Diastereoselective Intramolecular Cycloaddition of Vinylsilanes and Silyl Nitronates. Effective Control of Remote Acyclic Asymmetry

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A number of research groups have reported protocols through which Si tethers can be used to promote regio- and stereoselective transformations.[2] Related work from these laboratories has focused on the synthetic applications of chiral siloxanes,[3] obtained from diastereoselective Pt-catalyzed intramolecular hydrosilation.[4] Herein, we report on the intramolecular cycloaddition of vinyl silanes and silyl nitronates; in these transformations, high levels of diastereocontrol are effectively induced by a stereogenic carbon center that bears a Si substituent.

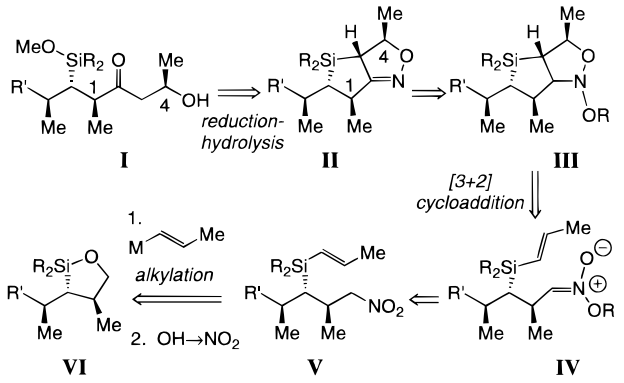
The present studies arose in the context of a total synthesis effort that required the stereoselective preparation of a fragment represented by **I** (Scheme 1). Specifically, we were interested in devising an efficient protocol for the control of the C1−C4 relative stereochemistry. One proposed plan involved the use of an intermediate vinylsilane (**V**), which would be converted to the corresponding nitronate **IV**.[5] A subsequent stereoselective [3 + 2] cycloaddition,[6] followed by silyloxide elimination, would deliver **II**. Reductive cleavage of **II** was envisioned to allow access to **I**. The requisite vinylsilane would be accessed through alkylation of the corresponding siloxanes **VI**, which would be prepared stereoselectively by Pt-catalyzed intramolecular hydrosilation.

To examine the feasibility of this approach, we prepared **2** by the Pt-catalyzed intramolecular hydrosilation of the siloxy hydride derived from **1** (Scheme 2). Subjection of **2** to 1.5 equiv of vinylmagnesium bromide resulted in the opening of the siloxane ring; subsequent conversion of the primary carbinol to nitro adduct **3** proceeded as illustrated in Scheme 2. Treatment of vinylsilane **3** with 2 equiv of TMSCl and Et_3N at 22 °C (CH_2Cl_2) for 12 h afforded bicyclic isoxazoline **5**, presumably via isooxazolidine **4**, in 90% isolated yield as a 4.5:1 mixture of stereoisomers.[7]

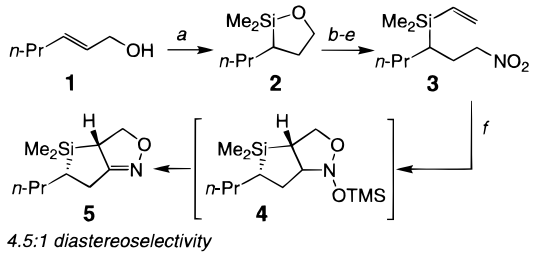
The transformation depicted in entry 1 of Table 1 is another illustration of the intramolecular cycloaddition with a vinylsilane: the reaction proceeds in 81% yield but with moderate levels of diastereoselectivity (**6** → **7**; 7:1). As illustrated in entry 2, when the vinyl unit is disubstituted, isoxazoline formation occurs efficiently (72%) but also with excellent stereocontrol (>20:1, 400 MHz ^{1}H NMR). Diastereoselective cycloadditions in entries 3−4 involve more highly functionalized substrates. The latter two reactions indicate that (a) both *cis*- and *trans*-vinylsilanes react selectively to afford the corresponding heterobicycles with complete relay of stereochemistry and (b) depending on the stereochemical identity of the substrate, in situ protodesilation[8] may occur to afford the derived heterocycle (**10** → **11** vs **12** → **13**). This difference in stability is likely due to the steric strain caused by the Me unit in the initial cycloadduct obtained from **10** (Me group is oriented toward the concave face of the cycloadduct); rupture of the C−Si bond leads to the relief of steric strain.

Transformations involving terminal vinyl silanes illustrated in entries 5 and 6 of Table 1 highlight two additional attributes of the present method: (a) In contrast to the reactions involving the less substituted **3** and **6**, transformations with the more functionalized **14** and **16** proceed with outstanding levels of stereochemical control. (b) Whereas reactions with silyl nitronates occur stereoselectively, the derived nitrile oxides[9] (condition B; formed by dehydration of the substrate with phenyl isocyanate) undergo cycloaddition with significantly lower levels of diastereoselection.

Scheme 1



Scheme 2[a]



[a] Key: (a) 1.5 equiv of 1,1,3,3-tetramethyldisilazane, 0.1 mol % Pt−divinylsiloxane, 22 °C, CH_2Cl_2; (b) 1.5 equiv of $H_2C{=}C(H)MgBr$, −78 → 0 °C, 6 h, THF; 67% from **1**; (c) 1.1 equiv of TsCl, 1.1 equiv of Et_3N, 0.1 equiv of DMAP, 22 °C, CH_2Cl_2, 12 h; 71%; (d) 5 equiv of LiI, 65 °C, THF, 7 h; 79%; (e) 1.7 equiv of H_2NCONH_2, 2.1 equiv of $NaNO_2$; DMF, 36 h, 35%; (f) 2 equiv of TMSCl, 2 equiv of Et_3N, 22 °C, 12 h, CH_2Cl_2; 90%.

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(2) For recent reviews on the utility of Si-containing compounds in synthesis, see: (a) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253−1277. (b) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063−2192.

(3) (a) Hale, M. R.; Hoveyda, A. H. *J. Org. Chem.* **1992**, *57*, 1643−1645. (b) Hale, M. R.; Hoveyda, A. H. *J. Org. Chem.* **1994**, *59*, 4370−4374. (c) Young, D. G. J.; Hale, M. R.; Hoveyda, A. H. *Tetrahedron Lett.* **1996**, *37*, 827−830.

(4) Tamao, K.; Nakajima, T.; Sumiya, R.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6090−6093.

(5) For a recent application of silylnitronates, see: Narayanan Namboothiri, I. N.; Hassner, A.; Gottlieb, H. E. *J. Org. Chem.* **1997**, *62*, 485−492.

(6) For recent examples of stereoselective [3 + 2] cycloaddition involving a Si-tethered substrate, see: (a) Righi, P.; Marotta, E.; Landuzzi, A.; Rosini, G. *J. Am. Chem. Soc.* **1996**, *118*, 9446−9447. (b) Garner, P.; Cox, P. B.; Anderson, J. T.; Protasiewicz, J.; Zaniewski, R. *J. Org. Chem.* **1997**, *62*, 493−498 and references therein. (c) Denmark, S. E.; Hurd, A. R.; Sacha, H. J. *J. Org. Chem.* **1997**, *62*, 1668−1674.

(7) The identity of the major diastereomers was established by NOE difference experiments.

(8) For recent reports on protodesilylation of siloxanes, see: (a) Reference 3a. (b) Reference 2a.

(9) (a) Wollenberg, R. H.; Goldstein, J. E. *Synthesis* **1980**, 757−758. (b) Kozikowski, A. P.; Stein, P. D. *J. Am. Chem. Soc.* **1982**, *104*, 4023−4024. (c) Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024−4026.

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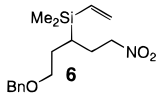
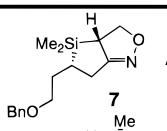
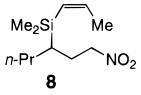
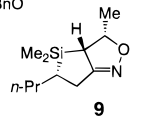
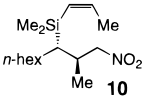
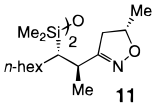
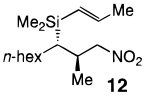
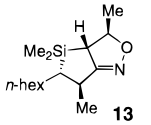
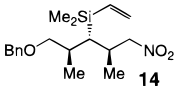
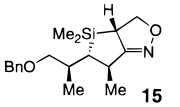
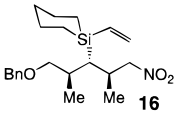
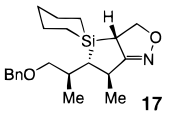
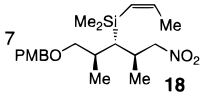
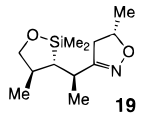
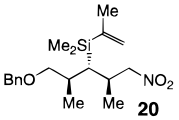
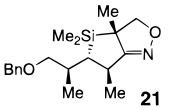
Table 1. Diastereoselective Intramolecular Vinylsilane−Silylnitronate Cycloadditions[a]

entry	substrate	cycloadduct	conditions, selectivity	yield,[b] (%)
1	 **6**	 **7**	A, 7:1	81
2	 **8**	 **9**	A, >20:1	72
3	 **10**	 **11**	A, >20:1	70
4	 **12**	 **13**	A, >20:1	78
5	 **14**	 **15**	A, >20:1 B, 1:2	61 82
6	 **16**	 **17**	A, >20:1 B, 1:2	63 76
7	 **18**	 **19**	A, >20:1	75
8	 **20**	 **21**	A, >20:1	74

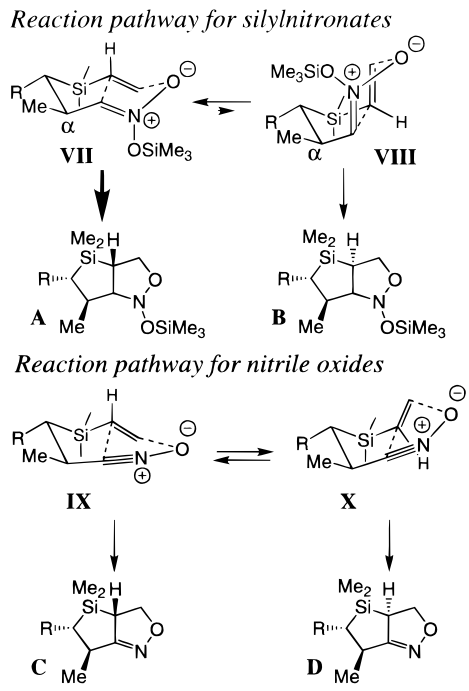
[a] Conditions: (A) 2 equiv of TMSCl, 2 equiv of Et_3N, 22 °C, 12 h, CH_2Cl_2; (B) 1.1 equiv of PhNCO, 1 mol % of Et_3N, C_6H_6, 70 °C. [b] Isolated yields after silica gel chromatography.

The reaction pathways presented in Scheme 3 suggest a plausible hypothesis for the observed difference in stereocontrol. The enhanced selectivity in reactions of silyl nitronates (favoring the intermediacy of **A**) may be due to allylic 1,3 strain involving the appropriate N−O bonds in **VII** and **VIII**; such unfavorable interactions are minimized in **VII**. The near-linear geometry of nitrile oxides (**IX** and **X**) precludes such stereodifferentiating elements, and therefore, **C** and **D** are produced indiscriminately. As depicted in Scheme 3, the intermediacy of **VII** and **VIII** is consistent with the higher levels of selectivity observed with substrates that bear an α Me group (e.g., **14** vs **6**); the steric interaction that destabilizes **VIII** is expected to be less pronounced in the absence of an α substituent.

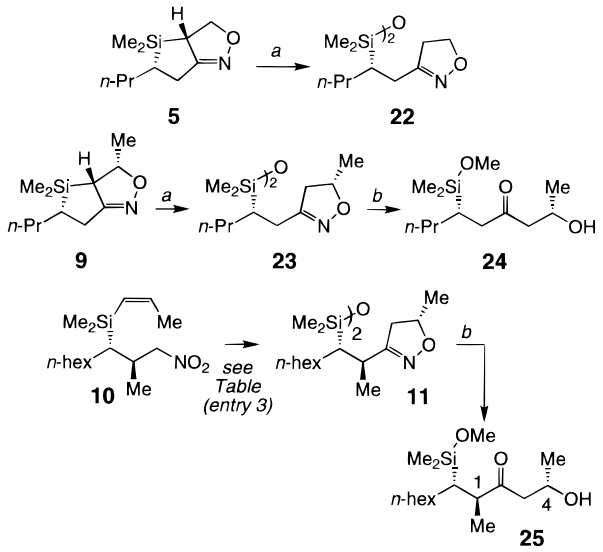
The cycloaddition presented in entry 7 proceeds with >20:1 stereoselectivity and provides the corresponding five-membered siloxane **19**. This observation indicates that, with a more labile neighboring alkoxy group, protodesilation may be initiated under relatively mild conditions. The reaction in entry 8 (**20** → **21**) illustrates that the present protocol allows for efficient control of quaternary stereogenic centers.

In addition to cycloadducts that are protodesilylated in situ (entries 3 and 7 of Table 1), the C−Si bond in other reaction products can be readily cleaved upon treatment with HCl in THF (e.g., **5** → **22** in Scheme 4). As shown in Scheme 4, the derived isoxazolines may be reduced and hydrolyzed to afford the corresponding ketones in synthetically useful yields.[10] As an example, the cycloaddition−reduction sequence converts nitroalkene **10** to β-siloxy ketone **25** in ∼50% overall yield (from vinyl silane) and with complete control of 1,4 relative stereochemistry.

Scheme 3



Scheme 4[a]



[a] Key: (a) HCl, THF; >98% for both cases; (b) 1.3 equiv of Raney Ni, MeOH, 1.5 h; 62% and 73% (for **23** and **24**, respectively).

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Supporting Information Available: Experimental procedures and spectral data for starting materials and reaction products.

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(10) For reports on the reductive cleavage of N−O bonds in isoxazolines, see: References 5 and 9.