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Control of Olefin Geometry in Macrocyclic Ring-Closing Metathesis Using a Removable Silyl Group

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Supporting Information

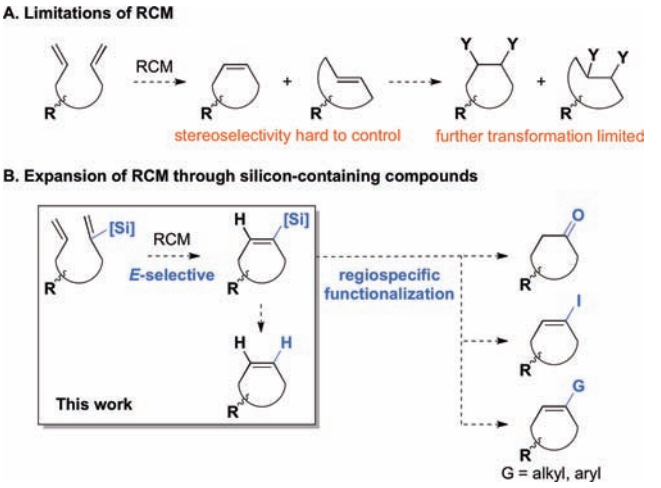
ABSTRACT: Introducing a silyl group at one of the internal olefin positions in diolefinic substrates results in *E*-selective olefin formation in macrocyclic ring-forming metathesis. The application of this method to a range of macrocyclic (*E*)-alkenylsiloxanes is described. Protodesilylation of alkenylsiloxane products yields novel *Z*-configured macrocycles.

Ring-closing metathesis (RCM) reactions[1] have enabled advances in materials science,[2] chemical biology,[3] and natural product,[4] medicinal,[5] and diversity-oriented synthetic chemistry.[6] However, in efforts to synthesize macrocyclic compounds via RCM reactions, control of the stereochemistry of the resulting olefin is often problematic (Scheme 1A). Since a variety of factors can determine the stereochemical outcome,[1d,7] general strategies that give rise to either *Z*- or *E*-configured products remain a significant challenge. Additionally, in the absence of a strong steric or electronic bias, the 1,2-disubstituted olefin in RCM products is difficult to modify regiospecifically, limiting the potential of further functionalization and diversification (Scheme 1A). Postmetathesis functionalization has in general been limited to "symmetrical" transformations such as hydrogenation, dihydroxylation,[6d,8] epoxidation,[8b,9] and aziridination.[10]

Two major advances that address the stereoselectivity of RCM reactions have been achieved. One approach involves ring-closing alkyne metathesis and selective reduction of the alkyne intermediate to yield *Z* or *E* olefins,[11] but it has been applied only to ring sizes of 12 and larger.[12] The other approach, which is based on the development of *Z*-selective catalysts,[13] has not yet been reported for macrocyclic RCM reactions. Both strategies generate 1,2-disubstituted olefins, which are primarily limited to symmetrical postmetathesis transformations. To address these limitations, we investigated the use of vinylsiloxanes as substrates to access trisubstituted macrocyclic silylalkenes.

We imagined that a silyl group at an internal position of one of the olefins could serve two purposes (Scheme 1B). First, the sterics of the silyl group would be expected to favor formation of the (*E*)-silylalkene product. The *Z*-disubstituted olefin would then be obtained following protodesilylation. Second, the exocyclic silyl substituent would be expected to enable functionalization of the RCM product, thus yielding specific trisubstituted olefins.[14] In this report, we explore the ability of vinylsiloxanes to undergo productive RCM reactions, their influence on the stereochemistry of the resulting products, and their protodesilylation following ring closure.

Scheme 1. RCM with Silyl Group Incorporation



Although the influence of various silyl groups on RCMs has not been studied extensively, there are many examples of their use in cross-metathesis (CM) reactions. Pietraszuk et al.[15] demonstrated that the influence of the silyl groups on the yield of CM reactions is associated with electronic effects of the substituents on silicon. Silyl groups with electron-withdrawing substituents such as EtO, AcO, and Cl gave better yields than those with Me and/or Ph groups. Accordingly, although vinyltrialkylsilanes yielded a variety of five- and six-membered rings, they failed to produce medium- and large-sized rings.[16] These observations are consistent with the few examples of RCM reactions leading to exocyclic vinylsilanes and vinylsiloxanes that have been reported in the literature.[17] With this knowledge, we next focused on vinylsiloxanes. We prepared several salicylate-derived substrates with one of the olefins bearing a triethoxysilyl group at the internal position. The vinylsiloxane substrates were obtained in excellent yields from the corresponding alkyne precursors through hydrosilylation.[17a,c] Using the second-generation Grubbs catalyst afforded a 14-membered salicylate macrocycle (**2a**), albeit in low yield (Scheme 2). When the same conditions were applied to substrate **3a**, the yield of the 15-membered ring **4a** dropped to 3% (Scheme 2). We used this demanding substrate to optimize the reaction conditions.

Received: March 14, 2011
Published: May 11, 2011

dx.doi.org/10.1021/ja202012s | *J. Am. Chem. Soc.* 2011, 133, 9196–9199

Scheme 2. Initial Successful Vinylsiloxane RCM and the Model Substrate Used for Reaction Optimization

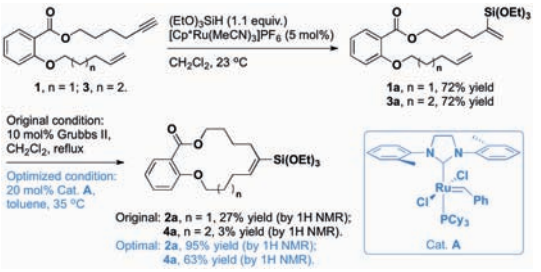
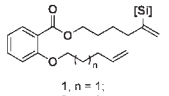


Table 1. Influence of the Silyl Group on the RCM Yield

Substrate	Entry	Silyl group	1[a]	3[a]
	a	$Si(OEt)_3$	92	60
	b	$Si(OEt)_2Me$	95	76
	c	$Si(OEt)Me_2$	81	62[b]
	d	$Si(OEt)_2Ph$	69[b]	35[b]
	e	$SiMe_2Ph$	54 (71[b])	32
	f	$SiEt_3$	10[b]	< 2

1, n = 1;
3, n = 2.

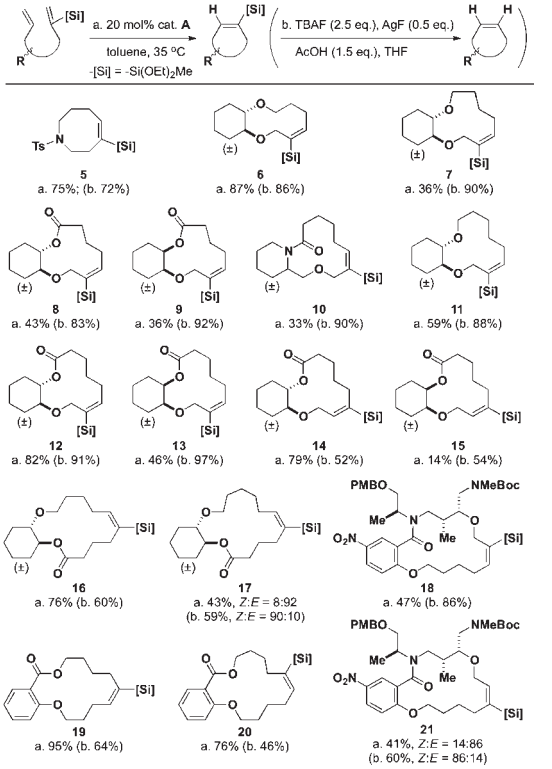
[a] Isolated % yield, unless otherwise indicated. [b] Yield determined by ^1H NMR analysis of the reaction mixture.

Among commercially available Ru-based metathesis catalysts, catalyst **A** was best able to increase the yield under the original reaction conditions [see the Supporting Information (SI) for details]. In contrast to the second-generation Grubbs catalyst, **A** bears one methyl group at the ortho position of each phenyl ring, making it less sterically hindered and more reactive.[18] After varying the solvent, temperature, and concentration, we found that optimal results (**4a**, 63%) were obtained using benzene or toluene as the solvent, a temperature of 35 °C, and a catalyst loading of 20 mol % (Scheme 2).

Under the optimal reaction conditions, unreacted starting material was still observed, indicating that the catalyst was deactivated before the reaction reached completion. To explore this observation further, catalyst stability studies were performed. It was determined that catalyst **A** decomposed at a similar rate upon treatment of any olefin substrate, with or without the silyl group (see the SI for details). In addition to the commonly observed decomposition pathways,[19] $C(sp^2)-H$ bond insertion in the *N*-aryl ring of the NHC ligand can also lead to fast deactivation of catalyst **A**.[20] Our results suggest that vinylsiloxane substrates do not intrinsically cause catalyst deterioration.

We next examined the influence of different silyl groups on the yield of the RCM reaction (Table 1). The results are in alignment with those for CM reactions. Generally, ethoxy substituents promote the formation of product and lead to higher yields in comparison with alkyl and/or aryl substituents (compare **a**–**d** with **e** and **f**). More ethoxy substituents are preferred over fewer (compare **b** with **c**). Pietraszuk and Fischer[21] noted that electron-withdrawing substituents shut down an undesired pathway that leads to catalyst deactivation. We suggest that these unproductive processes are operative in macrocyclization reactions as well and require the appropriate siloxane group to suppress them. In contrast to the CM precedents, the sterics of the silyl group also influenced the reaction yield. This effect was seen with the more demanding substrates **3a**–**f**, while substrates **1a**–**f** showed the same trend but to a lesser degree. Changing one of the ethoxy substituents to a methyl group (**3a** vs **3b**) improved the yield, while the change to a phenyl group (**3b** vs **3d**) halved the yield. Our results indicate that the diethoxymethylsilyl group delivers the best reaction outcomes by maintaining a balance between the steric and electronic effects.

Scheme 3. Yields for (a) RCMs and (b) Protodesilylation of Alkenylsiloxanes



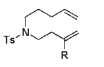
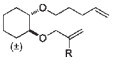
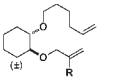
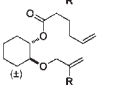
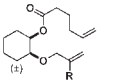
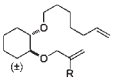
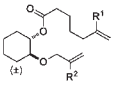
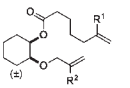
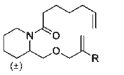
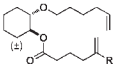
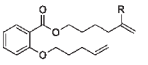
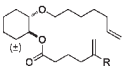
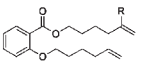
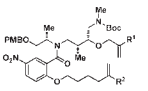
Using the diethoxymethylsilyl group, we synthesized macrocyclic alkenylsiloxane compounds with a range of ring sizes in moderate to excellent yields (Scheme 3). Diastereomers gave differing yields of purified products. For some substrates, a silyl group was incorporated at one or the other alkene terminus of the diene. The *trans*-cyclohexanediols with silyl groups at different termini behaved similarly (**12** and **14**), while the silyl regioisomers of *cis*-cyclohexanediols behaved differently (**13** and **15**). To test the generality of this method, two more complex substrates inspired by previous work[22] were prepared with vinylsiloxanes on different alkene termini. The 16-membered rings were both formed in moderate yields (**18** and **21**).

As envisaged, the trisubstituted olefins in the macrocyclic products had the *E* configuration (except for **17** and **21**, which were mixtures of both stereoisomers with high *E* selectivity). This suggests that one of the two productive metallocyclobutane intermediates is preferably formed, leading to the (*E*)-silylalkene; however, further mechanistic studies are required. All of the corresponding *Z*-disubstituted olefins were obtained by protodesilylation in good to excellent yields while maintaining the geometry of the olefins.

We next sought to understand the role of the silyl group in controlling the stereochemical outcome of the reaction. For comparison, all of the corresponding simple (non-silyl-containing) RCM precursors were synthesized in order to determine the intrinsic stereoselectivities of the substrates (Table 2). Upon treatment with the optimized reaction conditions as well as

dx.doi.org/10.1021/ja202012s | J. Am. Chem. Soc. 2011, 133, 9196–9199

Table 2. Influence of a Silyl Group on the Stereoselectivity of RCMs

	Substrate	R	Cond. I	Cond. II
1		[Si][a] H	Z[b] Z	- Z
2		[Si] H	Z c. mix.[c] (Z)[d]	- c. mix. (Z)
3		[Si] H	Z c. mix.	- c. mix.
4		[Si] H	Z c. mix. (24:76)	- c. mix. (24:76)
5		[Si] H	Z E	- E
6		[Si] H	Z c. mix. (Z)	- c. mix. (Z)
7		R1 / R2 [Si] / H H / [Si]	Z Z c. mix. (Z)	- - c. mix. (Z)
8		R1 / R2 [Si] / H H / [Si]	Z Z c. mix. (19:81)	- - c. mix. (19:81)
9		[Si] H	Z c. mix. (Z)	- c. mix. (Z)
10		[Si] H	Z c. mix. (76:24)	- c. mix. (76:24)
11		[Si] H	Z 81:19[e]	- 80:20[f]
12		[Si] H	90:10 28:72	- 24:76
13		[Si] H	Z 57:43[e]	- 54:46[f]
14		R1 / R2 [Si] / H H / [Si]	Z 86:14 36:64	- - -

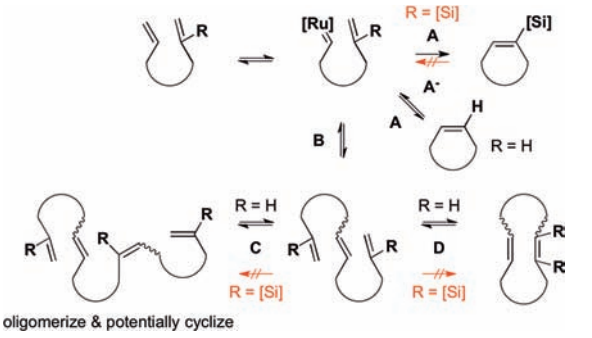
Conditions **I**: cat. **A** (20 mol %), toluene, 35 °C. Conditions **II**: Grubbs II (10 mol %), 1,4-benzoquinone (20 mol %), toluene, 35 °C. [a] For silylated substrates, the *Z*:*E* assignment is based on the protodesilylated products. [b] A single stereoisomer is reported for *Z*:*E* ratios >98:2. Otherwise the *Z*:*E* ratio determined by ^{1}H NMR analysis of the crude reaction mixture is given. [c] c. mix. = complex mixture of products (cyclized and uncyclized oligomers). [d] The stereochemistry of the cyclized monomer is reported in parentheses for all cases in which the proportion of that monomer within the complex mixture was sufficient for determination. [e] Reaction was performed at room temperature. [f] Reaction was performed in refluxing DCM.

typical RCM conditions using the second-generation Grubbs catalyst, *Z*-selective (entries **1**, **2**, **6**, **7**, **9**, **10**, and **11**), *E*-selective (entries **4**, **5**, **8**, **12**, and **14**), and nonselective (entry **13**) outcomes were observed. The introduction of the silyl group was found to reinforce the intrinsic stereoselectivity and, more dramatically, to override it completely for some substrates. This confirmed our initial hypothesis that a silyl group serves as an effective controlling group in macrocyclic RCM reactions.

It is also noteworthy that several of the simple substrates gave rise to complex mixtures of products (Table 2, entries **2**, **4**, and **6**−**10**), sometimes without detectable levels of cyclized monomer (entry **3**). LC−MS analysis of the crude reaction mixture indicated the formation of cyclized dimers and other polymeric byproducts. This is a general problem for macrocyclic RCM reactions of simple olefins.[23] While the reaction conditions for the simple substrates were not optimized, these results point to the ability of the silyl group to suppress the formation of undesired products.

On the basis of our data, we propose the model for the reaction pathways depicted in Scheme 4. Several unproductive pathways are involved in RCM reactions of simple olefins, including reopening of the monocyclized product ($\mathbf{A}^-$), CM to generate an acyclic dimer or oligomer (**B** or **C**), and possible cyclization at either of these stages (**C** or **D**). In contrast, when the silyl group is incorporated into one of the olefins, pathway **A** leading to the desired product is no longer reversible. When we resubjected the purified trisubstituted silylalkene product to the reaction conditions, no reactivity was observed. Pathway **B** to generate the acyclic dimers exists, but only through CM between the simple olefins—the 2-silylalkene remains a spectator to CM under our reaction conditions.[24] However, when resubjected to the reaction conditions, the purified acyclic cross-dimers of

Scheme 4. Reaction Pathways for Macrocyclic RCMs with and without a 2-Silyl Group



the silylated substrates yielded macrocyclic products with conversion comparable to that starting from monomer.[25] Additionally, since the 2-silylalkene remains a spectator to CM, pathway **C** is shut down. Pathway **D** is also blocked because the formation of a tetrasubstituted alkene with two silyl groups is highly disfavored.

Overall, the silyl group is able to lower the reactivity of the attached olefin, thereby suppressing nonproductive pathways while yielding the desired product. In accord with this analysis, for the substrates that gave low yields, only unreacted starting material, the acyclic cross-dimers, and a styrene derivative were observed along with the product. To explore the "trapping" role of the silyl group, the monocyclized (*Z*)-alkene compound **7b** (not observed in the RCM of the simple diene; Table 2, entry 3) obtained from protodesilylation of compound **7** was subjected to

dx.doi.org/10.1021/ja202012s |*J. Am. Chem. Soc.* 2011, 133, 9196–9199

reaction conditions **II**. Not surprisingly, it was almost completely consumed to generate dimers and oligomers (see the SI). Because the silyl group can be removed, this method offers a means of cyclizing recalcitrant substrates using RCM.

In summary, 8- to 16-membered macrocyclic rings containing *E*-trisubstituted silyl olefins and the corresponding *Z*-disubstituted olefins can be accessed using RCM of vinylsiloxane substrates. This study illustrates the use of a silyl group in controlling the stereoselectivity of RCM reactions in macrocyclic systems. Additionally, productive RCMs of vinylsiloxanes allow access to challenging simple olefin products that may be otherwise disfavored in comparison with acyclic or cyclic dimers and oligomers. Studies exploring the use of alkenylsiloxanes as chemical handles for further functionalization and diversification of the RCM products are underway.

■ ASSOCIATED CONTENT

Supporting Information. Complete refs 14b and 22, experimental procedures, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

We gratefully acknowledge Drs. Tuoping Luo, Drew Adams, Mingji Dai, Sivaraman Dandapani, Giovanni Muncipinto, Bhaumik Pandya, Eamon Comer, and Qiu Wang for helpful discussions and Christopher Johnson and Joachim Azzi for their assistance with SFC−MS analyses. This work was funded by the NIGMS-sponsored Center of Excellence in Chemical Methodology and Library Development (Broad Institute CMLD; P50 GM069721). S.L.S. is an Investigator with the Howard Hughes Medical Institute.

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