Communication

Diastereoselective Synthesis of Seven-Membered Ring trans-Alkenes from Dienes and Aldehydes by Silylene Transfer

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Diastereoselective Synthesis of Seven-Membered Ring *trans*-Alkenes from Dienes and Aldehydes by Silylene Transfer

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Supporting Information.

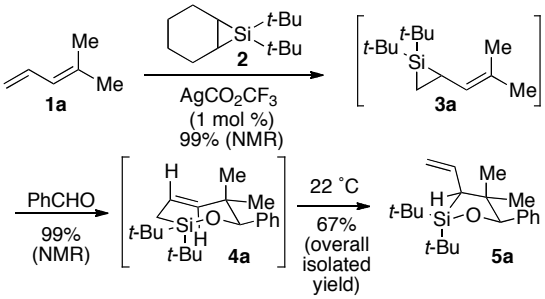
ABSTRACT: Silver-catalyzed silylene transfer to alkenes formed vinylsilacyclopropanes regioselectively. These allylic silanes underwent additions to aldehydes to form seven-membered ring *trans*-alkenes with high diastereoselectivity. The high reactivity of the trans alkenes is evidenced by their formal [1,3]-sigmatropic rearrangement reactions and their rapid additions of oxygen–hydrogen bonds across the carbon–carbon double bonds.

Investigations of the chemistry of seven-membered ring *trans*-alkenes have been limited by the difficulty of making such highly strained alkenes.[1] The development of methods for the synthesis of seven-membered cyclic *trans*-alkenes should lead to useful applications of these strained compounds, considering that advances in the preparation of the larger eight- and nine-membered ring *trans*-alkenes have enabled these highly reactive compounds to be used in synthesis[2,3,4,5] and bioconjugation.[6] In contrast to the larger cyclic *trans*-alkenes, however, no methods have been developed for the synthesis of functionalized seven-membered ring cyclic *trans*-alkenes. Photo-isomerization of *cis*-cycloheptene provides minute quantities of the trans isomer, which was unstable at –30 °C.[7] Trapping of transient *trans*-cycloheptenes has not proven to be synthetically useful,[8,9] and syntheses of seven-membered ring *trans*-alkenes containing heteroatoms in the ring are lengthy and not general.[10,11]

In this Communication, we report a one-flask synthesis of seven-membered ring *trans*-alkenes by regioselective, catalytic silylene transfer to a diene followed by a rapid diastereoselective addition of an aldehyde. Initial studies indicate that these strained alkenes are highly reactive.

Our diastereoselective synthesis of seven-membered ring *trans*-alkenes was predicated on the high reactivity of strained allylic silanes with aldehydes.[12,13,14,15] The preparation of the requisite allylic silane (such as **3a**, Scheme 1) could be challenging because it required a formal [2+1] cycloaddition of a silylene with a diene instead of the formal [4+2] cycloaddition that is typically observed.[16,17,18,19] The silver-catalyzed silylene transfer reaction to diene **1a**, however, gave vinyl silacyclopropane **3a** regioselectively (Scheme 1).[20] After the silylene transfer reaction was complete (less than ten minutes), one equivalent of benzaldehyde was added, and within ten minutes, the allylic silane underwent quantitative insertion of an aldehyde to afford the cyclic *trans*-alkene **4a** as a single diastereomer (as determined by ^{1}H NMR spectroscopy).[21] This seven-membered ring *trans*-alkene was highly reactive: attempts to isolate alkene **4a** led to addition reactions (vide infra). Even in the absence of additional reagents, the *trans*-cycloalkene **4a** underwent formal [1,3]-sigmatropic rearrangement over several hours to form an oxasilacyclopentane (**5a**) that could be isolated and purified.

Scheme 1. One-flask synthesis of seven-membered ring *trans*-alkenes.



A number of seven-membered ring *trans*-alkenes can be synthesized using different substituted dienes and aldehydes (eq 1, Table 1). In all cases, the silylene transfer reaction was regioselective and complete in less than ten minutes, and the addition to the aldehyde was diastereoselective and rapid (less than ten minutes, except for branched alkyl aldehydes, which required three hours). Silylene transfer to (*E*)-1-(triisopropylsiloxy)-1,3-butadiene (diene **1c**) occurred at the less electron-rich double bond even though silylene transfer generally occurs to the more electron-rich alkene.[22] The resulting vinylsilacyclopropane, however, reacted not as the enol ether, but as the allylic silane.[15,23]

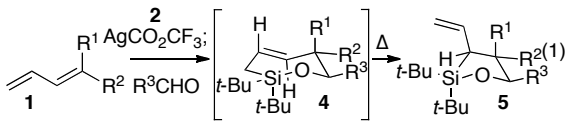
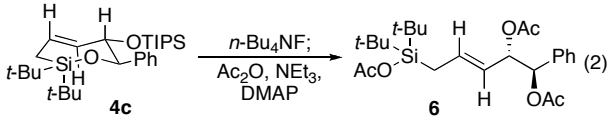


Table 1. Formation and rearrangement of trans-oxasilacycloheptene

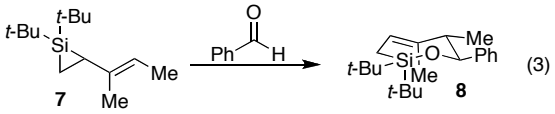
entry	R^1	R^2	R^3	**4**	%	**5**	%
1	Me	Me	Ph	**a**	99	**a**	67[a]
2	H	Me	Ph	**b**	99	**b**	51[a]
3	H	OTIPS	Ph	**c**	99	**c**	99[b]
4	H	OTIPS	*i*-Pr	**d**	75	**d**	80[b]
5	H	OTIPS	(*E*)-CHCHCH$_3$	**e**	84	**e**	86[b]
6	H	OTIPS	CHCH$_3$Ph	**f**	75	**f**	71[b]

[a] Δ = room temperature, isolated yield. [b] Δ = 60 °C, ^{1}H NMR yield based on comparison to mesitylene internal standard.

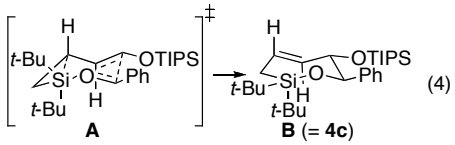
The stereochemical configuration of the seven-membered ring *trans*-alkene was determined by ^{1}H NMR spectroscopy and is consistent with the high reactivity of these compounds (vide infra). The vinyl protons of the unstable seven-membered ring *trans*-alkenes couple with coupling constants ranging from J = 17.2-17.6 Hz. These values are consistent with the reported coupling constants of *trans*-cycloheptene measured by low temperature NMR spectroscopy (J = 18 Hz).[7] In contrast, the vinyl protons of a stable *cis*-oxasilacycloheptene exhibit a much smaller coupling constant (J = 10.9 Hz).[16] Nuclear Overhauser Effect experiments are consistent with the assignment of the alkene geometry and the overall conformational preference depicted for compounds **4**: irradiation of each vinyl proton leads to NOE enhancements to substituents on opposite faces of the ring. Further evidence for the stereochemical assignment results from cleavage of the silicon–oxygen bond and isolation of the stable allylic silane **6**, which exhibits coupling between the vinylic protons (J = 15.2 Hz) that is consistent with other (*E*)-allylic silanes.[24,25]



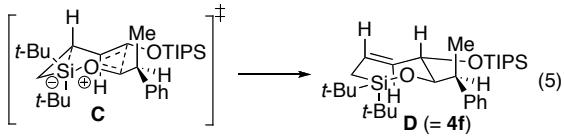
Although the seven-membered ring *trans*-alkene products hydrolyzed readily upon handling, they isomerized slowly to a product that could be isolated and purified (alkene **5**, eq 1). This [1,3]-silyl rearrangement to a stable oxasilacyclopentene, which would be expected to require high temperatures (500 °C),[26] occurred readily at room temperature in most cases. In the case of the *trans*-alkene derived from 3-methylpentadiene, isomerization did not occur, which is likely because this product would be sterically congested (eq 3). The half-lives for the formal [1,3]-sigmatropic rearrangement at room temperature average ten to twelve hours. The rearrangement from seven-membered ring *trans*-alkene to oxasilacyclopentane is likely a thermal process, because irradiation under a UV lamp (254 nm) did not accelerate the rearrangement. On the other hand, heating the *trans*-alkenes at 60 °C reduced the half-life to 30 minutes and improved its yield (Table 1). The ease of this transformation compared to known 1,3-silyl rearrangements[26] provides additional confirmation that the cyclic *trans*-alkene is highly strained.



The formation of the trans double bond in the seven-membered ring can be explained by considering the mechanism of insertion of the aldehyde. The Lewis acidic silicon atom.[12,13,27,28] of the vinylsilacyclopropane intermediate enables complexation of the aldehyde. Cyclization through closed, chair-like transition state[14,15,29] **A** would form the observed trans double bond in the product (eq 4).

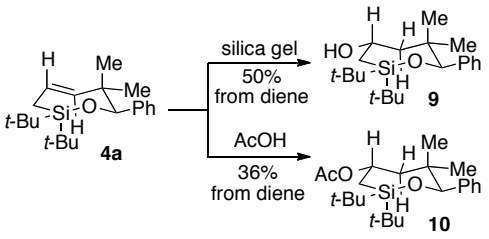


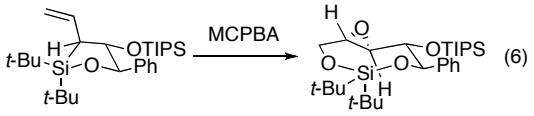
The highly organized transition state for the insertion also enables the mutual kinetic resolution[30] of a vinylsilacyclopropane and a chiral aldehyde. Insertion of racemic 2-phenylpropanal into the silacyclopropane derived from a silyloxydiene **1c** provided *trans*-oxasilacycloheptene **4f** as a single diastereomer (Table 1, entry 6). The X-ray crystal structure obtained after rearrangement to the oxasilacyclopentane revealed that the mutual kinetic resolution matched (*S*)-2-phenylpropanal with (*S*)-vinylsilacyclopropane **3c** (and the (*R*)-isomers with each other). Formation of this diastereomer is consistent with Felkin–Anh addition to the aldehyde, which minimizes *syn*-pentane interactions[31] (as shown for the (*S*,*S*)-pair in eq 5).



Preliminary studies revealed the high reactivity of the alkenes formed by these new reactions. Attempts to purify *trans*-alkene **4a** by silica gel chromatography resulted in the regioselective and stereoselective hydration of the double bond (Scheme 2). Acetic acid also added selectively across *trans*-cycloheptene **4a** (Scheme 2).[32] The double bond of the oxasilacyclopentane **5c** also underwent a highly stereoselective reaction: when it was treated with MCPBA, a single diastereomer of the trans-fused epoxide **9** was formed (eq 6). The oxasilacyclopentane likely underwent epoxidation followed by acid-catalyzed rearrangement to the eight-membered ring *trans*-alkene[33] then rapid epoxidation of this strained carbon–carbon double bond.

Scheme 2. Reactivity of the seven-membered ring *trans*-alkene 4a.





(6)

In conclusion, we have developed a rapid synthesis of seven-membered ring *trans*-alkenes by a single-flask reaction. This process involves silylene transfer to a diene followed by diastereoselective insertion of an aldehyde into the resultant allylic silane. The highly ordered transition state of this reaction enables a chiral aldehyde to discriminate between the enantiomers of the vinyl silacyclopropane.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data, including X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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