

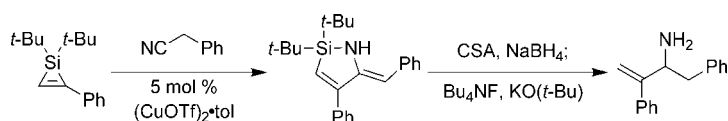
Formation and Utility of Azasilacyclopentadienes Derived from Silacyclopropenes and Nitriles

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ABSTRACT



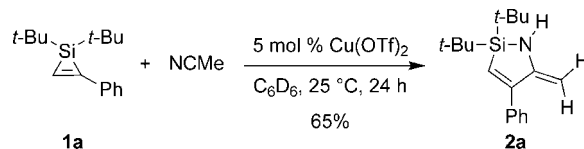
The copper-catalyzed insertions of nitriles into the Si–C bonds of silacyclopropenes provide azasilacyclopentadienes, which can be converted to allylic amines after reduction and protodesilylation. The enamine functionality of azasilacyclopentadienes also participates in 1,4-addition reactions and undergoes 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 paper, 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 hydroboration to form allylic amines and allylic amino alcohols.⁵

Copper salts proved to be efficient catalysts for the insertions of nitriles into silacyclopropenes. When a 1:1 mixture of acetonitrile and silacyclopropene **1a** in C₆D₆ was treated with 5 mol % of Cu(OTf)₂, silacyclopropene **1a** disappeared over 24 h, and enamine **2a** was formed as a single regioisomer (Scheme 1). Preference for the 1,2-insertion product, which was

Scheme 1. Insertion of Acetonitrile into the Si–C Bond of **1a**



confirmed by a ¹H–¹H NOESY experiment, is consistent with the regioselectivity of insertions of carbonyl compounds into silacyclopropenes and silacyclopentanes.^{2,6} The imine tautomer of **2a** was not observed in the product mixture 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

(1) For reviews that include methods for the synthesis of allylic amines, see: (a) Johanssen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1698–1708. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2943. (c) Carpenter, N. E. In *Organic Reactions*; Overman, L. E., Ed.; Wiley: New York, 2005; Vol. 66, pp 1–107. For examples of different methods for allylic amine synthesis, see: (d) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2003**, *125*, 761–768. (e) Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412–12413. (f) Yamashita, Y.; Gopalarathnam, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7508–7509. (g) Ngai, M.-Y.; Barchuk, A.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 12644–12645. (h) Lalic, G.; Krinsky, J. L.; Bergman, R. G. *J. Am. Chem. Soc.* **2008**, *130*, 4459–4465. (i) Kinder, R. E.; Zhang, Z.; Widenhofer, R. A. *Org. Lett.* **2008**, *10*, 3157–3159.

(2) Clark, T. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 9522–9523.

(3) Sakurai, H.; Kamiyama, Y.; Nakadaira, Y. *J. Chem. Soc., Chem. Commun.* **1978**, 80–81.

(4) For a related insertion of an imine, see: Seyferth, D.; Duncan, D. P.; Shannon, M. L. *Organometallics* **1984**, *3*, 579–583.

(5) For the synthesis of an allylic amine via a silaaziridine intermediate, see: Nevárez, Z.; Woerpel, K. A. *Org. Lett.* **2007**, *9*, 3773–3776.

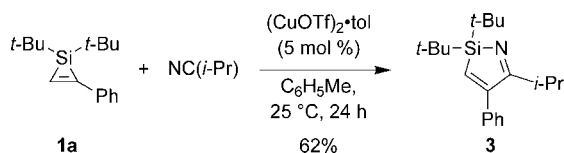
Table 1. Insertions of Nitriles into Monosubstituted Silacyclopropenes

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 ₂ OTBDMS	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)(OSiEt₃).

CuBr₂ or CuI. When the transformation was performed on a 1 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 and 6) 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

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

tautomer in this case may be disfavored because it would be destabilized 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

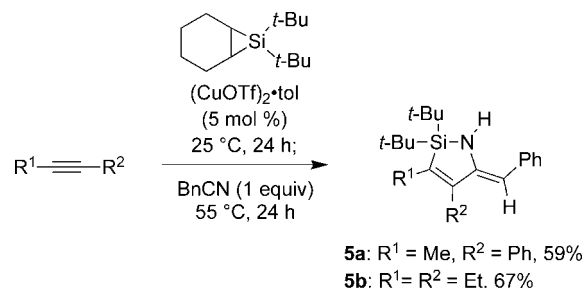
Table 2. Insertions of Nitriles into Disubstituted Silacyclopropenes

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	<i>n</i> -Bu	OTIPS	Ph	>10:1	5e , 85

^a X = CH(*i*-Pr)(OTIPS).

(CuOTf)₂·tol as the 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 degradation 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.⁹ With internal alkenes, a single metal salt, Cu(OTf)₂, was employed to catalyze both silylene transfer and insertion, as shown in Scheme 3. With terminal alkynes, Ag₃PO₄ was

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

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

(9) For transition-metal-mediated reductive coupling reactions of alkynes and imines, see: (a) Reference 1d. (b) Barchuk, A.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 8432–8433. (c) Reference 1g.

(6) (a) Franz, A. K.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 949–957. (b) Franz, A. K.; Woerpel, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4295–4299.

(7) All of the insertion products shown in Tables 1 and 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 ¹H–¹H NOESY experiments.

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 selectively by NaBH₄ in the presence of camphorsulfonic acid (CSA).¹¹ After aqueous workup, hydrolysis of the Si–N bond occurred to form the aminosilanol **6a–e** (Table 3). The unpurified products of these transformations were

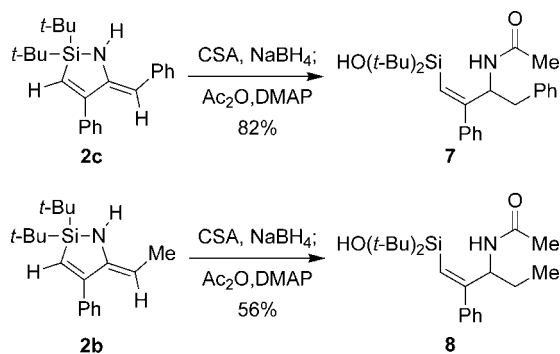
Table 3. Reduction of Azasilacyclopentadienes

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	<i>n</i> -Bu	OTIPS	Ph	6e , 88

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

isolated in high yields and were of sufficient purity (>90% as estimated by ¹H 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).

Scheme 4. Enamine Reduction and Amine Protection



Once conditions for the reduction of azasilacyclopentadienes had been determined, the protodesilylation of allylic

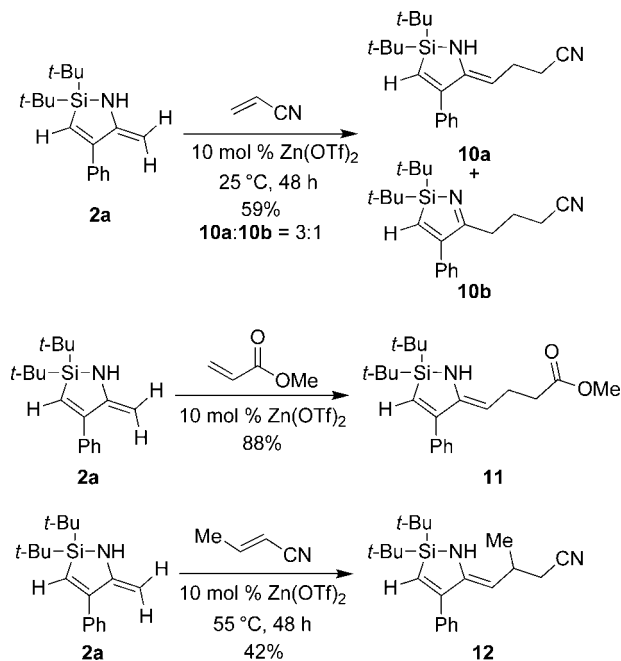
aminosilanol was investigated. Although protodesilylation under acidic conditions was not successful, treatment of **6a** with KO(*t*-Bu) and Bu₄NF in a mixture of DMSO and THF (4:1)^{2,5} provided the desired allylic amine **9a**. This procedure was general for the synthesis of a range of allylic amines and amides (Table 4).

Table 4. Protodesilylations of Allylic Aminosilanol

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

The enamine functionality of the azasilacyclopentadiene provided a handle to functionalize the nitrile insertion products. 1,4-Additions¹³ 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 azasila-

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



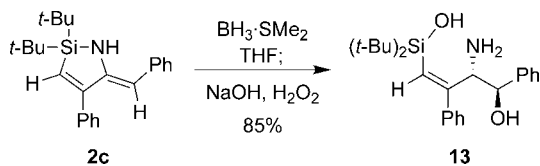
cyclopentadiene **2c** followed by oxidation with NaOH and H₂O₂ provided allylic amino alcohol **13** as a single stereoisomer

(10) Details are provided as Supporting Information.

(11) For recent examples of reductive amination under acidic conditions, see: (a) Reddy, P. S.; Kanjilal, S.; Sunitha, S.; Prasad, R. B. N. *Tetrahedron Lett.* **2007**, 48, 8807–8810. (b) Heydari, A.; Arefi, A.; Esfandiyari, M. J. *Mol. Catal. A: Chem.* **2007**, 274, 169–172.

(Scheme 6).^{14,15} These transformations showed that azasilacyclopentadienes can be functionalized at the enamine position to provide highly substituted allylic amine derivatives.

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



In summary, a procedure for the synthesis of azasilacyclopentadienes has been developed based on insertions of nitriles into the Si–C bonds of silacycloprenes. 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

(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.

well as a hydroboration and oxidation procedure to form an allylic amino alcohol.

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Supporting Information Available: Complete experimental procedures and product characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(13) For examples of additions of enamines to acrylonitrile and methyl acrylate, see: (a) de Jesso, B.; Pommier, J.-C. *J. Chem. Soc., Chem. Commun.* **1977**, 565–566. (b) Jones, R. C. F.; Hirst, S. C. *Tetrahedron Lett.* **1989**, 30, 5361–5364. (c) Pfau, M.; Ughetto-Monfrin, J. *Tetrahedron* **1979**, 35, 1899–1904. (d) Fourtignon, M.; de Jesso, B.; Pommier, J.-C. *J. Organomet. Chem.* **1985**, 289, 239–246.

(14) For examples of enamine hydroboration, see: (a) Butler, D. N.; Soloway, A. H. *J. Am. Chem. Soc.* **1966**, 88, 484–487. (b) Goralski, C. T.; Hasha, D. L.; Nicholson, L. W.; Zakett, D.; Fisher, G. B.; 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.