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Formation and Utility of Azasilacyclopentadienes Derived from Silacyclopropenes and Nitriles

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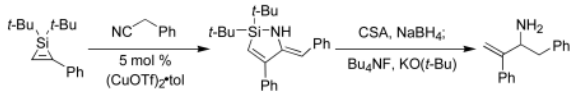
Abstract



The copper-catalyzed insertions of nitriles into the Si–C bonds of silacyclopropenes provide azasilacyclopentadienes, which can be converted to allylic amines after reduction and protodesilylation. The enamine functionality of azasilacyclopentadienes also participates in 1,4-addition reactions and undergoes a hydroboration and oxidation sequence to form an allylic 1,2-amino alcohol.

Allylic amines are useful intermediates in organic synthesis, and a number of methods have been developed for preparing these compounds.[1] Because the insertion of carbonyl compounds into silacyclopropenes provides a method for the synthesis of allylic alcohols,[2] we considered that reactions of silacyclopropenes with C–N multiple bonds could lead to a synthesis of allylic amines. Although the photochemical reactions of nitriles with a silacyclopropene have been reported,[3,4] the insertion products underwent further reactions in modest yields, and applications of these reactions in synthesis were not described.[3] In this Letter, we report the copper-catalyzed insertions of nitriles into the Si–C bonds of silacyclopropenes to form azasilacyclopentadienes. These compounds can be functionalized by reductions, 1,4-additions, and hydroborations to form allylic amines and allylic amino alcohols.[5]

Copper salts proved to be efficient catalysts for the insertion of nitriles into silacyclopropenes. When a 1:1 mixture of acetonitrile and silacyclopropene **1a** in C_6D_6 was treated with 5 mol % of $Cu(OTf)_2$, silacyclopropene **1a** disappeared over 24 hours, and enamine **2a** was formed as a single regioisomer (Scheme 1). Preference for the 1,2-insertion product, which was confirmed by a ^1H-^1H NOESY experiment, is consistent with the regioselectivity of insertions of carbonyl compounds into silacyclopropenes and silacyclopropanes.[2,6] The imine tautomer of **2a** was not observed in the product mixure or at any time during the transformation. A subsequent catalyst screen for the acetonitrile insertion of silacyclopropene **1a** showed that $Cu(OTf)_2$ and $(CuOTf)_2$·tol were more efficient catalysts than $CuBr_2$ or CuI. When the transformation was performed on a one mmol scale, $(CuOTf)_2$·tol gave higher yields than $Cu(OTf)_2$ (Table 1, entry 1).

The insertion of a nitrile into a monosubstituted silacyclopropene was general for a number of nitriles and silacyclopropenes (Table 1). Nitriles with alkyl, aryl, and silyloxy groups (Table 1, entries 1-4) and silacyclopropenes with silyl- and silyloxy substituents (Table 1, entries 5-6)

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Supporting Information Available Complete experimental procedures and product characterization. This information is available free of charge via the internet at http://www.pubs.acs.org.

were tolerated by the reaction conditions.[7] In all cases, the 1,2-insertion product and the *Z*-enamine were observed exclusively.[8] The imine tautomer of the azasilacyclopentadiene was only observed for the insertion of isobutyronitrile into the Si–C bond of silacyclopropene **1a** (Scheme 2). The formation of the enamine tautomer in this case may be disfavored because it would be destablized by interactions between the resulting isopropylidene group and the phenyl substituent.

The copper-catalyzed insertion of nitriles was also successful for disubstituted silacyclopropenes (Table 2). These transformations required mild heating but proceeded smoothly with $(CuOTf)_2$·tol as a catalyst. As with the analogous reactions of monosubstituted silacyclopropenes, a number of functional groups were tolerated. Consistent with the results described in Table 1, insertions into disubstituted silacyclopropenes favored the 1,2-regioisomer and *Z*-enamine products, although the regioselectivity of these insertions was lower than for the monosubstituted silacyclopropene reactions. Only a small degredation in regioselectivity was observed for 1-phenylpropyne-derived silacyclopropene **4a**, but a further decrease in regioselectivity was observed for the silyloxy-substituted silacyclopropene **4c**. These results suggest that steric effects are not the only factor contributing to regioselectivity.

A two-step, one-flask synthesis of azasilacyclopentadienes was developed to avoid the isolation of air-sensitive silacyclopropenes. With internal alkenes, a single metal salt, $Cu(OTf)_2$, was employed to catalyze both silylene transfer and insertion, as shown in Scheme 3.[9] With terminal alkynes, Ag_3PO_4 was employed for silylene transfer,[2] and, after filtration of the reaction mixture through glass fiber filter paper, copper salts were added to catalyze the insertion of the nitrile. [10]

Reduction of the enamine moiety of the nitrile insertion products served as the first step of a synthesis of allylic amines. Although metal-catalyzed hydrogenation reduced both the alkene and enamine functional groups,[10] the enamine functionality could be reduced selectivity by $NaBH_4$ in the presence of camphorsulfonic acid (CSA).[11] After aqueous workup, hydrolysis of the Si–N bond occurred to form the aminosilanols **6a-e** (Table 3). The unpurified products of these transformations were isolated in high yields and were of sufficient purity (>90% as estimated by ^{1}H NMR spectroscopy) to use in subsequent transformations. The purification of these compounds by chromatography, however, was challenging because of their amphiphilic nature.[12] Protection of the amino group of the products was investigated to facilitate purification of the reduction products, but the success of this approach was substrate-dependent (Scheme 4).

Once conditions for the reduction of azasilacyclopentadienes had been determined, the protodesilylation of allylic aminosilanols was investigated. Although protodesilylation under acidic conditions was not successful, treatment of **6a** with KO(*t*-Bu) and Bu_4NF in a mixture of DMSO and THF (4:1)[4,5] provided the desired allylic amine **9a**. This procedure was general for the synthesis of a range of allylic amines and amides (Table 4).

The enamine functionality of the azasilacyclopentadiene provided a handle to functionalize the nitrile insertion products. 1,4-Additions[13] of azasilacyclopentadiene **2a** to acrylonitrile gave a tautomeric mixture of the addition product **10**, but additions to methyl acrylate and crotononitrile were selective for the enamine tautomer (Scheme 5). Hydroboration of azasilacyclopentadiene **12c** followed by oxidation with NaOH and H_2O_2 provided allylic amino alcohol **13** as a single stereoisomer.[14,15] These transformations showed that azasilacyclopentadienes can be functionalized at the enamine position to provide highly substituted allylic amine derivatives.

In summary, a procedure for the synthesis of azasilacyclopentadienes has been developed based on insertions of nitriles into the Si–C bonds of silacyclopropenes. The synthetic utility of these

reactions has been demonstrated by conversions of the products to allylic amines and allylic amino alcohols. The azasilacyclopentadiene insertion products were also shown to undergo 1,4-addition reactions as well as a hydroboration and oxidation procedure to form an allylic amino alcohol.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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1. For reviews that include methods for the synthesis of allylic amines, see: a Johannsen M, Jørgensen KA. Chem Rev 1998;98:1698–1708. b Trost BM, Crawley ML. Chem Rev 2003;103:2921–2943. [PubMed: 12914486] c Overman LE, Carpenter NE. Org React 2005;66:1–107. For examples of different methods for allylic amine synthesis, see: d Wipf P, Kendall C, Stephenson CRJ. J Am Chem Soc 2003;125:761–768. [PubMed: 12526676] e Anderson CE, Overman LE. J Am Chem Soc 2003;125:12412–12413. [PubMed: 14531676] f Yamashita Y, Gopalarathnam A, Hartwig JF. J Am Chem Soc 2007;129:7508–7509. [PubMed: 17523648] g Ngai MY, Barchuk A, Krische M. J Am Chem Soc 2007;129:12644–12645. [PubMed: 17914825] h Lalic G, Krinsky JL, Bergman RG. J Am Chem Soc 2008;130:4459–4465. [PubMed: 18327942] i Kinder RE, Zhang Z, Widenhoefer RA. Org Lett 2008;10:3157–3159. [PubMed: 18570376]
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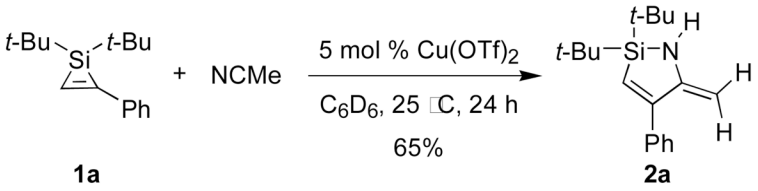
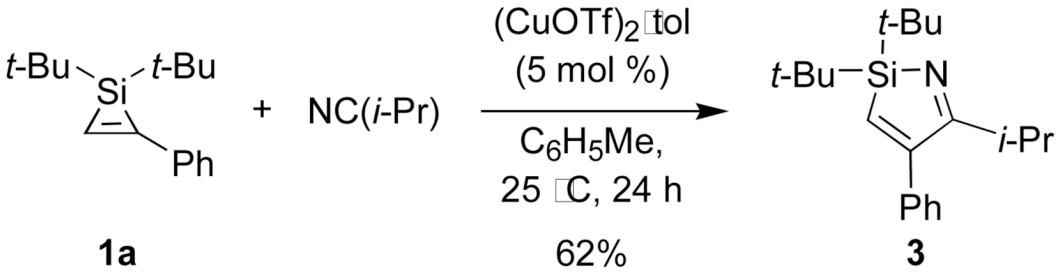
7. All of the insertion products shown in Table 1 and Scheme 2 were isolated and purified by a hexane extraction from an acetonitrile solution of the reaction mixture in an inert atmosphere glovebox. This procedure allowed the products to be separated from the copper catalyst and avoided hydrolysis of the Si–N bonds of these sensitive products. Additional confirmation of structure was obtained for the corresponding hydrolysis products; details are provided as Supporting Information.
8. The enamine stereochemistry was determined by ^{1}H-^{1}H NOESY experiments.
9. For transition metal-mediated reductive coupling reactions of alkynes and imines, see: a Wipf P, Kendall C, Stephenson CRJ. J Am Chem Soc 2003;125:76–768. b Barchuk A, Ngai MY, Krische MJ. J Am Chem Soc 2007;129:8432–8433. [PubMed: 17571894] c Ngai MY, Barchuk A, Krische M. J Am Chem Soc 2007;129:12644–12645. [PubMed: 17914825]
10. Details are provided as Supporting Information.
11. For recent examples of reductive amination under acidic conditions, see: a Reddy PS, Kanjilal S, Sunitha S, Prasad RBN. Tetrahedron Lett 2007;48:8807–8810. b Heydari A, Arefi A, Esfandyari M. J Mol Catal A: Chem 2007;274:169–172.
12. A purified sample of 6a was resubjected to chromatography conditions, and only 78% of the pure material was recovered. This observation suggested that a similar loss in yield occurred during the initial purification and accounted for the discrepancy between the unpurified and purified yields

shown in Table 3. Attempts to solve the purification problems by buffering the eluant with Et_3N or using silanized silica gel or alumina did not improve the purification.

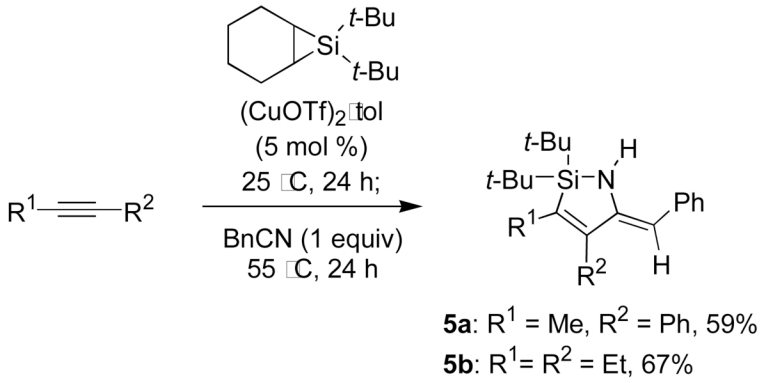
13. For examples of additions of enamines to acrylonitrile and methyl acrylate, see: a de Jeso B, Pommier JC. J Chem Soc, Chem Commun 1977:565–566. b Jones RCF, Hirst SC. Tetrahedron Lett 1989;30:5361–5364. c Pfau M, Ughetto-Monfrin J. Tetrahedron 1979;35:1899–1904. d Fourtinon M, de Jeso B, Pommier JC. J Organomet Chem 1985;289:239–246.
14. For examples of enamine hydroboration, see: a Butler DN, Soloway AH. J Am Chem Soc 1966;88:484–487. b Goralski CT, Hasha DL, Nicholson LW, Zakett D, Fisher GB, Singaram B. Tetrahedron Lett 1994;35:3251–3254.
15. The allylic amino alcohol was isolated in 85% yield with >90% purity. This compound was of sufficient purity to be used in subsequent reactions. Purification by chromatography provided a 44% yield of the allylic amino alcohol.



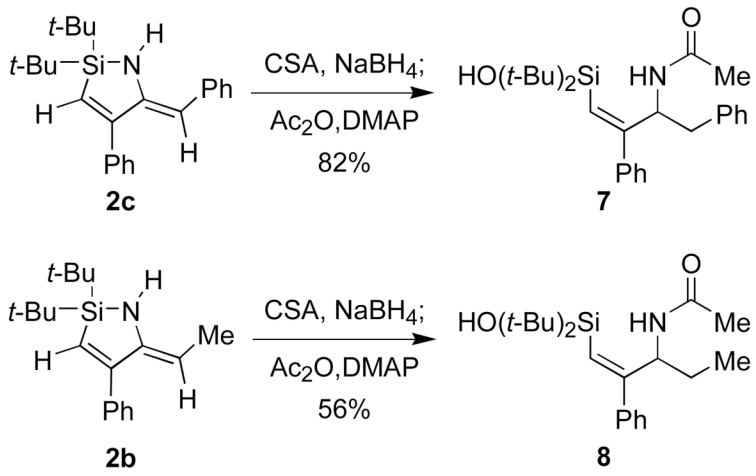
Scheme 1.
Insertion of acetonitrile into the Si–C bond of **1a**.



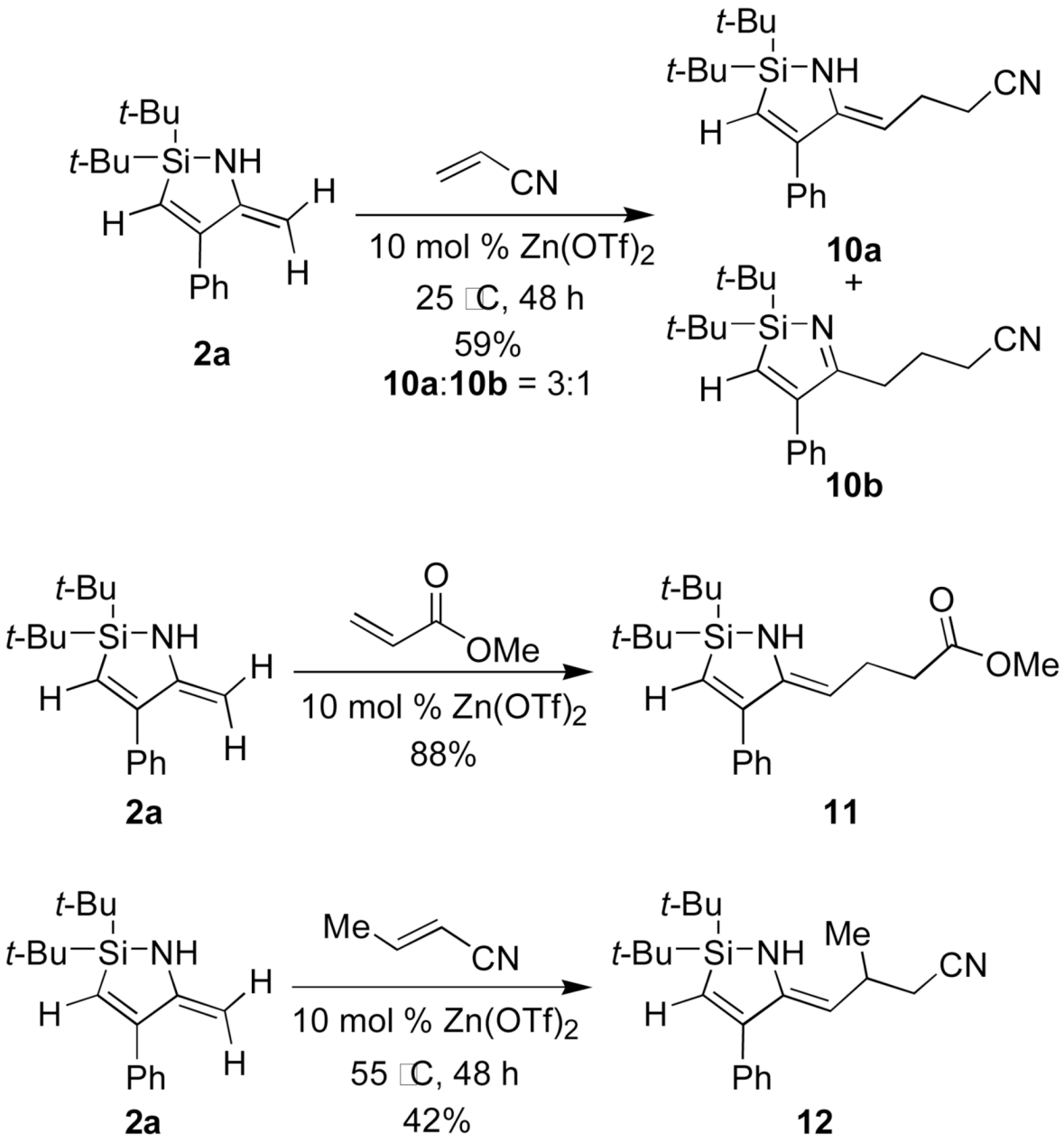
Scheme 2.
Insertion of isobutyronitrile into **1a**.



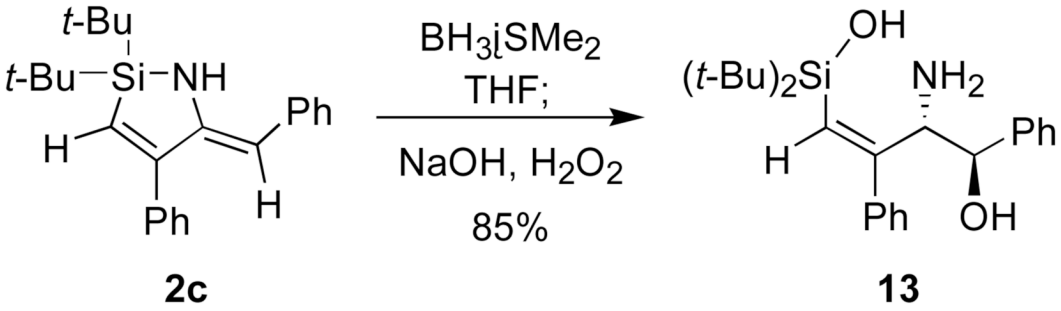
Scheme 3.
Two-Step, One-Flask, Single Catalyst Synthesis of Azasilacyclopentadienes



Scheme 4.
Enamine reduction and amine protection.



Scheme 5.
1,4-Addition Reactions of **2a**.

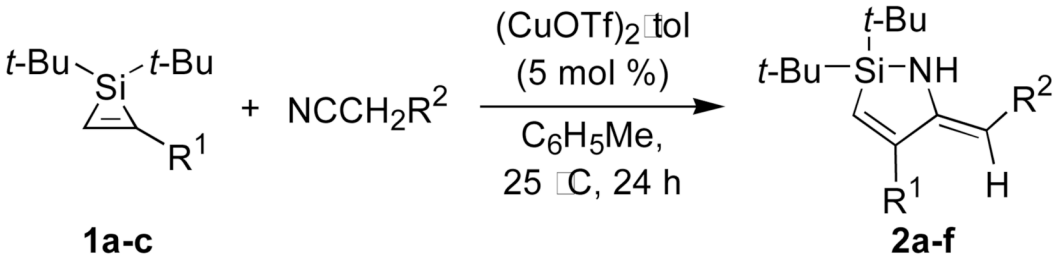


2c **13**

Scheme 6.
Hydroboration and Oxidation of **2c**.

Table 1

Insertions of nitriles into monosubstituted silacyclopropenes.



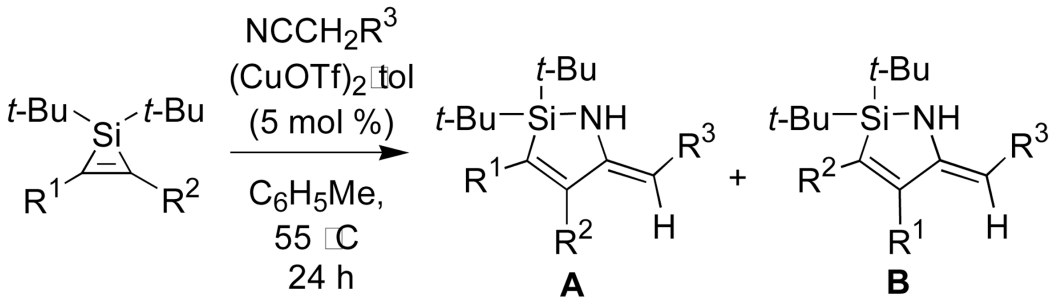
1a-c **2a-f**

entry	R^1	R^2	product, % yield
1	Ph	H	**2a**, 82
2	Ph	Me	**2b**, 86
3	Ph	Ph	**2c**, 84
4	Ph	$CH_2OTBDMS$	**2d**, 83
5[a]	$SiMe_3$	Ph	**2e**, 65
6	X	Ph	**2f**, 82

[a] $Cu(OTf)_2$ was used as a catalyst. X = CH(Ph)($OSiEt_3$).

Table 2

Insertions of nitriles into disubstituted silacyclopropenes.



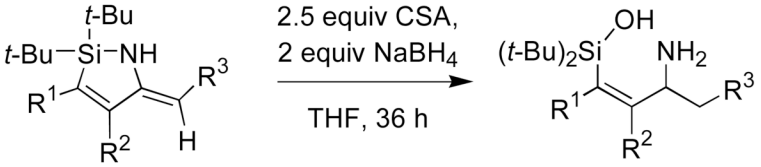
4a-d **5a-e**

entry	R^1	R^2	R^3	A:B	product, % yield
1	Me	Ph	Ph	10:1	**5a**, 85
2	Et	Et	Ph	na	**5b**, 86
3	Me	X	Me	3:2	**5c**, 96
4	Me	X	Ph	3:1	**5d**, 83
5	*n*-Bu	OTIPS	Ph	>10:1	**5e**, 85

[a] X = CH(*i*-Pr)(OTIPS)

Table 3

Reduction of azasilacyclopentadienes.



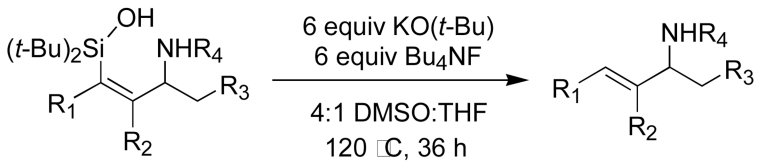
2b,**c**; **5a**,**b**,**e** **6a-e**

entry	R^1	R^2	R^3	product, % yield[a]
1	H	Ph	Ph	**6a**, 90 (59)
2	H	Ph	Me	**6b**, 95 (60)
3	Me	Ph	Ph	**6c**, 80 (32)
4	Et	Et	Ph	**6d**, 82
5	*n*-Bu	OTIPS	Ph	**6e**, 88

[a]Isolated yields of unpurified products are reported. Yields after chromatography are shown in parentheses.

Table 4

Protodesilylations of allylic aminosilanols.



6a,**c**,**d**; **7**, **8** → **9a-e**

entry	R_1	R_2	R_3	R_4	% yield
1	H	Ph	Ph	H	**9a**, 74
2	H	Ph	Ph	COMe	**9b**, 55
3	H	Ph	Me	COMe	**9c**, 74
4	Et	Et	Ph	H	**9d**, 58
5	Me	Ph	Ph	H	**9e**, 54