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Efficient Asymmetric Synthesis of Silanediol Precursors from 1,5-Dihydrosiloles

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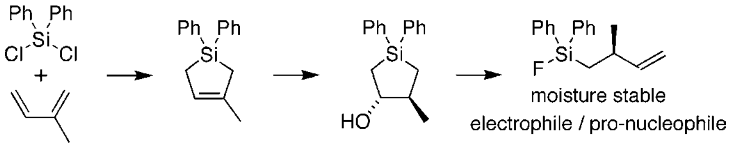
ABSTRACT



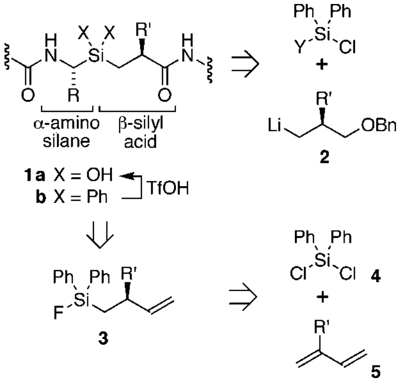
Dihydrosiloles are easily prepared from 1,3-dienes and dichlorosilanes, even on kilogram scale. Asymmetric hydroboration of a 3-alkyl-1,5-dihydrosilole, prepared from a 2-alkyl-1,3-diene, followed by treatment with aqueous HF results in Peterson fragmentation, forming optically active 3-alkyl-4-fluorosilyl-1-butenes. The fluorosilanes are stable to moisture but very reactive toward nucleophiles. In addition, they can be converted to nucleophilic silyllithium reagents.

Preparative methods for the synthesis of enantiomerically enriched organosilane intermediates have provided useful platforms from which to reach challenging targets and synthetic goals.[1] As part of our continuing exploration of silanediol-based protease inhibitors **1a**, Scheme 1, we have sought simple and economical approaches to the two asymmetric silicon substituents inherent in the structure, α-amino silanes and β-silyl acids.[2] We describe here a straightforward and scalable assembly of optically active α-alkyl-β-silyl acids.

Our first method for β-silyl acid synthesis used an organolithium reagent carrying the chiral center, **2**. While effective, this approach suffered from length, cost, and scalability.[3] We describe here a general procedure that can be performed on large scale and that produces the *moisture-insensitive* fluorosilane intermediate **3**. Fluorosilane **3**, while much more convenient to handle than a chlorosilane, remains very reactive toward nucleophiles and can also be converted to a nucleophilic silyllithium reagent. The starting materials for preparation of **3** are the commodity reagent dichlorodiphenylsilane, **4**, and 2-alkyl-1,3-diene, **5**.

The cornerstone of this chemistry is the magnesium-mediated one-step "cycloaddition" of 1,3-dienes with dichlorosilanes, Scheme 2. This reaction is effective with a broad set of dialkyl and diaryl dichlorosilanes and can proceed by two different mechanisms. An initial complex between magnesium and the 1,3-diene will react with dichlorodiphenylsilane to give 1,5-dihydrosilole, **6**.[4] Alternatively, an intermediate silylene can add to the 1,3-diene.[5] We have limited our investigation to diphenylsilane, because our synthesis of functionalized silanediols is predicated on the acidic hydrolysis of diphenylsilanes (Scheme 1).[2,3b] The

Scheme 1. Methods for Silanediol Protease Inhibitor Synthesis



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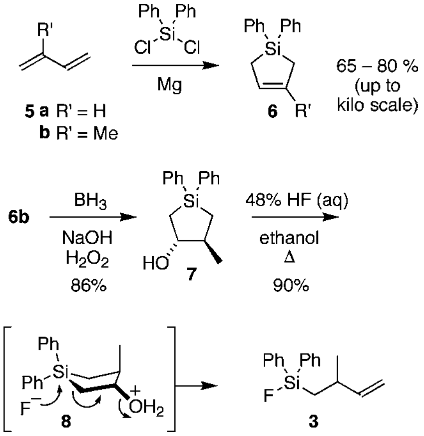
Scheme 2. Formation and Fragmentation of Dihydrosilole **6b**



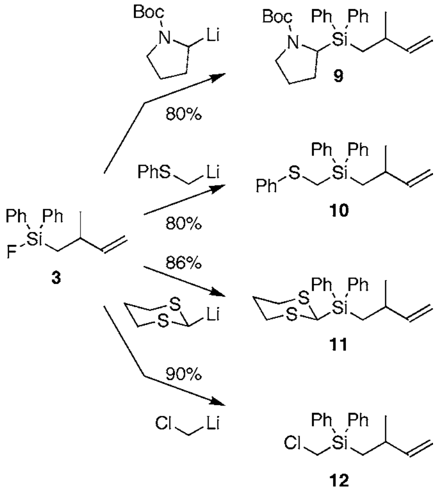
magnesium−diene complex can be prepared using magnesium turnings, powder, or Reike's magnesium and can be formed either prior to addition of the dichlorosilane or in the presence of the dichlorosilane. A detailed literature procedure for the preparation of 0.33 kg of distilled **6a** using a single 6-L flask is indicative of the utility of this chemistry.[6] We have routinely prepared **6b** from isoprene **5b** on 20-g scale. Hydroboration of this alkene yields the *trans*-alcohol **7** in good yield.

Alcohol **7**, when dissolved in a mixture of ethanol and commercial 48% HF and heated to reflux, forms fluorosilane **3** as the only observed product, which can be isolated by extraction and purified by distillation or by standard flash column chromatography in 90% yield.[7] This reaction is essentially a Peterson olefination[8] that we envision proceeding through protonated alcohol **8**, fragmenting by nucleophilic attack of fluoride on the silicon.[9] In principle, acidic cleavage of the phenyl−silicon bonds could compete with ring cleavage, and could also complicate the product isolation by replacement of phenyl by additional fluoride. Nonetheless, the stability of the phenyl silicon bond in **7** is sufficient to be noncompetetive with the fragmentation. It is likely that that electronegative fluorine in **3** attenuates the nucleophilicity of the phenyl groups and thereby limits further reactivity under the acidic reaction conditions. The clean and reproducible HF reaction of **7** contrasts with extension of this reaction to the corresponding chlorosilane, a reaction that is highly solvent dependent as well as plagued by elimination and substitution reactions, and will be described elsewhere.

The fluorine−silicon bond, one of the strongest covalent bonds, endows fluorotrialkyl(aryl)silanes with stability to water under acidic and neutral conditions. This stability, however, does not preclude their reactivity with nucleophiles. Indeed, more than 50 years ago Eaborn reported that, for the synthesis of sterically congested silanes, fluorosilanes are more reactive electrophiles than the corresponding chlorosilanes.[10]

A variety of nucleophiles react with fluorosilane **3**, such as lithiated Boc-protected pyrrolidine that yields silane **9**, Scheme 3. Similarly, metalated thioanisole and 2-lithio-1,3-dithiane give adducts **10** and **11** in good yield. Even the rather sensitive chloromethyllithium gave the chloromethyl product **12** in high yield.

Scheme 3. Fluorosilane as an Electrophile



In addition to acting as a reactive electrophile, fluorosilane **3** can be converted to a nucleophilic silyllithium reagent **13**, Scheme 4. While this is not surprising in view of the comparable use of chlorosilanes in silyllithium synthesis, we

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(9) For a closely related reaction involving a six-membered ring, see: Soderquist, J. A.; Negron, A. *Tetrahedron Lett.* **1998**, *39*, 9397−9400. 3,4-Epoxy tetrahydrosiloles undergo fragmentation when treated with tetrabutylammonium bromide: Park, Y. T.; Manuel, G.; Bau, R.; Zhao, D.; Weber, W. P. *Organometallics* **1991**, *10*, 1586−1591.

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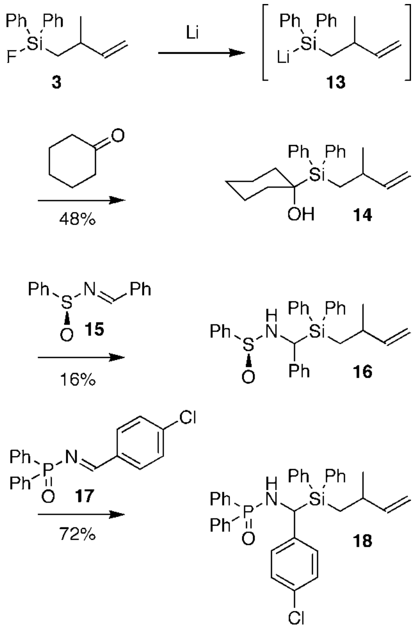
are not aware of other examples of fluorosilanes being used for this purpose. Following standard methods (lithium metal, THF), the conversion of the fluorosilane to a lithium reagent appears to be more sluggish than a comparable chlorosilane; the reaction proceeds normally, with the exception of a precipitation of lithium fluoride.

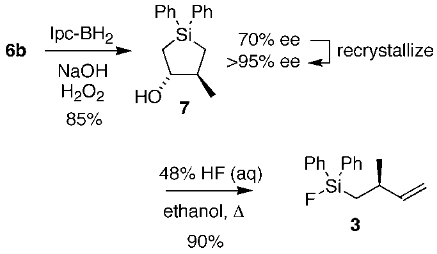
Scheme 4. Fluorosilane Converted to a Nucleophile



Diphenyl substitution of the silicon lowers the nucleophilicity of the silyl anion (e.g., dimethylphenylsilyllithium is more nucleophilic than methyldiphenylsilyllithum). Nevertheless, lithum reagent **13** undergoes addition to cyclohexanone to give the α-hydroxysilane **14** in moderate yield. As originally reported by Scheidt,[11] diphenylsilyllithium reagents are only marginally reactive enough to form adducts with the Davis sulfoximine **15**. While the yield for adduct **16** is low, only two diastereomers were detectable, suggesting that diastereocontrol by the sulfoximine group was high. A higher yield for the silyllithium addition was found with the more reactive, albeit achiral, phosphonimine **17**.

Fluorosilane **3** can also be prepared in optically active form. Treatment of alkene **6b** with mono-isopinocamphylborane followed by oxidative workup gave alcohol **7**. Mosher ester analysis found the alcohol to have an optical purity of 70% ee, similar to that reported by Brown for the comparable hydroboration of 1-methylcyclopentene.[12] A single recrystallization of **7**, however, brought the enantiomeric excess to at least 95%. Fragmentation of **7** under standard conditions gave the optically active fluorosilane **3** (Scheme 5).

Scheme 5. Asymmetric Preparation of **3**



The use of isoprene in the three-step sequence described here, leads to the chiral 3-methyl-4-(fluorodiphenylsilyl)-1-butene reagent **3**. A broad set of other 1,3-dienes have been shown to participate in the 1,5-dihydrosilole synthesis that constitutes the first step of this sequence.[13] Each of the three steps can be easily performed in multigram scale, and no chromatography is required, although all intermediates are stable to chromatography. The chiral product **3** is a moisture-insensitive reagent yet is reactive with a variety of carbon nucleophiles or can be converted to a moderately nucleophilic silyl anion. Oxidative cleavage of the alkene provides ready access to the β-silyl acids that form one-half of the silicon-based protease inhibitors that provided the incentive for development of this chemistry.[2]

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Supporting Information Available: Experimental procedures, characterization data, and ^{1}H NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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