Strained Molecules

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High Reactivity of Strained Seven-Membered-Ring *trans*-Alkenes

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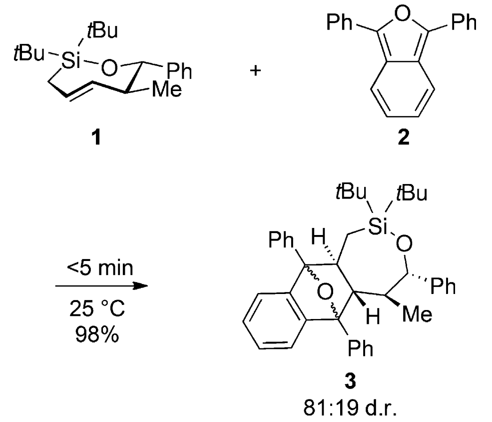
Abstract: *trans-Oxasilacycloheptenes are highly reactive strained alkenes. Competition reactions showed that these seven-membered ring trans-alkenes underwent [4+2] cycloaddition reactions faster than a trans-cyclooctene. They also reacted with quinones and dimethyl acetylenedicarboxylate to form adducts with high diastereoselectivity. Kinetic studies showed that ring strain increases nucleophilicity by approximately* 10^9.

Strain-promoted reactions have emerged as important transformations in organic synthesis[1] and chemical biology.[2] Among the strained systems investigated, the eight-membered-ring *trans*-alkenes have found numerous applications.[3–8] In contrast, studies of the reactivity of seven-membered-ring *trans*-alkenes are much less common because these compounds are particularly difficult to prepare.[9–11] Limited studies of the chemistry of *trans*-cycloheptenes demonstrate that they undergo transformations typical of reactions of alkenes, such as dihydroxylations[11,12] and reactions with acids.[12–14] They also participate in reactions observed for *trans*-cyclooctenes, such as [4+2] cycloadditions,[3,10] but those reactions were generally low-yielding.

Herein, we demonstrate that highly strained *trans*-oxasilacycloheptenes undergo fast, high-yielding, and, in most cases, stereoselective reactions. These strained alkenes are more reactive in a [4+2] cycloaddition than the most reactive *trans*-cyclooctene.[15,16] The tunable synthesis of these seven-membered-ring *trans*-alkenes allows access to new strain-promoted reactions, including stereoselective reactions with substrates containing electron-deficient π-bonds.

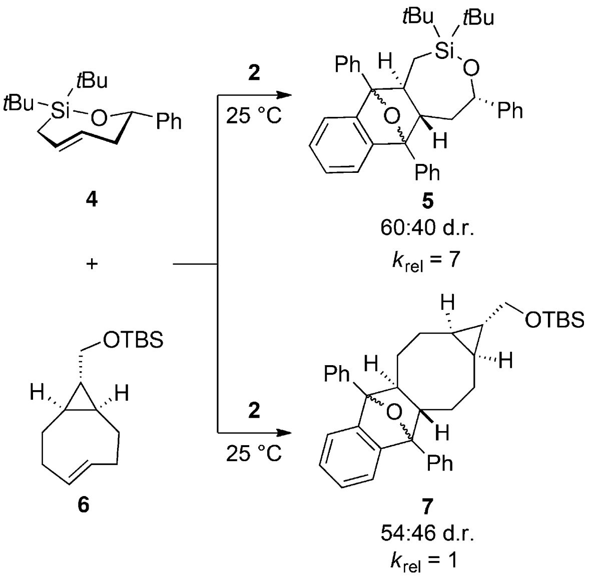
Initial studies revealed that *trans*-alkene **1** was highly reactive in a [4+2] cycloaddition reaction. This seven-membered-ring *trans*-alkene, which was synthesized from 1,3-pentadiene, benzaldehyde, and a di-*tert*-butyl silylene source,[14] reacted with diene **2** within five minutes (Scheme 1). Purification of the product afforded cycloadduct **3** in 98% yield. Although the cycloaddition occurred with retention of the geometry of the *trans*-alkene,[17] poor facial selectivity on the diene occurred.[18]



Scheme 1. Reaction of *trans*-oxasilacycloheptene **1** with diene **2**.

A competition experiment established the high reactivity of *trans*-oxasilacycloheptenes. Rates of cycloaddition reactions of the seven-membered-ring system were compared to *trans*-cyclooctene **6**,[19] a protected variant of a *trans*-cyclooctene reported to react faster than other strained alkenes in cycloadditions.[2,16] To control for steric effects,[20] the *trans*-alkene **4** was used.[21] Initial experiments were performed to characterize and isolate cycloadducts **5** and **7** (≥97% isolated yield). The relative reactivities of the different strained alkenes were established by a competition experiment (Scheme 2). This experiment revealed that *trans*-alkene **4** reacted seven-times faster with diene **2** than *trans*-cyclooctene **6** did. The enhanced reactivity of alkene **4** is likely due to the higher distortion of the *trans* double bond[12] compared to *trans*-cyclooctene **6**, which is itself conformationally distorted.[16]

Seven-membered-ring *trans*-alkenes are so reactive that they undergo cycloaddition reactions with the highly sub-



Scheme 2. Competition reactions of diene **2** with *trans*-alkenes **4** and **6**.

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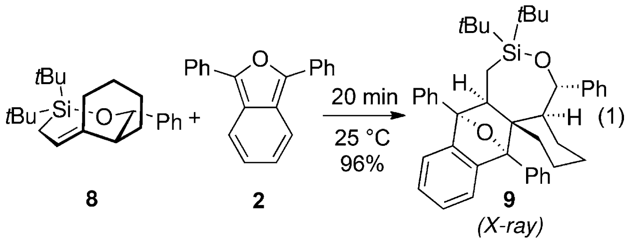
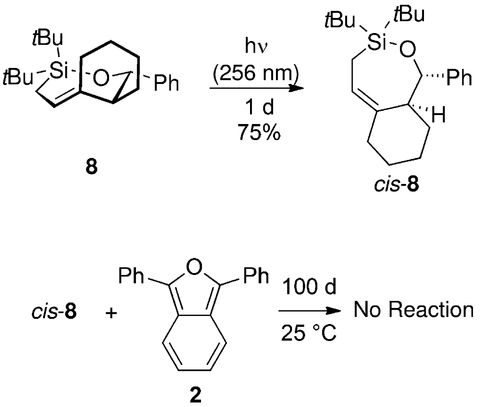
stituted diene **2**, even when the alkene is sterically hindered. Cycloaddition of diene **2** with trisubstituted alkene **8** required only 20 minutes to form cycloadduct **9** as a single diastereomer in 96 % yield [Eq. (1)]. This stereoisomer is likely favored because it minimizes developing steric interactions between a phenyl group of the diene and the fused six-membered ring of the alkene.



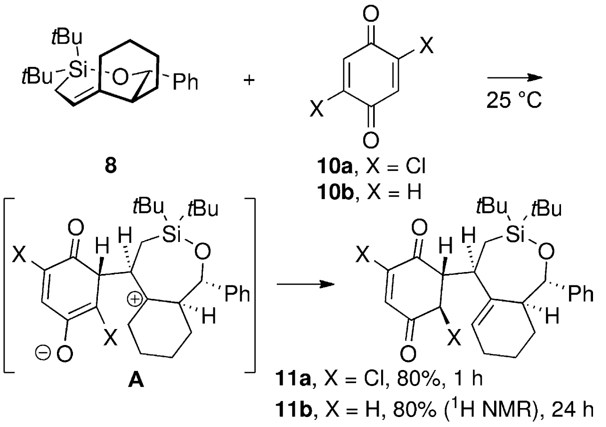
Control experiments suggest that strain is responsible for the high reactivity of seven-membered-ring *trans*-alkenes. The less-strained *cis*-alkene isomer of **8** (*cis*-**8**) was prepared by photochemical isomerization of *trans*-**8** (Scheme 3). This alkene was unreactive in cycloaddition reactions even after 100 days.



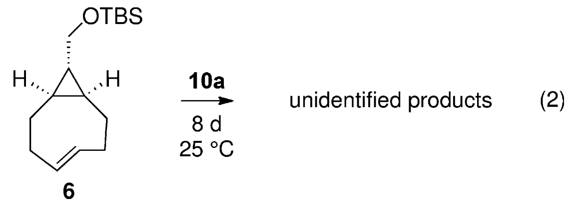
Scheme 3. Synthesis of *cis*-**8** and attempted reaction with diene **2**.

The high reactivity of these compounds permitted the development of new strain-promoted reactions. Trisubstituted alkene **8** reacted with benzoquinone **10a** to form enone **11a** as a single diastereomer (Scheme 4).[22,23] There was even a reaction with the quinone **10b**, which is over 1000-times less electrophilic than quinone **10a**.[24] Although the enones **11a** and **11b** could arise from concerted ene reactions between the alkene and the quinone, these reactions likely proceed by stepwise mechanisms involving zwitterionic intermediates (intermediate **A**, Scheme 4).[24] As with cycloaddition reactions, the alkene must be strained: the less strained alkene *cis*-**8** did not react with **10a** even after several days.

In comparison to *trans*-alkene **8**, *trans*-cyclooctene **6** was much less reactive. Even with the more reactive quinone **10a** [Eq. (2)], reactions were considerably slower, requiring eight days compared to one hour. At least six products were formed, as determined by ^{1}H NMR spectroscopy, but none were formed in sufficient quantities to assign structures.

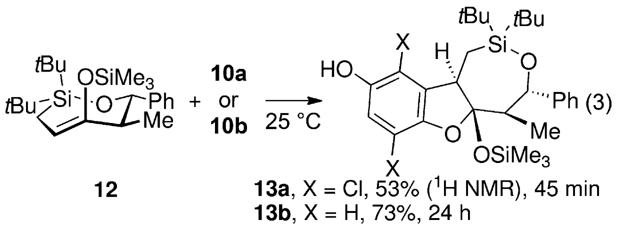


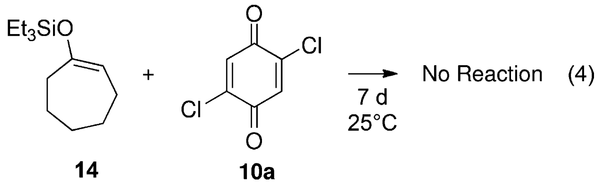
Scheme 4. Formation of enones **11a** and **11b**.



The reaction with quinone **10a** permits the estimation of how much ring strain increases the nucleophilicity of *trans*-alkene **8**. Kinetic studies of the reaction between alkene **8** and quinone **10a** showed that the rate constant was comparable to that of the reaction between a silyl ketene acetal and quinone **10a**.[24] Considering how much more nucleophilic silyl ketene acetals[25] are than trisubstituted alkenes,[26] the strain of alkene **8** accounts for a rate acceleration of approximately 10^9.

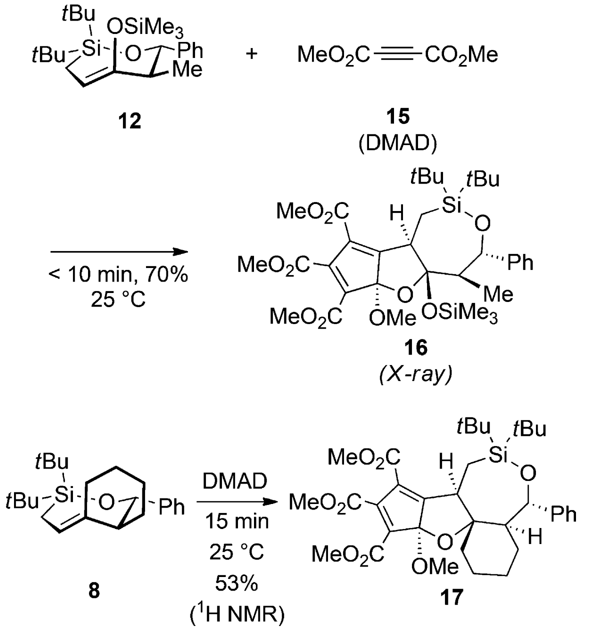
The modular assembly of seven-membered-ring *trans*-alkenes from dienes and aldehydes by silylene transfer[14] enables the synthesis of other electron-rich *trans*-cycloalkenes. Strained silyl enol ether **12**, the first example of a silyl enol ether incorporated into a *trans*-cycloalkene, was even more reactive with quinones.[27] Upon exposure to quinone **10a** or **10b**, phenols **13a** and **13b**, respectively, were formed as single stereoisomers [Eq. (3)]. These reactions, which likely involve addition of silyl enol ether **12** to the quinone followed by cyclization onto the resulting oxocarbenium ion intermediate,[24] preserved the geometry of the alkene in the product. The observation that unstrained cyclic silyl enol





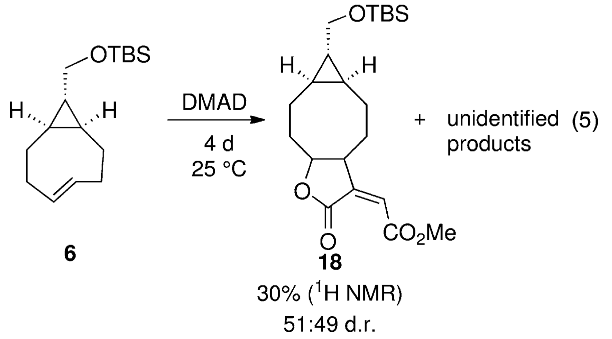
ether **14** did not react with quinone **10a** after one week [Eq. (4)] indicates that the reactions of alkene **12** are strain-promoted.[28]

Seven-membered-ring *trans*-alkenes were also highly reactive with an electron-deficient alkyne (Scheme 5). *trans*-Enol ether **12** reacted with two equivalents of dimethyl acetylenedicarboxylate (DMAD)[29] in less than ten minutes to form acetal **16** as a single diastereomer.[30] An enol ether was not required for this reaction: bicyclic alkene **8** reacted with DMAD in 15 minutes to form acetal **17** as a single stereoisomer (Scheme 5). These reactions likely proceed by conjugate addition to DMAD and ring-closure to form an oxocarbenium ion intermediate. Addition of a second equivalent of DMAD and subsequent cyclization forms the acetal product.[31]

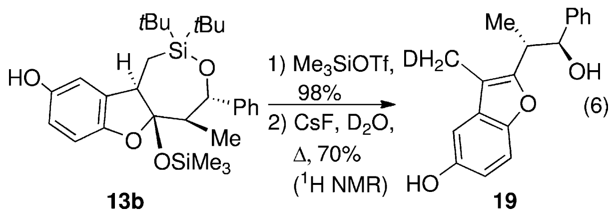


Scheme 5. Reactions of *trans*-cycloalkenes **12** and **8** with DMAD.

The high reactivity of the *trans*-oxasilacycloheptenes with DMAD contrasts with the reactivity of this alkyne with other alkenes. In comparison to the seven-membered-ring system, *trans*-cyclooctene **6** reacted slowly (four days compared to ≤ 15 minutes) and unselectively with DMAD, resulting in a mixture of at least four products [Eq. (5)]. Only lactone **18** could be identified from that mixture. The slow and unselective reaction of *trans*-alkene **6** with DMAD is consistent with earlier studies of reactions of strained alkenes with this alkyne.[30,32] Unstrained silyl enol ether **14** and alkene *cis*-**8** also did not react with DMAD even after 45 days.



The products of reactions of *trans*-oxasilacycloheptenes can be functionalized to afford products without silicon atoms. Treatment of **13b** with a Lewis acid eliminated Me_3SiOH [Eq. (6)], and desilylation in the presence of D_2O provided the deuterium-labeled benzofuran **19**. The benzofuran moiety is found in compounds displaying *anti*-inflammatory and *anti*-tumor activities.[33]



In conclusion, seven-membered-ring *trans*-alkenes are highly reactive species in a number of reactions. They are more reactive in Diels–Alder cycloadditions than *trans*-cyclooctenes. Substituted *trans*-alkenes undergo rapid and stereoselective reactions with quinones and DMAD.

Acknowledgements

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[17] The relative configurations for all products were confirmed by X-ray crystallography and nuclear Overhauser enhancement measurements. Details are provided in the Supporting Information.

[18] The relative configuration of the oxabicyclic framework could not be assigned spectroscopically.

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[22] Silver trifluoroacetate does not catalyze these reactions. Addition of excess silver trifluoroacetate (6 mol% vs. 1 mol%) had no effect on the reaction rate.

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