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Asymmetric Synthesis of α-Amino Allyl, Benzyl, and Propargyl Silanes by Metalation and Rearrangement

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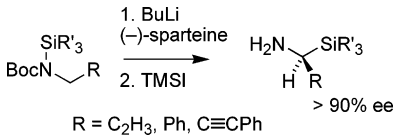
ABSTRACT



Metalation of a Boc-protected *N*-silylamine α to nitrogen results in migration of the silicon from nitrogen to carbon (reverse aza-Brook rearrangement), yielding an α-amino silane. The Boc group acts initially as a metalation-directing group and then to stabilize the nitrogen anion, providing a driving force for the rearrangement. In the presence of (−)-sparteine, the new chiral center is formed in >90% ee from allyl, benzyl, and propargylamines.

Allylsilanes and other β,γ-unsaturated silanes[1] have received extensive attention as reagents and synthetic intermediates because of annulation reactivity[2,3] and their predictable S_E2' nucleophilicity.[4] Transfer of stereochemistry in these reactions, when chirality lies between the silicon and the unsaturation, is generally high.[5]

Construction of optically active allylsilanes, with carbon as the stereogenic atom, has been achieved from enantiomerically pure precursors[6] and by catalytic asymmetric synthesis.[7]

During our study of silicon-based peptidomimetics as novel pharmaceuticals,[8] we have explored methods for α-aminosilane preparation[9] and describe here the use of the reverse aza-Brook rearrangement as a convergent and efficient approach to such structures. The α-aminosilanes are produced as versatile Boc-protected primary amines.

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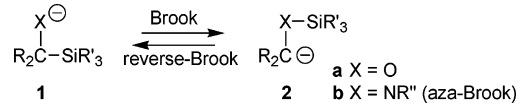
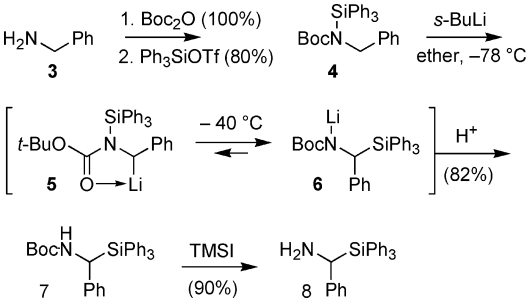
Scheme 1. Brook and aza-Brook Rearrangement



The anion-mediated migration of silicon from carbon to oxygen (Brook rearrangement[10]), Scheme 1, transforming an alkoxide (**1a**) to a carbanion (**2a**), has been studied for more than forty years.[11] The equilibrium of this organosilane−alkoxide/silyl ether−carbanion rearrangement is driven by the relative stabilities of the anions and the strengths of the silicon−carbon and silicon−oxygen bonds (ca. 375 and 475 kJ/mol, respectively[12]). Useful versions of the reverse Brook rearrangement have been developed for the synthesis of α-hydroxy silanes (protonated **1a**).[13] Both ionic and radical[14] Brook rearrangements are known, although the former are by far the most common.

The aza-Brook rearrangement (**1b** → **2b**) has been studied almost as long as the oxygen-based original,[15] but the high basicity of nitrogen anion **1b** leads to side reactions, reducing its utility. Derivatization of an amine with a Boc group, however, greatly acidifies the nitrogen, providing a driving force favoring **1b**, as well as acting as a metalation-directing group.[9a,16]

Scheme 2. Metalation/Rearrangement of Benzylamine



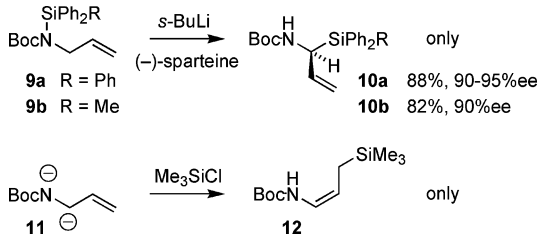
Benzylamine **3** is a typical example, Scheme 2. Treatment with di-*tert*-butyl dicarbonate followed by triphenylsilyl triflate, as described by Roby and Voyer[17] gave **4** in good yield. While somewhat moisture sensitive, this product is readily purified by crystallization or chromatography over alumina. Treatment of **4** at −78 °C with *sec*-butyllithium and warming to ca. −40 °C followed by a standard workup gave α-aminosilane **7** in high yield. Voyer et al. have shown that carbanion intermediate **5** (TMS, TBS, and TIPS instead of triphenylsilyl) can be trapped with deuterium or carbon dioxide without silicon migration, to give other useful products.[18]

The Boc group of silane **7** can be removed with trifluoroacetic acid, but sodium iodide/chlorotrimethylsilane in acetonitrile[19] is a more general procedure for acid-sensitive products (see below).

The new stereogenic center in **7** can also be prepared enantioselectively. Deprotonation of **4** with a mixture of *sec*-butyllithium and (−)-sparteine in ether led to **7** with 66% ee (Mosher derivative). Changing the solvent from ether to toluene improved the ee value to 97%. This solvent-dependent selectivity is similar to that reported by Beak et al.[20] and suggests that the deprotonation is the stereochemistry-determining step.

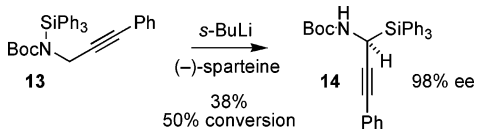
When benzylamine was replaced with allylamine to give **9**, Scheme 3, rearrangement gave the product of 1,2-

Scheme 3. Allyl Amines **9** Yields Only 1,2-Migration Product, whereas Dianion Gives Only Silylation of (*Z*)-γ-Product **12**



rearrangement, allylsilane **10**. Use of the (−)-sparteine−*sec*-butyllithium complex in toluene gave this allylsilane with >90% ee. Only 1,2-migration of the silicon was observed for these reactions. This contrasts with the product derived from silylation of dianion **11** by Resek and Beak where reaction with chlorotrimethylsilane gave only silyl enamide **12**.[21,22] The absolute stereochemistry of **10b** was determined to be (*S*)- by X-ray crystallography of a derivative (Scheme 5).

Scheme 4. Propargyl Amine Derivative **13** Rearranges to Propargylaminosilane **14**



The use of a propargylamine gave a similar outcome, Scheme 4.[23] This anion of **13**, more stabilized than those

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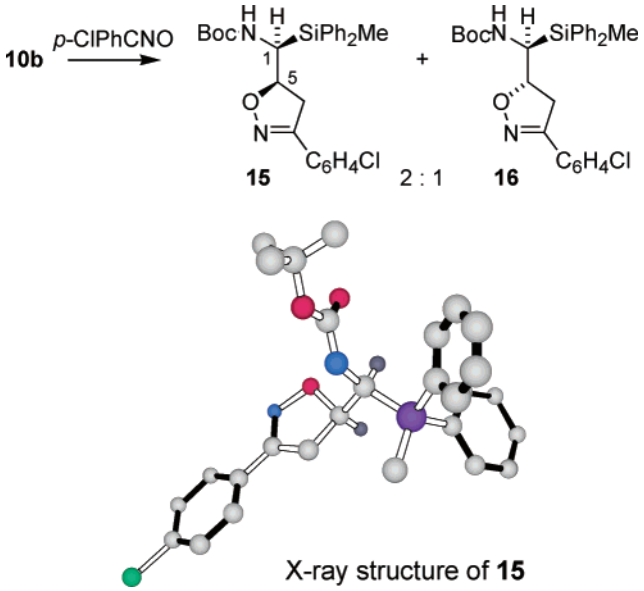
Scheme 5. Addition of Phenyl Nitrile Oxide to Allylsilane **10** Gives a Mixture of Diastereomers[a]



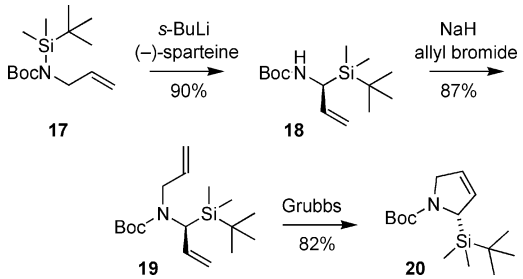
[a] Crystallography of **15** identified the absolute stereochemistry.

derived from **4** and **9**, is slower to rearrange, taking several hours at −40 °C. Following metalation, holding compound **13** for 1 h at −40 °C gave a 50% conversion to the rearrangement product. Nevertheless, the rearrangement proceeds with high enantioselectivity. Removal of the Boc group of **14** and conversion of the amine a Mosher amide found the product to have 98% ee.

Several α-aminoallylsilanes have been described previously but generally not as primary amine derivatives.[24] In the case of α-dialkylamino allylsilanes, the reactivity patterns are altered.[24c] To test the influence of the amino and silyl groups on the alkene reactivity of **10b**, it was subjected to nitrile oxide cycloaddition, Scheme 5. Little diastereoselectivity was observed; however, the major product **15** led to the crystal structure shown in Scheme 5, with the absolute stereochemistry found to be (1*S*,5*R*)-, as shown. Asymmetric rearrangement products from benzyl and propargylamines using (−)-sparteine (Schemes 2 and 4, respectively) are assumed to have the same (*S*)- absolute stereochemistry.

Transformation of an α-amino-α-vinylsilane to a pyrrolidine derivative was examined, Scheme 6. Rearrangement

Scheme 6. Methathesis Converts Silane **19** to Dihydropyrrole **20**



of TBS-protected allyl carbamate **17** gave **18** in good yield. N-Allylation of **18** gave 1,6-diene **19**, which when treated with Grubbs first-generation catalyst[25] rapidly gave dihydropyrrole **20** in high yield. This product proved to be somewhat air sensitive, undergoing oxidation upon standing to yield the corresponding *N*-Boc 2-silylpyrrole.

The metalation and rearrangement chemistry described here is the first general method for preparing α-substituted α-aminesilanes. As protected primary amines, they can be readily converted to primary, secondary, and tertiary amines (see Schemes 2 and 6). The use of (−)-sparteine to prepare the new stereogenic center led to high levels of asymmetric induction in all cases tested. The newly reported equivalent to (+)-sparteine[26] should allow either antipode to be available.

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Supporting Information Available: Procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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