh, S. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3298−3300. (b) Sellier, O.; Van de Weghe, P.; Eustache, J. *Tetrahedron Lett.* **1999**, *40*, 5859−5860. (c) Wood, J. L.; Holubec, A. A.; Stoltz, B. M.; Weiss, M. M.; Dixon, J. A.; Doan, B. D.; Shamji, M. F.; Chen, J. M.; Heffron, T. P. *J. Am. Chem. Soc.* **1999**, *121*, 6326−6327.

(5) E.g., citronellene (**2c**) has been previously ring-closed with the Dupont tungsten metathesis catalyst. Nugent, W. A.; Feldman, J.; Calabrese, J. *J. Am. Chem. Soc.* **1995**, *117*, 8992−8998.

(6) The only new compound described in this paper, ether **2d**, gave satisfactory ^1H NMR, ^{13}C NMR, IR, and HRMS data.

(7) A representative plot of change in product ratios with time (and % conversion) is shown here for the **2b**/**2c** competition experiment.



(8) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 169−171.

(9) Crimmins, M. T.; King, B. W.; *J. Org. Chem.* **1996**, *61*, 4192−4193.