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Diastereoselective Silacyclopropanations of Functionalized Chiral Alkenes

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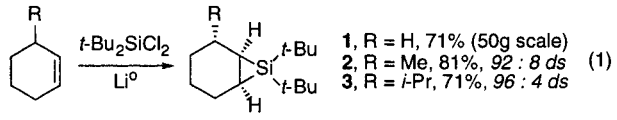
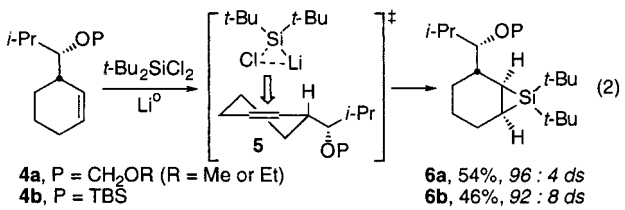
Stereoselective carbon−carbon bond-forming reactions of silacyclopropanes have proven the utility of these silanes as intermediates for organic synthesis.[1] Despite these advances, earlier reports from our laboratory[1] and others[2−6] have employed only silacyclopropanes derived from achiral alkenes without functionalization. In this communication we report that functionalized, chiral alkenes undergo highly diastereoselective silacyclopropanations to afford complex silacycles[7] that can be further elaborated to polyoxygenated structures. We have employed two methods reported by Boudjouk[4,5] to generate the silylene species for silacyclopropanation: (1) generation of di-*tert*-butylsilylenoid by the lithium reduction of *t*-Bu_2SiCl_2,[4] and (2) generation of di-*tert*-butylsilylene by thermolysis of cyclohexene-derived silacyclopropane (**1**, eq 1).[5] To



compare to the related diastereoselective cyclopropanations of olefins with lithium and zinc carbenoid species,[8−10] we have investigated the influence of oxygen functionalities and steric interactions on the diastereoselectivity of silacyclopropanation.

Initial reactions of simple chiral cyclohexenes demonstrated that steric interactions govern the diastereoselectivity of silacyclopropanation (eq 1).[11] Silacyclopropanation of 3-methyl-1-cyclohexene by reduction of *t*-Bu_2SiCl_2 afforded silacycle **2** with 92:8 diastereoselectivity.[12] Increasing the size of the allylic substituent from methyl to isopropyl enhanced the diastereoselectivity to 96:4.[12] Thermal transfer (125 °C) of di-*tert*-butylsilylene from silacycle **1** to 3-methyl-1-cyclohexene afforded a 50:50 mixture of silacycles **1** and **2**, presumably due to their similar silylene transfer abilities and similar product stabilities.

Silacyclopropanations of homoallylic ethers **4** were investigated to determine the effect of an ether substituent on diastereoselectivity. Silacyclopropanations with the lithium reduction conditions afforded the functionalized *trans*-silacyclopropanes **6** with excellent diastereoselectivity (eq 2).[11,13] In contrast to the oxygen-directing



effects observed for cyclopropanations,[8−10] the trans stereochemistry[14] indicates that the lithium silylenoid intermediate[4] approaches the olefin from the less sterically encumbered direction (**5**) and the ether functionality does not direct silacyclopropanation.[14]

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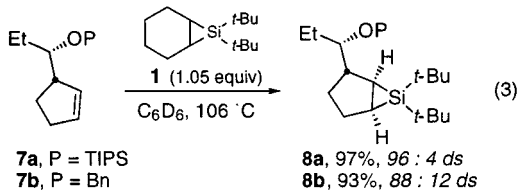
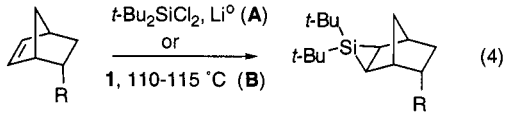
Thermolysis conditions proved to be optimal for the diastereoselective silacyclopropanation of functionalized cyclopentenes **7**, illustrating the complementary nature of the thermal transfer and lithium reduction methods. In contrast to the limited thermal transfer to substituted cyclohexenes, quantitative silylene transfer occurred to form *trans*-silacyclopropane **8a** with 96:4 diastereoselectivity (eq 3).[11,14,15] No formation of silacyclopropane **8a** was observed when



the lithium reduction of *t*-Bu_2SiCl_2 was employed. Silacyclopropanation of benzyl ether **7b** was also accomplished by using the thermal silylene transfer to afford silacyclopropane **8b** with 88:12 diastereoselectivity. The complete transfer of di-*tert*-butylsilylene from silacyclopropane **1** to the acceptor cyclopentenes **7a** and **7b** is driven presumably by the formation of a more stable silacyclopropane product (**8**) relative to silacycle **1**.[16,17]

The broad functional group tolerance exhibited by the thermolysis conditions was demonstrated by silacyclopropanation of a series of 5-*endo*-substituted norbornenes (eq 4, Table 1). Thermal transfer of di-*tert*-butylsilylene to norbornenes **9**−**13** afforded functionalized silacycles **14**−**18**, each as a single diastereomer.[11,15] The observed stereochemistry for silacyclopropanes **14**−**18** results from exo-approach[18] of the silylene intermediate to the olefin.[14] While the lithium reduction of *t*-Bu_2SiCl_2 also afforded silanes **14** and **15** in good yield,[12] submission of norbornenes **11**−**13** to the lithium reduction conditions resulted in decomposition of the norbornene substrate.

Table 1. Silacyclopropanation of 5-*endo*-Substituted Norbornenes



alkene	R	method	silacycle	ds[a]	yield (%)
9	H	**A**	**14**	>99:1	83[b]
9	H	**B**	**14**	>99:1	87[c]
10	CMe_2OMe	**A**	**15**	>99:1	67[b]
10	CMe_2OMe	**B**	**15**	>99:1	82[c,d]
11	CH_2OBn	**B**	**16**	>99:1	90[c,d]
12	CH_2OMEM	**B**	**17**	>99:1	98[c,d]
13	CO_2Me	**B**	**18**	>99:1	91[c,d]

[a] Based on analysis of ^1H and ^{29}Si NMR spectra. [b] Yield is for isolated product. [c] Yield is based on analysis of ^1H NMR with $PhSiMe_3$ as an internal standard. [d] Li°/*t*-Bu_2SiCl_2 led to decomposition of norbornene.

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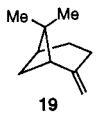
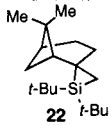
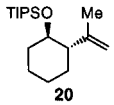
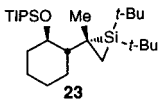
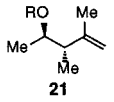
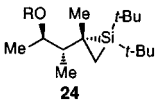
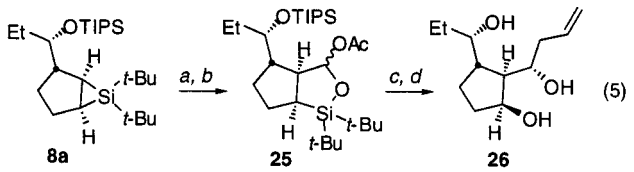
Table 2. Diastereoselective Silacyclopropanation of 1,1-Disubstituted Alkenes (R = CH_2OEt) by Lithium Reduction of *t*-Bu_2SiCl_2

alkene	ds[a]	silacycle	yield (%)[b]
 **19**	98:2	 **22**	71[c]
 **20**	97:3	 **23**	61[d]
 **21**	>99:1	 **24**	43[d]

[a] Based on analysis of ^1H and ^{29}Si NMR spectra. [b] Based on analysis of ^1H NMR spectra with 1,3,5-trimethoxybenzene as an internal standard. [c] Thermal transfer afforded **22** with 70:30 diastereoselectivity. [d] Thermal transfer led to decomposition of silacyclopropane **1**.

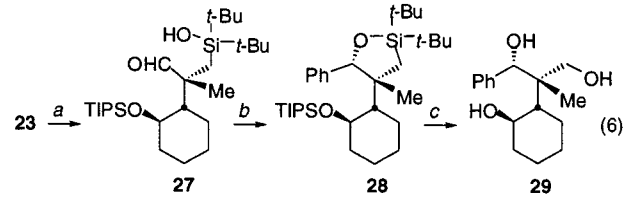
Silacyclopropanation of a series of 1,1-disubstituted alkenes (**19**−**21**) proceeded with excellent diastereoselectivity (≥97:3) using the lithium reduction conditions (Table 2). We believe that minimization of 1,2-allylic strain accounts for the acyclic stereocontrol observed for formation of silacyclopropanes **22**−**24**.[19,20] Silacyclopropanation of 1,1-disubstituted alkenes with the thermolysis conditions led to decomposition of silacycle **1** and reduced diastereoselectivities (70:30) due to the elevated temperatures (125 °C) required for silylene transfer.

The synthetic utility of diastereoselective silacyclopropanation was demonstrated by elaboration of the strained silanes **8a** and **23** to afford complex polyoxygenated structures. Metal-catalyzed formamide insertion,[21] followed by nucleophilic addition and oxidation of the C−Si bond,[22,23] afforded cyclopentane **26** in high yield and with excellent regio- and stereoselectivity (eq 5).[14] Stereo-



a) i. 10 mol% CuI, BnN(Me)CHO; ii. $CuSO_4$, H_2O, 53% from alkene **7a**; b) Ac_2O, DMAP, *i*-Pr_2NEt, 98%; c) allylTMS, $SnBr_4$, >99%, 98:2 ds; d) KH, *t*-BuOOH, TBAF, 81%.

and regioselective isocyanide insertion[24,25] was employed for the ring expansion of 1,1-disubstituted silacycle **23** (eq 6).[14] Formation of the triol **29** from silacycle **23** established an efficient route to construct quaternary carbon centers from 1,1-disubstituted alkenes (eq 6).



a) ArNC; 1M HCl, 56% over 2 steps from *t*-Bu_2SiCl_2; b) PhMgBr; 3M HCl, 88%, >98:2 ds; c) CsOH, CsF, *t*-BuOOH, 85%.

We have shown that thermal silylene transfer and lithium reduction of *t*-Bu_2SiCl_2 are complementary methods for the diastereoselective silacyclopropanations of functionalized alkenes. Our results demonstrate that steric interactions, rather than oxygen-directing effects, control the diastereoselectivity for silacyclopropanation, most likely because the sterically demanding nature of the di-*tert*-butylsilylene species prevents coordination. Thermolysis conditions exhibit broad functional group tolerance and increased yields relative to lithium reduction conditions; the elevated temperatures required for silylene transfer, however, cannot be employed for silacyclopropanation of cyclohexenes and 1,1-disubstituted alkenes. Ultimately, we envision employing a mild one-step protocol with broad substrate generality for silacyclopropanation and ring-expansion to convert a chiral functionalized alkene to a complex polyoxygenated product.

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Supporting Information Available: Experimental procedures, spectral data for all compounds, and crystallographic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Silacyclopropanes are moderately air-sensitive. Typically, the products are characterized based on ^1H and ^{29}Si NMR spectral data, and employed in subsequent insertion reactions without further purification.
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(11) Diastereoselectivity of silacyclopropanation was determined by analysis of ^1H and ^{29}Si NMR spectral data.
(12) Yields are reported for isolated silacyclopropanes purified by using bulb-to-bulb distillation.
(13) Yields for lithium reduction conditions were determined by analysis of ^1H NMR spectral data with 1,3,5-trimethoxybenzene as an internal standard.
(14) Stereochemistry was proven by X-ray crystallographic analysis of the resultant ring-expansion products. The details of crystallographic studies are provided as Supporting Information.
(15) Yields for silacycles prepared by thermal transfer are reported based on analysis of ^{1}NMR spectral data with $PhSiMe_3$ as an internal standard.
(16) The transfer of di-*tert*-butylsilylene from cyclopentene-derived silacyclopropane requires increased temperatures (130 °C) and longer reaction time (36 h) relative to silylene transfer with silacyclopropane **1**.
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