Stereoselective Insertion of Formamides into the C−Si Bond of Siliranes

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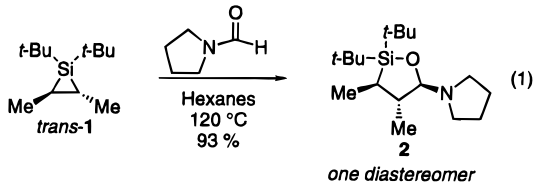
The carbonyl groups of amides, although electrophilic enough to react with potent nucleophiles such as alkyllithium or -magnesium reagents,[1] are unreactive toward many other carbon nucleophiles. Consequently, they can be employed as solvents in carbon−carbon bond-forming reactions.[2] For example, silicon-containing nucleophiles, such as hypercoordinate siliconates[3,4] and allylsilanes,[5] add to aldehydes in *N*,*N*-dimethylformamide (DMF) solutions. In the course of our research on the reactions of aldehydes with siliranes,[6] we observed that DMF reacts with these strained silanes. In this paper, we report that the insertions of formamides into siliranes, as compared to the insertion of benzaldehyde,[7] proceed in higher yield and with higher stereoselectivity. This transformation not only demonstrates a new reaction manifold for siliranes, but it suggests that the Lewis acidity of these strained silanes controls their reactivity. The significance of these observations is demonstrated by the use of an *N*,*O*-acetal product to synthesize a compound that would not have been accessible using the aldehyde insertion reaction.

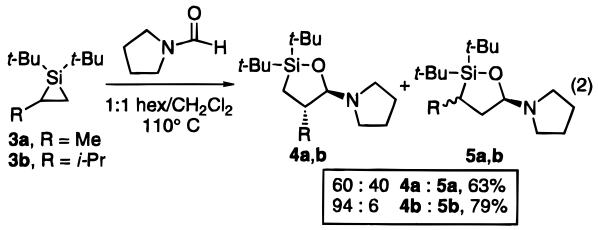
The silirane *trans*-**1**[8] reacts with 1-formylpyrrolidine in hexane[9] at elevated temperatures in a sealed reaction vessel to provide the insertion product **2** as a single stereoisomer (by ^{1}H NMR spectroscopy) in high yield (eq 1). This result stands in marked contrast to the reaction



with benzaldehyde, which occurs with 75% diastereoselection and in only 50% yield.[7] Unlike the aldehyde insertion,[7] the formamide insertion was not catalyzed by additives such as fluoride or *tert*-butoxide ion. Other formamides such as DMF and Et_2NCHO also undergo the thermal insertion reaction to provide single stereoisomers of insertion products, but 1-formylpyrrolidine gave superior yields. The generality of this reaction is not of significant concern, since all *N*,*O*-acetal products afford the same hemiacetals upon hydrolysis (*vide infra*).

The formamide insertion reaction proceeds with retention of silirane configuration as was observed for the benzaldehyde insertion reaction.[7] Whereas the stereochemistry of the acetal center is tentatively assigned, the relative configuration between the methyl groups has been shown unambiguously to be trans.[10] No intermediates were observed when the reaction was monitored by ^{1}H NMR spectroscopy (sealed NMR tube of a C_6D_{12} solution), and no isomerization of the silirane was observed. The stereospecificity of the formamide insertion reaction could not be evaluated since the cis isomer of silirane **1** decomposed under the conditions of this reaction.

The unsymmetrical siliranes **3a**[11] and **3b** were employed to probe the regioselectivity of the formamide insertion reaction. Insertion of 1-formylpyrrolidine into methylsilirane **3a** occurred with little selectivity, while insertion into the isopropylsilirane **3b** proceeded with high regioselectivity (**4b**:**5b** = 94:6, as determined by ^{1}H NMR spectroscopy) and stereoselectivity (eq 2). The



oxasilacyclopentane product **4b** was formed with exclusive trans stereochemistry.[10] Contrary to what would be expected from steric considerations, an increase in the bulk at one of the carbon centers dramatically increased the propensity for bond formation at that center.

Competition experiments between several carbonyl compounds shed further light on the amide insertion reaction. When *trans*-**1** was heated in the presence of an equal amount of benzaldehyde and 1-formylpyrrolidine, only ethers **6** derived from aldehyde insertion were observed (Scheme 1). The product distribution was consistent with the thermal rather than the catalyzed reaction manifold,[7] indicating that the formamide does not catalyze the aldehyde insertion. The preference for aldehyde insertion over amide insertion is not general, however: when *trans*-**1** was heated in the presence of isobutyraldehyde and 1-formylpyrrolidine, only the formamide insertion product **2** was observed. Formamide insertion is favored over formate ester insertion as well. The greater reactivity of an amide versus an ester or alkyl aldehyde toward carbon−carbon bond formation finds little precedent.[12]

The *N*,*O*-acetal product **2** obtained from the insertion reaction is a labile compound that hydrolyzed readily in the presence of even traces amounts of acid. In preparative experiments, unpurified **2** was hydrolyzed immediately with AcOH in THF/H_2O to afford the hemiacetal **7** as a 4:1 mixture of anomers (eq 3, 86% overall yield from silirane *trans*-**1**).[13] Acylation of the mixture of hemiacetals **7** with Ac_2O provided a single acetate **8** (by ^{1}H and

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(9) Other solvents (for example, CH_2Cl_2, C_6H_6, and THF) afforded diminished yields of insertion product **2**.
(10) The stereochemistry was proven by a combination of methods, including ^{1}H NMR spectroscopy and chemical correlation. Details of the stereochemical proof are provided as Supporting Information.
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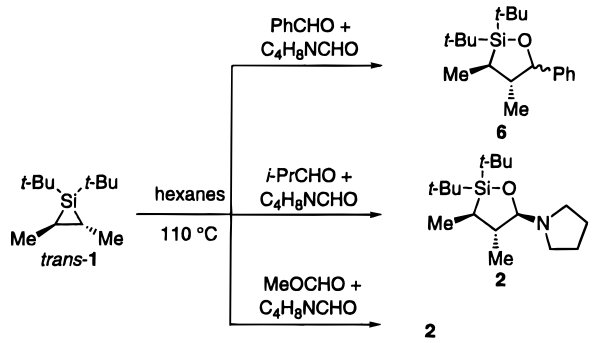
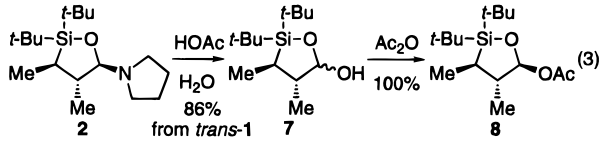
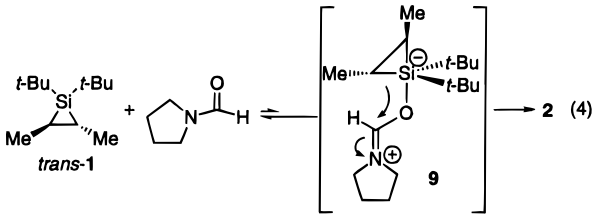
Scheme 1



^{13}C NMR spectroscopy[10]) in quantitative yield after chromatography (eq 3).

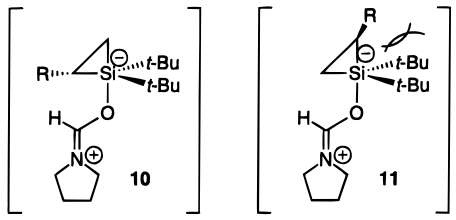


Although other mechanisms cannot be ruled out at this early stage, our working mechanism for the insertion reaction involves coordination of the carbonyl oxygen to the Lewis-acidic silicon center in the silacyclopropane to produce a pentacoordinate[14] siliconate **9** (eq 4). Since



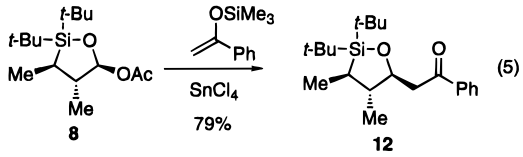
ring strain of silacyclobutanes confers Lewis acidity to these silacycles,[15−17] similar (and possibly enhanced) Lewis acidity would be expected for silacyclopropanes because they are even more strained.[18] The intermediacy of a pentacoordinate siliconate would also explain the greater reactivity of formamides over esters and alkyl aldehydes, because the reactivity trend parallels the basicity of the carbonyl oxygens. Coordination of the amide to the silirane would have two effects: the pentacoordinate siliconate **9** would become nucleophilic[3,7,14] and the formyl group would become activated for nucleophilic attack.[19] Carbon−carbon bond formation involving the intermediate[20] **9** would require an organized transition state and would be consistent with the observed high stereoselectivity.

The regioselectivity demonstrated in eq 2 can be explained by invoking pentacoordinate siliconate intermediates. In the case of unsymmetrical siliranes, two trigonal bipyramidal siliconates must be considered. The alkyl substituent can either reside in the equatorial position (as in **10**) or the apical position (as in **11**). Steric



effects would destabilize the latter because the three bulky substituents are positioned nearer to each other. Therefore, product formation would occur from intermediate **10**, and the regioselectivity would increase with increasing size of the substituent, in agreement with the experimental data (eq 2).

The formamide insertion reaction circumvents a significant limitation of the aldehyde insertion reaction, a transformation that occurs only for aryl aldehydes.[7] Coupling the amide insertion reaction with nucleophilic carbon−carbon bond formation permits access to structures inaccessible by the aldehyde reaction. Addition of the silylenol ether of acetophenone[21] to the acetate **8** in the presence of $SnCl_4$ yielded the oxasilacyclopentane **12** with high diastereoselectivity (92:8, eq 5). The proximal stereocenter directs the nucleophile away from the methyl group of the presumed oxocarbenium ion[22] intermediate. The stereochemistry of the oxasilacyclopentane **12** was proven by using our recently reported oxidation procedure to prepare the corresponding 1,3-diol.[10,23]



We have shown that formamides will insert into the C−Si bond of siliranes stereoselectively and regioselectively. The disparate reactivity between the formamide, aldehyde, and formate ester can be accounted for on the basis of their propensity to bind silirane and undergo nucleophilic attack.

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Supporting Information Available: Full experimental procedures and analytical data (11 pages).

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