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Ruthenium-Catalyzed Silyl Ether Formation and Enyne Metathesis Sequence: Synthesis of Siloxacycles from Terminal Alkenyl Alcohols and Alkynylsilanes

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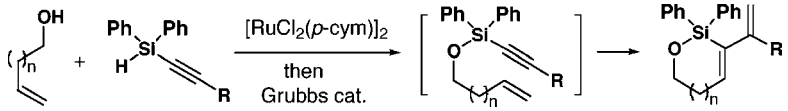
ABSTRACT



Two consecutive ruthenium-catalyzed reactions have been achieved for the synthesis of siloxacycles from terminal alkenyl carbenols and alkynylsilanes. The metal-catalyzed dehydrogenative condensation between alcohols and silanes, generating molecular hydrogen as the only byproduct, allows for the subsequent enyne metathesis without isolating the intermediate silyl ethers. This system provides a streamlined synthesis of synthetically useful building blocks.

Enyne metathesis is a powerful carbon−carbon bond-forming process.[1] Unlike diene[2] and diyne[3] metathesis, which only regenerate functionality of their own kind, enyne metathesis generates a conjugated 1,3-diene from an alkene and an alkyne. Despite this significant advantage, enyne metathesis has been underdeveloped and far less used in natural product synthesis.[4] Efforts to expand the scope of this useful synthetic method have successfully embraced various heteroatom (B, N, O, P)-substituted alkynes[5] to generate those functionalized 1,3-dienes (eq 1) yet, to the best of our knowledge, the corresponding Si-substituted alkynes have not been engaged previously (eq 2), despite the versatility of the resultant

(1) For recent reviews of enyne metathesis, see: (a) Mori, M. *Top. Organomet. Chem.* **1998**, *1*, 133. (b) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1. (c) Mori, M. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 2, pp 176−204. (d) Giessert, A. J.; Diver, S. T. *Chem. Rev.* **2004**, *104*, 1317.

(2) (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013. (d) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. (e) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592.

(3) (a) Katz, T. J.; McGinnis, J. *J. Am. Chem. Soc.* **1975**, *97*, 1592. (b) Wengrovius, J. H.; Sancho, J. *J. Am. Chem. Soc.* **1981**, *103*, 3932. (c) Schrock, R. R.; Clark, D. N.; Sancho, J.; Wengrovius, J. H.; Rocklage, S. M.; Pedersen, S. F. *Organometallics* **1982**, *1*, 1645. (d) Fürstner, A.; Seidel, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 1734. (e) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108.

(4) Examples of completed total synthesis of natural products with enyne metathesis as a key step, see: (a) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356. (b) Hoye, T. R.; Donaldson, S. M.; Vos, T. J. *Org. Lett.* **1999**, *1*, 277. (c) Mori, M.; Tonogaki, K.; Nishiguchi, N. *J. Org. Chem.* **2002**, *67*, 224. (d) Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773. (e) Fukumoto, H.; Esumi, T.; Ishihara, J.; Hatakeyama, S. *Tetrahedron Lett.* **2003**, *44*, 8047. (f) Brennema, J. B.; Martin, S. F. *Org. Lett.* **2004**, *6*, 1329. (g) Aggarwal, V. K.; Astle, C. J.; Rogers-Evans, M. *Org. Lett.* **2004**, *6*, 1469. (h) Mori, M.; Tomita, T.; Kita, Y.; Kitamura, T. *Tetrahedron Lett.* **2004**, *45*, 4397.

(5) Other heteroatom-containing enyne RCM, see the following. With boron: (a) Micalizio, G.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 3272. (b) Renaud, J.; Graf, C.-D.; Oberer, L. *Angew. Chem., Int. Ed.* **2000**, *39*, 3101. With nitrogen: (c) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417. (d) Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803. With oxygen: (e) Clark, J. S.; Trevitt, G. P.; Boyall, D.; Stammen, B. *Chem. Commun.* **1998**, 2629. (f) Clark, J. S.; Elustondo, F.; Trevitt, G. P.; Boyall, D.; Robertson, J.; Blake, A. J.; Wilson, C.; Stammen, B. *Tetrahedron* **2002**, *58*, 1973. (g) Schramm, M. P.; Reddy, D. S.; Kozmin, S. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4274. (h) Reddy, D. S.; Kozmin, S. A. *J. Org. Chem.* published online June 12, http://dx.doi.org/10.1021/jo049431g. With phosphorous: Schramm, M. P.; Reddy, D. S.; Kozmin, S. *Angew. Chem., Int. Ed.* **2002**, *40*, 4274. With phosphorus: (i) Timmer, M. S. M.; Ovaa, H.; Filippov, D. V.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **2001**, *42*, 8231.

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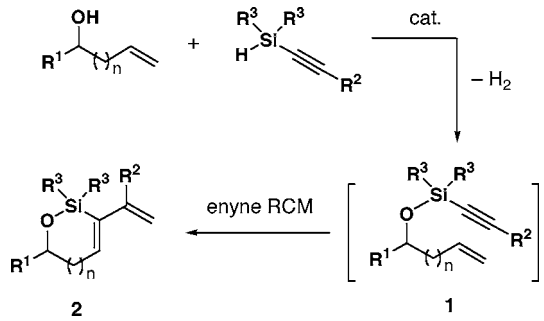
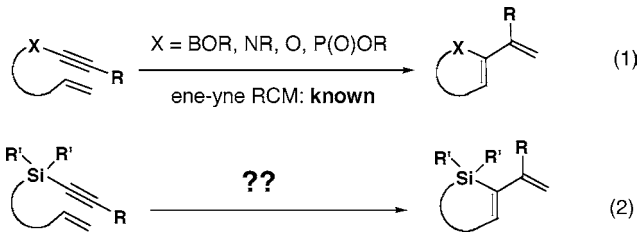
Scheme 1



vinylsilane in organic synthesis. This disparity could be due to the observed detrimental effect of the bulky silyl group, lowering the reactivity of the silyl-substituted alkyne toward enyne metathesis.[5e,f,6]



In our continuing efforts to develop efficient enyne RCM substrate platforms,[7] as well as to broaden the scope of the enyne metathesis reaction, we became interested in the RCM reaction of alkynyl silyloxy-tethered enyne **1** (Scheme 1).[8,9] We envisioned that the temporary connection of alkenyl alcohols and alkynylsilanes followed by metathesis would allow for prompt access to a variety of stereochemically defined 1,3-dienylvinylsilanes **2**, which can be further manipulated, for example, via a silicon-based cross-coupling reaction extensively studied by Denmark and co-workers.[10] As such, the enyne metathesis converting **1** to **2** constitutes a powerful synthetic method,[11,12] whereby a less regio- and stereoselective cross-metathesis between alkenes and alkynes can be performed in a more selective intramolecular fashion.[13] Herein we report our development of an efficient procedure for the consecutive ruthenium-catalyzed synthesis of alkynylsilyl ethers (**1**) and their enyne RCM reactions to generate siloxacycles (**2**).[14]

In the initial attempt for the preparation of alkynylsilyl ether **1**, we recognized its instability toward workup and isolation. To improve the overall synthetic efficiency by eliminating the problematic isolation step, we decided to sequentially carry out silyl ether formation and the RCM reaction without isolation of the silyl ether. Toward this end, we were intrigued by the possibility of employing the transition metal-catalyzed dehydrogenative condensation reaction of alcohols with silanes to generate silyl ethers.[15] Because molecular hydrogen is the only byproduct in this reaction, the isolation of the unstable silyl ether **1** might not be necessary for the subsequent RCM reaction. However, hydrogenation and hydrosilylation of the unsaturated functionality was of concern for most of the known catalytic systems.

We examined various transition metal complexes to identify a catalyst that would effectively promote the dehydrogenative condensation but would not catalyze hydrogenation or hydrosilylation. Most of the metal complexes screened ($[Rh(COD)Cl]_2$, $RhCl(PPh_3)_3$, $Rh(acac)(CO)_2$, $RuCl_2(PPh)_3$, $[RuCl_2(p\text{-cymene})]_2$, $RuCl_2(binap)$, $Co_2(CO)_8$, $Pd(OCOCF_3)_2$, $PtCl_2$, $Cu(OTf)_2$, $Ag(OTf)$) were effective for silyl ether formation from alcohols and silanes (Me_2PhSiH, $MePh_2SiH$, Ph_2SiH_2, Ph_3SiH, $(PhCC)Me_2SiH$, Et_3SiH, and t-$BuMe_2SiH$), yet hydrogenation of alkenes and hydrosilylation of alkynes were also observed. Only the reactions performed with $[RuCl_2(p\text{-cymene})]_2$ left alkene and alkyne functionalities intact. On the basis of these observations, $[RuCl_2(p\text{-cymene})]_2$ was further examined for its generality in the reactions of various alcohols containing unsaturated functionalities and assorted silanes under solvent-free conditions (Table 1).[16] Alcohols with disubstituted (entries 1, 2, and 7), trisubstituted (entries 3 and 5), and terminal (entry 6) alkenes or alkynes (entries 4, 8, 9, and 10) were reacted

(6) Kim, S.-H.; Zeurcher, W. J.; Bowden, N.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073.

(7) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2003**, *125*, 9582.

(8) For an alternative method of making alkynylsilyl ethers see: Stork, G.; Keitz, P. F. *Tetrahedron Lett.* **1989**, *30*, 6981.

(9) For the use of alkynylsilyloxy-tethered ene−ynes in other reactions, see: (a) Petit, M.; Chouraqui, G.; Aubert, C.; Malacria, M. *Org. Lett.* **2003**, *5*, 2037. (b) Chouraqui, G.; Petit, M.; Aubert, C.; Malacria, M. *Org. Lett.* **2004**, 6, 1519.

(10) Reviews, see: (a) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835. (b) Denmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull.* **2002**, *50*, 1531. (c) Denmark, S. E.; Ober, M. H. *Aldrichim. Acta* **2003**, *36*, 75. For mechanistic studies, see: (d) Denmark, S. E.; Sweis, R. F.; Wehrli, D. *J. Am. Chem. Soc.* **2004**, *126*, 4865. (e) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2004**, *126*, 4876.

(11) Examples of silyloxy-tethered diene RCM reactions, see: (a) Chang, S.; Grubbs, R. H. *Tetrahedron Lett.* **1997**, *38*, 4757. (b) Evans, P. A.; Murthy, S. *J. Org. Chem.* **1998**, *63*, 6768. (c) Hoye, T. R.; Promo, M. A. *Tetrahedron Lett.* **1999**, *40*, 1429. (d) Shu, S. S.; Cefalo, D. R.; La, D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 8251. (e) Taylor, R. E.; Engelhardt, F. C.; Schmitt, M. J.; Yuan, H. *J. Am. Chem. Soc.* **2001**, *123*, 2964. (f) Kiely, A. F.; Jernelius, J. A.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 2868. (g) Van de Weghe, P.; Aoun, D.; Boiteau, J.-G.; Eustache, J. *Org. Lett.* **2002**, *4*, 4105. (h) Evans, P. A.; Cui, J.; Buffone, G. P. *Angew. Chem., Int. Ed.* **2003**, *42*, 1734. (i) Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H.-R. *J. Am. Chem. Soc.* **2003**, *125*, 14702.

(12) Examples of silyloxy-tethered enyne RCM, see: (a) Semeril, D.; Cleran, M.; Bruneau, C.; Dixneuf, P. H. *Adv. Synth. Catal.* **2001**, *343*, 184. (b) Yao, Q. *Org. Lett.* **2001**, *3*, 2069. (c) Semeril, D.; Cleran, M.; Perez, A. J.; Bruneau, C.; Dixneuf, P. H. *J. Mol. Catal. A.* **2002**, *190*, 9.

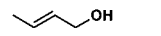
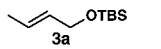
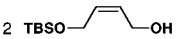
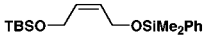
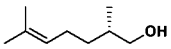
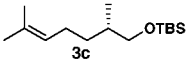
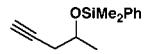
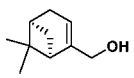
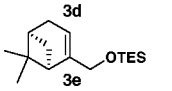
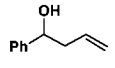
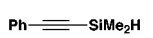
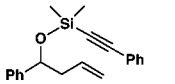
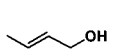
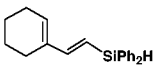
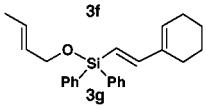
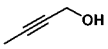
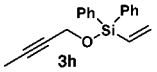
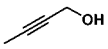
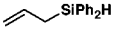
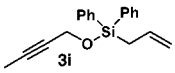
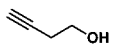
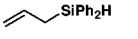
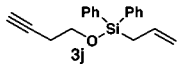
(13) For general reviews on silicon tether, see: (a) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253. (b) Fensterbank, L.; Malacria, M.; Sieburth, S. McN. *Synthesis* **1997**, 813. (c) Gauthier, D. R., Jr.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2290.

(14) Synthesis of related siloxacycles by ruthenium-catalyzed intramolecular hydrosilylation, see: Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2003**, *125*, 30.

(15) (a) Ojima, I.; Kogure, T.; Nihonyangi, M.; Kono, H.; Inaba, S. *Chem. Lett.* **1973**, 501. (b) Luo, X.-L.; Crabtree, R. H. *J. Am. Chem. Soc.* **1989**, *111*, 2527. (c) Yamamoto, K.; Takemae, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2111. (d) Doyle, M. P.; High, K. G.; Bagheri, V.; Pieters, R. J.; Lewis, P. J.; Pearson, M. M. *J. Org. Chem.* **1990**, *55*, 6082. (e) Maifeld, S. V.; Miller, R. L.; Lee, D. *Tetrahedron Lett.* **2002**, *43*, 6363.

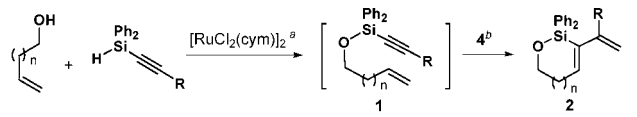
(16) The ratio of O- to C-silylation is highly dependent on solvents, see: (a) Zhang, C.; Laine, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 6979. (b) In CH_2Cl_2, 3-butyn-1-ol (entry 10 in Table 1) undergoes preferential C-silylation, see: Na, Y.; Chang, S. *Org. Lett.* **2000**, *2*, 1887. For a review of solvent free reactions, see: (c) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025.

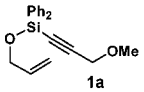
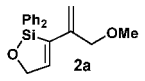
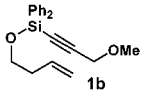
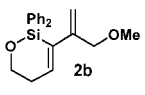
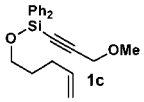
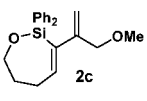
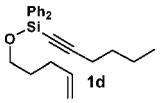
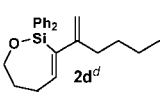
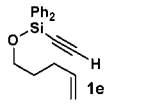
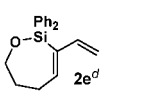
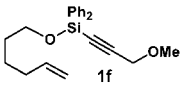
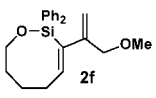
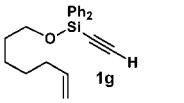
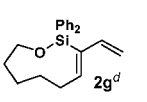
Table 1. Silyl Ether Synthesis under Optimized Conditions[a]

entry	alcohol	silane	temp (°C) / h	silyl ether	conversion (%)[b]
1		*t*-BuMe$_2$SiH	50 / 6	 **3a**	>95
2		Me$_2$PhSiH	25 / 6	 **3b**	>95
3		*t*-BuMe$_2$SiH	50 / 6	 **3c**	>95
4		Me$_2$PhSiH	0 / 6	 **3d**	88
5		Et$_3$SiH	50 / 6	 **3e**	>95
6			25 / 6	 **3f**	>95
7			25 / 6	 **3g**	72[c,d]
8			25 / 6	 **3h**	72[e,f,h]
9			0 / 10	 **3i**	84[e,g,h]
10			0 / 8	 **3j**	75[e,g,h]

[a] All reactions are carried out with 0.2−1.0 mmol of the alcohol, 1.0 equiv of silane and 0.1−0.5 mol % of catalyst. [b] Conversion of the starting alcohol and silane to silyl ether determined by ^{1}H NMR of the crude reaction mixture. [c] The silane was prepared from 1-ethynylcyclohexene and diphenylsilane with Rh(binap)Cl. [d] The relatively low yield is due to the instability of the silyl ether. [e] 0.5 mol % of catalyst employed. [f] 5% triple bond hydrosilylation. [g] 0.9 equiv of silane employed. [h] Isolated yields.

Table 2. Consecutive Ruthenium Catalysis for the Synthesis of Siloxacycle



entry	silyl ether	RCM-product	(δ)[c]	yield (%)[e,f]
1	 **1a**	 **2a**	7.09	52 (23)
2	 **1b**	 **2b**	7.06	85 (50)
3	 **1c**	 **2c**	6.89	67 (33)
4	 **1d**	 **2d**[d]	6.91	70 (50)
5	 **1e**	 **2e**[d]	6.75	81 (30)
6	 **1f**	 **2f**	6.68	50 (33)
7	 **1g**	 **2g**[d]	6.56	63 (27)
8	**1h**	**2h**	6.38	30

[a] 0.5 mol % of [RuCl$_2$(*p*-cym)]$_2$ was used to form the silyl ether. [b] All reactions are carried out in refluxing CH_2Cl_2, with substrate concentrations of 0.003 M and a catalyst loading of 7.5 mol %. [c] Chemical shift in ppm of the endocyclic vinyl signal, relative to the internal standard TMS. [d] 10−15% hydrogenation of the alkyne occurred during silyl ether formation. [e] Two-step combined isolated yields for the reactions having filtration after the first step. [f] The yields in parentheses are the two-step combined yield for the one-pot reaction.

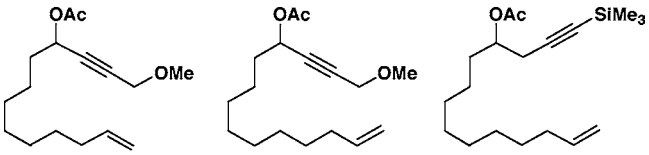
with alkyl, aryl, vinyl, and alkynylsilanes without loss of unsaturation. An alcohol having a cis double bond and existing silyl ether functionality cleanly yielded the expected bis-silyl ether (entry 2). Most trialkylsilanes required elevated temperature (ca. 50 °C) to generate the corresponding *tert*-butyldimethylsilyl or triethylsilyl ethers (entries 1, 3, and 5). The formation of silyl ethers with both terminal and internal alkynyl alcohols with vinyl or allyl silanes (entries 6−10) was also realized uneventfully. In general, most reactions are so efficient that ^{1}H NMR of the crude reaction mixtures showed no byproducts present; filtration through a silica plug to remove catalyst (if necessary) was the only refinement needed to give pure silyl ethers. Also, these reactions are readily scalable such that multigram quantities of silyl ethers could be prepared with comparable efficiency.[17]

Securing the highly efficient synthesis of a variety of structurally diverse silyl ethers using as low as 0.1 mol % of [RuCl$_2$(*p*-cymene)]$_2$ as the catalyst loading, we next prepared alkynylsilyl ethers **1a**−**h** from terminal alkenyl primary alcohols and alkynylsilanes. These silyl ethers were then either filtered on a pad of silica gel or directly subjected to enyne metathesis conditions with Grubbs' second generation catalyst (**4**, (H$_2$Imes)(PCy$_3$)(Cl)$_2$Ru=CHPh; 7.5 mol %, 0.003 M in CH_2Cl_2, reflux). Clean RCM products **2a**−**h** were isolated in moderate to good yields within short (60−90 min) reaction times (Table 2). For the one-pot silyl ether formation and enyne RCM reaction sequence, after the complete consumption of the starting alcohols and alkynylsilyl ethers, the reaction mixture was diluted with CH_2Cl_2 to an appropriate concentration and treated with **4** under reflux. The efficiency of the RCM reaction is generally higher if the catalyst in the first step is removed by filtration through a silica plug. Both the terminal (**1e** and **1g**) and internal alkynes are appropriate yne counterparts for this RCM reaction. The oxygen substituent at the propargylic carbon had a beneficial effect, slowing down the hydrogenation of the triple bond, but did not affect the efficiency of the RCM reaction (e.g.,

(17) When entry 5 in Table 1 was repeated with 5.0 g (32.8 mmol) of myrtenol, 8.16 g (93% yield) of the corresponding silyl ether was obtained.

1c vs **1d**). The ring size-dependent characteristic chemical shifts of the vinyl protons (β to the silicon atom) of the cyclization products are noteworthy and facilitate the unambiguous assignment of the ring size of each siloxacycle.

The facile enyne RCM reactions to form not only small- to medium-sized siloxacycles ranging from 5 to 9 (entries 1−7) but also the 13-membered macrocycle **2h** (entry 8) underscore the highly activating nature of the alkynylsilyloxy tether for the enyne RCM reaction. Contrary to the facile RCM reaction of enynes **1a**−**h**, the corresponding all carbon-tethered enyne substrates **5**−**7** did not undergo ring closure under the same reaction conditions. This difference may be the consequence of the two additional aryl substituents on the silicon tether, thereby manifesting the well-known Thorpe−Ingold effect.[18]



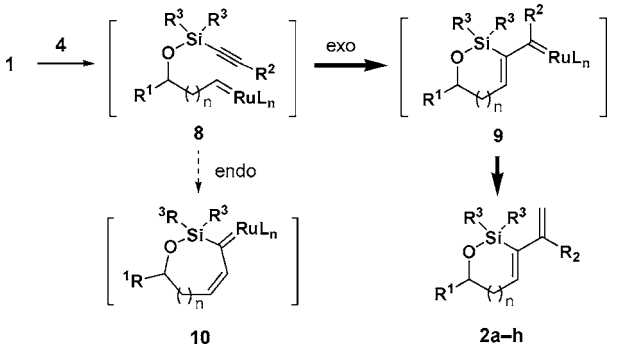
5 **6** **7**

Furthermore, silyl ethers **1a**−**h** underwent enyne RCM to provide only exo products, showing no transition from the exo to endo mode of ring closure,[7] even with a ring size favoring the endo mode ring closure (entry 8 in Table 2).

We believe that the metathesis process starts from the terminal alkene moiety, thereby generating **8** as an initial intermediate (Scheme 2). The endo mode RCM of this alkylidene **8** would be disfavored due to the formation of the sterically hindered silicon-substituted alkylidene **10** possessing the bulky ruthenium complex at the same carbon bearing the silicon atom. Favorable formation of the other intermediate alkylidene **9** would relieve steric congestion around the metal center and would deliver the observed product **2a**−**h**.

(18) (a) Beesely, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080. (b) Lightstone, F. C.; Bruice, T. C. *J. Am. Chem. Soc.* **1994**, *116*, 10789 and references therein.

Scheme 2. Rationale for the Formation of *exo*-Product **2**



In summary, we have developed an efficient ruthenium-catalyzed silyl ether formation and subsequent ring closing enyne metathesis to form siloxacycles from terminal alkenyl alcohols and alkynylsilanes. The excellent reactivity profile of alkynylsilyloxy-tethered enynes toward the RCM reaction allows for the formation of a variety of ring structures having synthetically useful 1,3-dienyl-vinylsilanes ranging from small-membered rings to macrocycles. Further study to broaden the scope of alkynylsilyloxy-tethered enyne metathesis with chiral secondary alcohols and silaketals is in progress.

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Supporting Information Available: General procedures for the synthesis of silanes, silyl ethers, and siloxacycles, as well as characterization of represented compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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