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Kinetically Controlled Cross-Metathesis Reactions with High *E*-Olefin Selectivities

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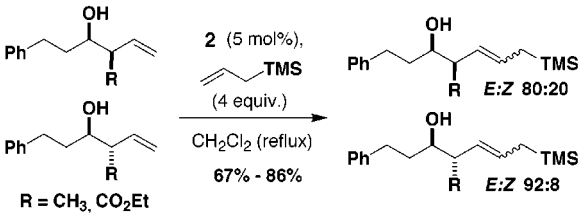
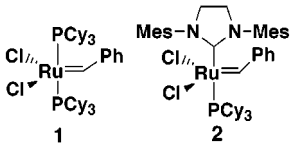
ABSTRACT



Homoallylic alcohols with *anti*-allylic substituents display enhanced *E*-olefin selectivity in cross-metathesis (CM) reactions with allyltrimethylsilane. The high selectivity can be explained via a five-membered chelate intermediate in which the hydroxyl group of the homoallylic alcohol coordinates to the ruthenium metal center of Grubbs' catalyst.

Olefin metathesis chemistry and its application to organic synthesis have advanced significantly in the past few years.[1] The primary engine for the recent growth of metathesis chemistry was the development of an air-stable ruthenium benzylidene catalyst **1**. The benzylidene catalyst (Grubbs'



catalyst) has consistently displayed its wide tolerance of functional groups and versatility in a variety of metathesis reactions.[1] These characteristics coupled with its stability have easily made it the most prevalent metathesis catalyst in the current literature. Our group has successfully employed the use of **1** in the ring closing metathesis (RCM) reaction for the synthesis of allylsilane homoallylic alcohols (AHAs) as cyclopropane precursors.[2]

In our initial studies, we were limited to the use of the ruthenium benzylidene catalyst **1**.[2] It quickly became apparent that while catalyst **1** was effective in RCM reactions, it reacted sluggishly in cross-metathesis (CM) reactions between unprotected homoallylic alcohols and allyltrimethylsilane (Table 1).[3] However, within the past year and the advent of the second-generation benzylidene catalyst **2** containing the 1,3-dimesityl-4,5-dihydroimidazol-2-ylidine ligand,[4] we again explored the more concise CM route to our cyclopropane precursors.[5] In that account we first

(1) For recent reviews of olefin metathesis, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) 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. (c) Roy, R.; Das, S. K. *Chem. Commun.* **2000**, 519. (d) Grubbs, R. H.; Trnka, T. M. *Acc. Chem. Res.* **2001**, *34*, 18. (e) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.

(2) (a) Taylor, R. E.; Engelhardt, F. C.; Yuan, H. *Org. Lett.* **1999**, *1*, 1257. (b) Taylor, R. E.; Schmitt, M. J.; Yuan, H. *Org. Lett.* **2000**, *2*, 601.

(3) Unpublished results: The lack of reactivity of benzylidene catalyst **1** in the presence of a free hydroxyl in the homoallylic position is well-established. To circumvent the low reactivity problem in the CM reactions, we employed high catalyst concentrations (40−50 mol %) of **1**. Though effective in facilitating the CM reaction (yields 20−40%), the highly colored metathesis products proved difficult to purify. Additionally, the highly colored products gave poor yields in later reactions due to lingering catalyst contaminants.

(4) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(5) Taylor, R. E.; Engelhardt, F. C.; Schmitt, M. J.; Yuan, H. Q. *J. Am. Chem. Soc.* **2001**, *123*, 2964.

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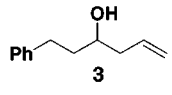
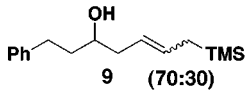
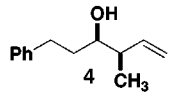
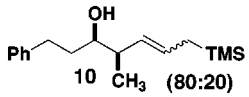
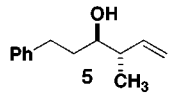
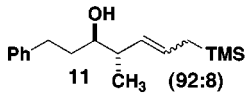
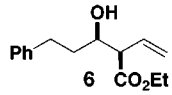
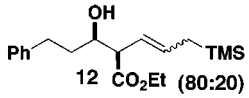
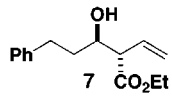
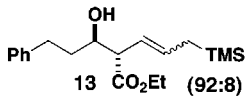
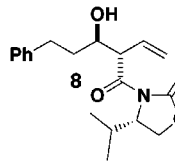
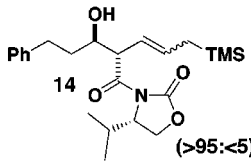
Table 1. Cross-Metathesis Reaction of Homoallylic Alcohols with Allyltrimethylsilane[a]

Homoallylic Alcohol	Cross-Metathesis Product (*E*:*Z*)*
	
	
	
	
	
	

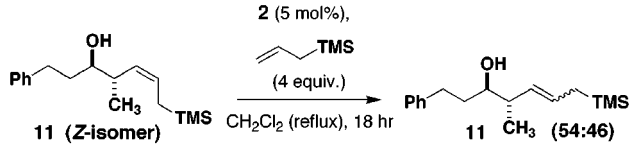
[a] Reaction conditions: (a) allyltrimethylsilane (4 equiv), **2** (5 mol %), CH_2Cl_2 reflux, 4 h. *(*E*:*Z*) ratios were determined by using both ^1H and ^{13}C NMR.

observed the high *E*-olefin selectivity in the cross-metathesis reactions of *anti*-hydroxypropionates with allyltrimethylsilane. This Letter will further report on these observed enhancements and elaborate on the potential origin.

The first substrate subjected to the cross-metathesis reaction with allyltrimethylsilane was homoallylic alcohol **3** derived from hydrocinnamaldehyde. With no allylic substituent, this substrate easily afforded the desired CM product **9** as an inseparable mixture of *E*- and *Z*-isomers (70:30) in 84% yield.[6] Similarly, the *syn*-allylic substituted homoallylic alcohols **4** and **6** provided their corresponding CM products **10** and **12**, again in good yield, with typically observed *E*:*Z* ratios (80:20).[6] However, when the relative stereochemistry between the hydroxyl group and the allylic substituents was *anti*, increased selectivity for the *E*-olefin was observed. Both *anti*-allylic substituted homoallylic alcohols **5** and **7** provided the desired CM products, but with notably higher selectivities for the *E*-isomer (92:8). This increased selectivity was even more pronounced when the enantiopure substrate **8** was subjected to CM conditions. In the product mixture **14**, the *Z*-isomer was not detected by either ^1H or ^{13}C NMR, suggesting a greater than 95:5 selectivity in favor of the *E*-olefin. *Thus, when the relative stereochemistry between the homoallylic hydroxyl group and the allylic substituent is anti, there is a noticeable preference for the E-olefin products.*

In two recent independent publications, Fürstner[7a] and Smith[7b] have noted the reversible nature of the olefin metathesis reactions using the newer ruthenium metathesis catalysts, specifically catalyst **2**. Intrigued by these results, we first explored the possibility that the observed difference in our *E*:*Z* ratios was a result of a reversible thermodynamic process. To evaluate this, we subjected isomerically pure *Z*-olefin **11** to the CM conditions with catalyst **2**, affording an *E*:*Z* mixture of olefins (54:46) after 18 h (Scheme 1).

Scheme 1. Reversible Nature of Cross-Metathesis Reaction



This served to verify the reversibility of the reaction, but the isomerization was slow relative to the time scale of the CM reactions in Table 1 (4 h). In fact, the product ratios in Table 1 were also shown to be independent of both reaction time and concentration.[8] These observations, combined with our results in Scheme 1, suggested that on the time scale of our CM reactions, isomerization of the olefin is slow and the observed product ratios in Table 1 are not thermodynamically controlled. Rather, the product ratios are better explained using a kinetic rationale based only on the relative energy differences of the corresponding metallacyclobutane intermediates.

It is well established that the active form of Grubbs' catalyst **1** is a 14-electron species derived from the dissociation of a tricyclohexylphosphine group.[9] In this electron-deficient state, an available lone pair of electrons can easily electronically subsidize the metal center. Such an interaction typically occurs intramolecularly and usually only serves to deactivate the catalyst. Work by several groups[10] has described this phenomenon. In the case of homoallylic alcohols or esters, the oxygen moiety is coordinated to the ruthenium center of catalyst **1**, essentially sequestering the catalyst in an unreactive form.[11] Recently, Hoveyda[12] reported that with 2-isopropoxystyrene the ruthenium center

(6) For comparable (*E*:*Z*) ratios in similar cross-metathesis reactions, see ref 1 and the following: (a) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751. (b) Crowe, W. E.; Goldberg, D. R.; Zhang, Z. J. *Tetrahedron Lett.* **1996**, *37*, 2117.

(7) (a) Fürstner, A.; Thiel, O. R.; Ackermann, L. *Org. Lett.* **2001**, *3*, 449. (b) Smith, A. B., III; Adams, C. M.; Kozmin, S. A. *J. Am. Chem. Soc.* **2001**, *123*, 990.

(8) The CM reactions in Table 1 were run at varying concentrations (0.1−0.01 M) and reaction times (1−24 h) for several substrates. Despite the variant of conditions used, the observed *E*:*Z* ratio for the CM products was always the same for the respective substrate.

(9) (a) Grubbs, R. H.; Dias, E. L.; Nguyen, SB. T. *J. Am. Chem. Soc.* **1997**, *119*, 3887. (b) Schaaf, P. A. V. D.; Kolly, R.; Hafner, A. *Chem. Commun.* **2000**, 1045.

(10) (a) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130. (b) Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651. (c) Roy, R.; Das, S. K. *Chem. Commun.* **2000**, 519.

of either catalyst **1** or **2** not only chelates to oxygen but actually forms a new stable, isolable carbene. Grubbs has also added credence to these chelate models, providing evidence for stable five- and six-membered ring chelates between catalyst **2** and the carbonyl of an amide functional group.[13] Most interesting in this last paper though is the proposal that the metallacycle intermediate itself can also be involved in the chelation.

In the CM reaction, once the ruthenium benzylidene catalyst **2** reacts with the terminal olefin of a homoallylic alcohol (such as **5**), a new alkylidene **15** is generated (Figure 1). After which, a dynamic equilibrium ensues where the

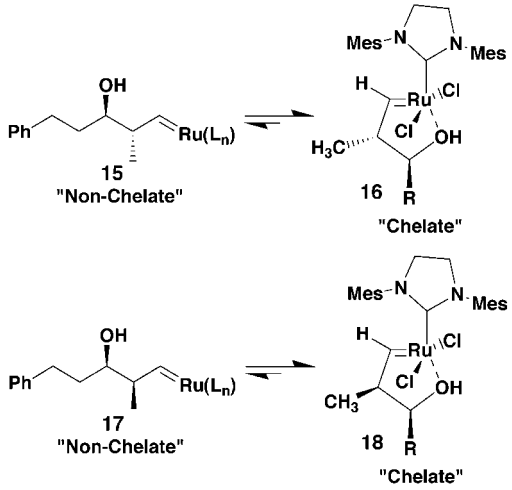


Figure 1. Five-membered chelate of alkylidene with Grubbs' catalyst.

ruthenium center coordinates with the free hydroxyl group in **15** to generate chelate **16**. On the basis of ^{1}H NMR and the upfield shift[14] (17.18 ppm) of the carbene proton, it appears that chelate **16** is the favored structure (Figure 1).[12a] Similarly alkylidene **17**, arising from the *syn*-substituted homoallylic alcohol **4**, provides chelate **18**. Interestingly, despite being chelated, the catalyst retains reactivity, suggesting that the chelate is highlighted by a labile oxygen−ruthenium bond. This lability allows the catalyst to undergo further metathesis reactions[10] rather than siphoning the catalyst into an unreactive reservoir. The presence of a chelate also defines a sterically biased environment and from this the enhanced *E*-olefin selectivities can be rationalized.

Analyzing the chelate of *anti*-propionate homoallylic alcohol **16**, it is apparent that both faces of the Ru═C carbene are somewhat blocked by substituents. The α-face is blocked by the methyl group while the *β*-face is inhibited by the large R group ($PhCH_2CH_2$-). For the *syn*-propionate chelate **18**, the *β*-face is blocked by both the methyl and the R group, while the α-face is completely uninhibited. As a result of these chelates, new steric considerations emerge, biasing the approach of allyltrimethylsilane to form the metallacyclobutane intermediates (Figure 2). It is in these metallacycle

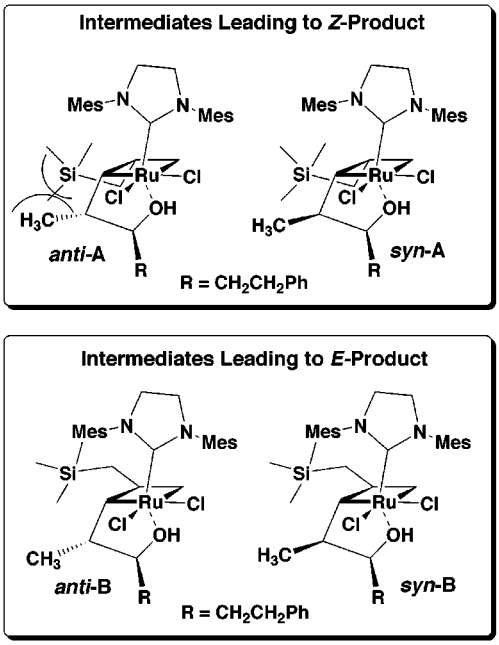


Figure 2. Metallacyclobutane intermediates with five-membered ring chelate.

intermediates that the enhancement in *E*-olefin selectivity can be understood.

For simplicity, the following discussion will be limited to intermediates formed from the approach of allyltrimethylsilane from the α-face of chelated structures **16** and **18**.[15] The intermediates *anti*-**A** and *anti*-**B** are drawn for the formation of the metallacycle between allyltrimethylsilane and the ruthenium alkylidene of **16** (Figure 1). As all of these metathesis reactions are reversible, these two intermediates can either break down to starting materials or go on to

(11) This sequestering effect sufficiently explains our difficulty in using catalyst **1** in the CM reaction of unprotected homoallylic alcohols with allyltrimethylsilane (ref 3).

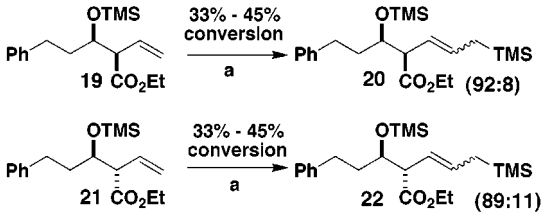
(12) (a) Hoveyda, A. H.; Bonitatebus, P. J., Jr.; Harrity, J. P. A.; Kingsbury, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 791. (b) Hoveyda, A. H.; Gray, B. L.; Kingsbury, J. S.; Garber, S. B. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

(13) Choi, T.-L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277.

(14) All NMR work was performed in $CDCl_3$ and chemical shifts were reported relative to residual $CHCl_3$ (^{1}H: δ 7.26 ppm). The carbene proton in the parent benzylidene catalyst **2** appears 19.14 ppm, while the propagating methylidene appears at 17.78 ppm. The upfield shift of the carbene proton in structure **15**/**16** is highly suggestive of a chelate and matches well with Hoveyda's results of similar oxygen−ruthenium chelated structures (ref 12a).

(15) It is important to note that with the *syn*-alkylidene **18** the formation of the metallacycle intermediate will be controlled by the two substituents on the *β*-face. The approach of the allyltrimethylsilane to **18** will occur predominantly from the α-face, as it is unfavorable to approach from the more hindered *β*-face; thus no added steric interactions occur, leading to typical *E*:*Z* ratios in the CM products. However, with *anti*-alkylidene **16**, approach from the *β*-face is still a possibility. In this new metallacycle intermediate, similar steric interactions exist (*anti*-**A**), but now between the R group ($-CH_2CH_2Ph$) and trimethylsilane, providing a similar argument for the enhanced *E*-olefin selectivity.

Scheme 2. Silylated Alcohols as Non-Chelating Systems



Reaction Conditions: (a) Allyltrimethylsilane (4 equiv.), **2** (5 mol%), CH_2Cl_2 reflux, 24 hrs.

product. If they break down productively, then *anti*-**A** will provide the *Z*-olefin product and *anti*-**B** the *E*-olefin product.

In these intermediates as drawn, it becomes readily apparent that the allylic substituent can have an effect on their relative energies. The allylic methyl group in **16** can significantly hinder the approach of the allylsilane, favoring *anti*-**B**, where the silyl group rotates away from its cross-coupling partner, the homoallylic alcohol. It is clear that an unfavorable steric interaction exists between the bulky trimethylsilane and the allylic methyl group of the homoallylic alcohol in *anti*-**A** (Figure 2). This steric congestion can be relieved though as seen in *anti*-**B**. The added steric considerations in intermediate *anti*-**A** are significant enough for the favored reaction pathway to proceed through intermediate *anti*-**B**, ultimately leading to a higher preference for the *E*-olefin product ($k_{anti-\mathbf{B}} > k_{anti-\mathbf{A}}$). When the analogous metallacycle intermediates are drawn for the *syn*-"propionate" homoallylic alcohol **18**, we see that no added steric considerations exist in either *syn*-**A** or in *syn*-**B** ($k_{syn-\mathbf{B}} \approx k_{syn-\mathbf{A}}$). *Using a chelate model, it is the steric congestion caused by having the allylic substituent anti to the hydroxyl group in a homoallylic alcohol that enhances selectivity for the E-olefin favoring the reaction pathway with a less sterically crowded intermediate.*

Throughout this discussion, we have made the assumption that the propagating alkylidene species of the catalyst is the homoallylic alcohol alkylidene. It is important to remember, however, that regardless of the propagating alkylidene the same common metallacycle intermediates will be accessed. *Thus, the identity of the propagating alkylidene species is irrelevant and only the relative energies of the respective chelated intermediates (Figure 2) are important in rationalizing the observed olefin selectivities.*

Finally, we attempted to both verify and disrupt the chelated model proposed in Figure 1. We anticipated that silyl ethers would disfavor the chelated intermediates. Subjecting terminal alkenes **19** and **21** to the conditions provided their corresponding CM products albeit in low conversions[16] (Scheme 2). Silyl ether **19** provided allylsilane **20** (*E*:*Z* = 92:8), while silyl ether **21** yielded allylsilane **22** (*E*:*Z* = 89:11).[17] The presence of the silyl protecting group in both systems does appear to disrupt the proposed chelate, and the enhanced selectivity for the *anti* substrate is no longer observed.

In conclusion, allylic substituted homoallylic alcohols are excellent cross-metathesis partners with allyltrimethylsilane and result in enhanced *E*-olefin selectivities if the relative stereochemistry between the alcohol and the allylic substituent is *anti*. These enhancements are rationalized by the chelation of the ruthenium metal center in a five-membered ring to the free hydroxyl of the homoallylic alcohol in the metallacycle intermediate. The resulting ordered intermediates impose added steric considerations in the cross-metathesis reactions, ultimately leading to higher selectivities for the *E*-olefin cross-metathesis products via a kinetic process.

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Note Added in Proof: Concurrent to our most recent publication (ref 5), Cossy et al. (*J. Organomet. Chem.* **2001**, *624*, 327) reported the use of a variety of homoallylic alcohols as cross-metathesis partners with α,β-unsaturated aldehydes, esters, and allyltrimethylsilane. High *E*-selectivities were observed with α,β-unsaturated aldehydes and esters while the single example reported for allyltrimethylsilane provided a selectivity similar to the observations reported herein (**3** → **9**).

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(16) The low conversions of the silyl ethers to their corresponding CM products suggest a more sterically encumbered environment. This limitation can be overcome by recharging the reaction flask with more allyltrimethylsilane (4 equiv) and fresh catalyst **2** (5 mol %). Ultimately conversions of >80% for the CM product **22** were achievable. The *E*:*Z* ratios were independent of the percent conversion to the CM product.

(17) The *E*:*Z* ratios were based on reactions of low conversion and determined using ^{1}H NMR. The higher *E*:*Z* ratios observed for **20** and **22** indicate the additional steric bulk incorporated into the molecules by the large TMS protecting group.