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# Silicon Tethered Ring-Closing Metathesis Reactions for Self- and Cross-Coupling of Alkenols

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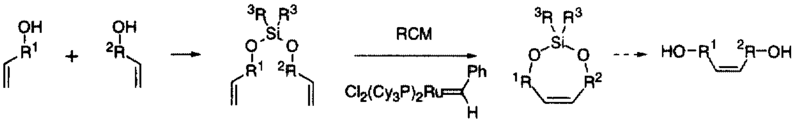
**Abstract:** *The title process can be used to couple allylic, homoallylic, and bishomoallylic alkenols. Cyclic silaketals with ring sizes from 7-11 members can all be formed. This constitutes a general and versatile strategy for approximately doubling the molecular complexity of readily available alkenol precursors.*

Selective cross-coupling reactions of two reactants are valuable transformations. They are accompanied by a rapid increase in molecular complexity and enable highly convergent synthesis strategies. Some important examples include the Julia, Wittig, and palladium(0)-catalyzed classes of coupling reactions. The value of any cross-coupling method is related to the ease of incorporation of activating functionality required for the coupling event. Likewise, the generality of a method derives from its compatibility with potentially reactive functionality elsewhere in the reactants. Olefin-metathesis[1] has tremendous potential in both of the above regards, as evidenced by recent efforts to develop various metathetic cross-coupling strategies.[2] An efficient and practical method using temporary silicon-tethering[3] to achieve homo-coupling of secondary, chiral allylic alcohols to produce $C_2$-symmetric 1,4-diol derivatives was recently reported by Evans and Murthy.[4] Reported here are some of our related studies in which we demonstrate that various 1,m-alkenols (m = 2-4; i.e., allylic, homoallylic, and bishomoallylic) can be either self- or cross-coupled via ring-closing-metathesis (RCM) of the silaketals **1** to generate 1,n-diol (n = 2m = 4-8) derivatives **3** (Scheme 1).[5]

**Scheme 1**



*1* *2* *3*

We initially studied the symmetrical silaketals shown in Table 1.[6] These incorporate a diphenylsilyl linker, which decreases volatility and acid lability[7] and which we anticipated would later permit selective sequential loading of two different alkenols.[8] The ring closing metathesis reactions were performed in methylene chloride using 10 mol% of Grubbs' initiator **2**.[9] A solution of **2** was slowly added to a solution of each of the silaketals **4a-g** (0.005 M in $CH_2Cl_2$) to provide the cyclic silaketals **5a-f**. Substrates **a-c** (derived from propen-1-ol, 3-buten-1-ol, and 4-penten-1-ol, respectively) were examined in order to determine if various ring sizes could be accommodated by these RCM reaction conditions.

Although the bis-allyloxy ketal **4a** cyclized more rapidly than ketals **4b** and **4c**, the latter pair could be completely converted if the initiator **2** was added over 10 h to constantly provide a supply of active carbene.[10] Rapid addition of **2** often resulted in incomplete reactions due to inactivation of the ruthenium species. Not surprisingly, the more hindered bis-1,2-disubstituted alkene substrate **4d** cyclized to **5a** more slowly than the

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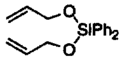
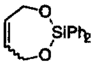
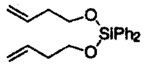
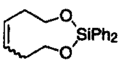
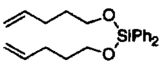
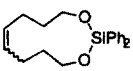
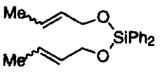
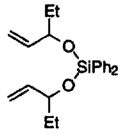
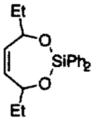
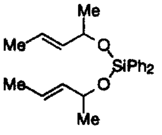
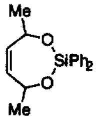
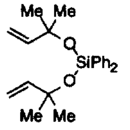
terminal diene **4a**. The symmetrical silaketal **4e** [derived from the secondary alcohol (±)-1-penten-3-ol] likewise underwent RCM at 55 °C to give an ~1:1 mixture of diastereomeric *meso* and *d,l*- cyclic silaketals **5e**. This diastereomeric ratio was uniform throughout the course of the reaction, implying little or no diastereoselectivity in the overall RCM event. The analogously branched, bis-1,2-disubstituted diene **4f** gave only 18% conversion to cyclized products even after 120 h at 55 °C. (Reaction at 80 °C in 1,2-dichloroethane for 24 h resulted in only 1% conversion.) Finally, the hindered ketal **4g**, containing doubly branched allylic carbons,[11] did not cyclize under these conditions.

An added virtue of the silicon tether is the influence it imparts over the olefin geometry in the cyclic products. The inability to control *E/Z*-selectivity in metathesis cross-coupling events is often a limitation. For the unsubstituted silacycles **5a-c**, the *Z*-olefin predominated,[12] although 3-8% of a second isomer (gc-ms ratios), assigned as the *E*-alkene,[13] was always observed. For the branched allylic systems, which led to the 4,7-dialkyl substituted silaketals **5e** and **5f**, only a single alkene isomer was observed, consistent with the results of Evans and Murthy.[4]

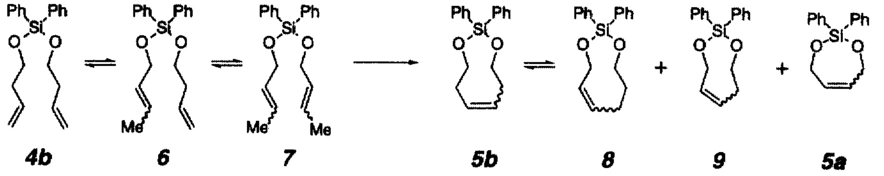
**Table 1.** RCM cyclizations of symmetrical silaketals **4** to give 7-, 9-, and 11-membered cyclic alkenes **5**.[a]

| | substrate | rxn temp (°C) | addition time for **2** (h) | rxn time (h) | yield (%) | | product | *Z* : *E* |
|---|---|---|---|---|---|---|---|---|
| **4a** |  | 25 | 1 | 1 | 84 | **5a** |  | 97:3 |
| **4b** |  | 25 | 10 | 24 | 85 | **5b** |  | 95:5 |
| **4c** |  | 25 | 10 | 10 | 78 | **5c** |  | 92:8 |
| **4d** |  | 45 | 1 | 12 | 61 | **5a** | | 96:4 |
| **4e** |  | 55 | 1 | 24 | 91 | **5e** |  | >99:1[b,c] |
| **4f** |  | 55 | 1 | 120 | 18 | **5f** |  | >99:1[b,c,d] |
| **4g** |  | 80 | 1 | 17 | n.r. | | | |

[a] All reactions were performed in dry $CH_2Cl_2$ at a substrate concentration of 5 mM under an Ar atmosphere using 10 mol% of **2**, which was added by syringe pump as a $CH_2Cl_2$ solution. [b] Growth of an ~1:1 mixture of *meso:d,l* products was observed throughout the course of the reaction. [c] A second alkene isomer could not be detected by gc-ms analysis. [d] Not isolated; % of cyclized products (~1:1, *meso:d,l*) vs. starting material by integration of gc/ms.

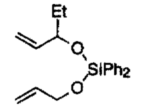
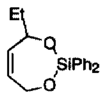
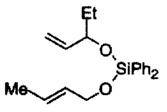
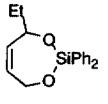
Ring closing metatheses of the bis-3-butenyloxy (**4b**) and bis-4-pentenyloxy substrates (**4c**) were also examined at higher concentrations (0.1 and 0.45 M) but with the same initiator loading (10 mol%). The product mixtures, now more complex, were analyzed using gc-ms. Aliquots taken at ~50% conversion gave evidence for isomerized starting material as well as a variety of different cyclization products.[14] For example, in the case of **4b** (Scheme 2) we observed mass spectral evidence for isomers **6** (both *E* and *Z*) and **7** of the starting silaketal. In addition to the expected cyclized products **5b**, the regioisomer **8** was observed along with the one- and two-methylene-deletion products **9** and **5a**. These were identified by correlation of their retention times and mass spectral fragmentation patterns with those of authentic samples. Apparently, at the higher *initiator* concentrations used in these experiments (final [**2**] = 10 and 45 mM compared with 0.5 mM for the reactions reported in Table 1) a greater extent of bimolecular catalyst decomposition was occurring, which, in turn, promoted the olefin isomerization (**4b** to **6** to **7** and **5b** to **8**), perhaps via ruthenium hydride species from background decomposition events. Subsequent RCM cyclization of **6** and **7** would then lead to **9** and **5a**, respectively. Gc-ms evidence for an analogous yet more complex manifold of isomerization/RCM cyclization events was observed for the bis-4-pentenyloxy substrates **5c** at the higher substrate/initiator concentrations.

**Scheme 2**



Mixed silaketals **10a** and **10b** cyclized to the seven membered silaketal **11** in good yields (Table 2). The mixed ketal **10a** underwent cyclization at room temperature, in contrast to the related substrates **10b**, **4d** or **4e**, all of which were slow to cyclize unless heated to 45-55 °C. The ruthenium carbene presumably reacts first at the less hindered allyl moiety in **10a** and then rapidly cyclizes. Since **10a** reacts with a rate comparable to **4a** and faster than **10b** and **4e**, we can conclude that bimolecular reaction between the substrate diene and carrier carbene $Cl_2(Cy_3P)_2Ru{=}CH_2$ is the likely rate limiting step under these dilute reaction conditions.

**Table 2.** RCM cyclizations of unsymmetrical silaketals **10**[a] to give **11**.[b]

| | substrate | rxn temp (°C) | addition time for **2** (h) | rxn time (h) | yield (%) | | product | Z : E |
|---|---|---|---|---|---|---|---|---|
| **10a** |  | 25 | 1 | 1 | 62 | **11** |  | >99:1 |
| **10b** |  | 50 | 1 | 24 | 57 | **11** |  | >99:1 |

[a] Formed by sequential reaction of equimolar amounts of $Ph_2SiCl_2$, pyridine, and pent-1-en-3-ol in toluene followed by one equiv of allyl or crotyl alcohol. After chromatography **10** was isolated in 60% yield and contained ~5% of each of the two possible symmetrical silaketals. [b] All reactions were performed in dry $CH_2Cl_2$ at a *substrate* concentration of 5 mM under an Ar atmosphere using 10 mol% of **2**, which was added by syringe pump as a $CH_2Cl_2$ solution.

In summary, we have demonstrated a convenient method for both self- and cross coupling of alkenols on a silaketal template via ring closing metathesis. Various ring sizes are accommodated, which means alkenols with a variety of spacings between the carbinol and alkene centers can be accommodated. Slow, constant addition of Grubbs' initiator **2** is advantageous. We speculate that maintaining a lower concentration of **2** reduces bimolecular decomposition that might lead to species responsible for undesirable, competitive events. For example, the formation of isomeric dienes arising from alkene isomerization in the starting material can be minimized using slow addition of **2**. Since subsequent RCM leads to cyclic products having fewer carbon atoms in the skeleton, it is obviously desirable to suppress such events. Studies to further define optimal conditions for these and related RCM reactions continue.

**Acknowledgments** This research was supported by Research Project Grant #DHP-140 from the American Cancer Society and by the National Institutes of Health (CA-76497).

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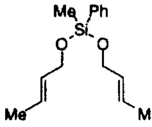
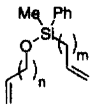
4. Evans, P. A.; Murthy, V. S. *J. Org. Chem.* **1998**, *63*, 6768-6769.
5. Other examples of tethered RCM reactions using substrates **i-iv** have been described.



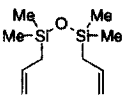
***i***

ref 5a



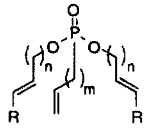
***ii***

ref 5b-d



***iii***

ref 5e



***iv***

ref 5f

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6. Preparation of the symmetrical silaketals **4a-f** was easily accomplished by adding two equivalents of the precursor alkenol to $Ph_2SiCl_2$ either in the presence of $Et_3N$ in $CH_2Cl_2$ or pyridine in toluene (DMAP was used to catalyze the formation of the hindered ketal **4g**) The yields of silaketal formation were: **4a** (84%), **4b** (82%), **4c** (60%), **4d** (55%), **4e** (73%), **4f** (60%), **4g** (75%), **10a** (60%), and **10b** (60%).
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8. a) Chu, H. K.; Johnson, M. D.; Frye, C. L. *J. Organomet. Chem.* **1984**, *271*, 327-336. b) Chan, T. H.; Peng, Q.-J.; Wang, D.; Guo, J. A. *J. Chem. Soc., Chem. Commun.* **1987**, 325-326.
9. Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100-110.
10. We have observed other instances in which slow addition of initiator carbene was advantageous and will report on these observations elsewhere.
11. *t*-Butylethylene also shows a negligible rate of reaction with **2**: Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484-2489.
12. An authentic sample of each Z-cyclic ketal was made from the corresponding Z-alkene-1,ω-diol and $Ph_2SiCl_2$.
13. $^1H$ NMR resonances for the minor isomer in each case indicated that it was a symmetrical structure, thereby ruling out the possibility of regioisomeric alkenes.
14. a) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 123-126. b) Joe, D.; Overman, L. E. *Tetrahedron Lett.* **1997**, *38*, 8635-8638. These previous examples of formation of cyclic alkenes having one fewer carbon than expected were proposed to have been preceded by alkene isomerization. Our experimental evidence now directly supports that suggestion. Also, the earlier examples were obtained using a Schrock molybdenum carbene; the observations described here are to our knowledge the first example where a ruthenium carbene has induced this event.