Direct Electrophilic Silylation of Terminal Alkynes
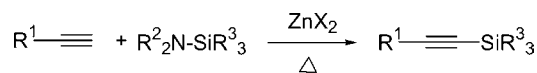
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ABSTRACT

$$R^1{-}{\equiv} \ + \ R^2{}_2N\text{-}SiR^3{}_3 \ \xrightarrow[\triangle]{ZnX_2} \ R^1{-}{\equiv}{-}SiR^3{}_3$$

*15 examples
up to 100 mmol scale
68-96%*

A variety of alkynylsilanes were efficiently prepared via direct silylation of terminal alkynes with aminosilanes in the presence of zinc halides. Base- and nucleophile-sensitive functionalities were perfectly tolerated under the above reaction conditions. Initial mechanistic studies support the electrophilic character of this transformation.

Silylalkynes are important synthons for organic chemistry.[1] They are usually synthesized in one-pot procedures involving the deprotonation of terminal alkynes with organolithium or Grignard reagents, followed by trapping of the resulting metal acetylides with the appropriate silyl electrophiles: such as halo-,[2] alkoxy-,[3] and acyloxysilanes,[4] silyl sulfonates,[5] siloxanes,[6] or silylimidazoles.[7] However, more attractive, complementary methods not involving the use of strong bases are not well developed. The only reported procedure for the direct synthesis of various silylalkynes[8] is not practical, as it requires heating the terminal alkyne, silyl chloride, and excess Zn powder in acetonotrile in a sealed tube.[9] Attempts to perform this reaction at atmospheric pressure employing either Zn/Cu[9] couple or Zn powder[10] proved nonselective, producing inseparable mixtures containing the product and reduced alkene byproducts. Herein, we wish to report a selective zinc halide-mediated direct silylation of terminal alkynes with aminosilanes,[11] providing an efficient route to differently substituted silylalkynes in good to very high yields.

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(1) For silyl protection of terminal alkynes, see: (a) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999. For directing an addition reaction to internal double or triple bonds in the presence of silyl-protected terminal alkynes, see: (b) Palmer, C. J.; Casida, J. E. *Tetrahedron Lett.* **1990**, *31*, 1539. (c) Schmidt, H. M.; Arens, J. F. *Recl. Trav. Chim. Pays Bas* **1967**, *86*, 1138. (d) Holmes, A. B.; Raphael, R. A.; Wellard, N. K. *Tetrahedron Lett.* **1976**, 1539. For selective electrophilic attack, see for example: (e) Shi Shun, A. L. K.; Chernick, E. T.; Eisler, S.; Tykwinski, R. P. *J. Org. Chem.* **2003**, *68*, 1339−1347. (f) Kawanami, Y.; Katsuki, I.; Yamaguchi, M. *Tetrahedron Lett.* **1983**, *24*, 5131. (g) Brikofer, L.; Rittir, A.; Uhlenbrauck, H. *Chem. Ber.* **1963**, *96*, 3280.

(2) See for example: (a) Jager, V.; Viehe, G. Metoden zur Herstellung und Umwandlung von Alkine. In *Houben-Weyl*, *Metoden der Organischen Chemie*; Thieme: Stuttgart, Germany, 1977; Vol. 2a. (b) Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, The Netherlands, 1988.

(3) (a) Shibata, T.; Yamashita, K.; Ohta, T.; Soai, K. *Tetrahedron* **2000**, *56*, 9259. (b) Medvedeva, A. S.; Novokshonov, V. V.; Demina, M. M.; Voronkov, M. G. *J. Organomet. Chem.* **1998**, *553*, 481. (c) Hoeyer, T.; Kjaer, A.; Lykkesfeldt, J. *Collect. Czech. Chem. Commun.* **1991**, *56*, 1042.

(4) Renga, J. M.; Wang, P. C. *Tetrahedron Lett.* **1985**, *26*, 1175.

(5) See, for example: (a) Patel, S. T.; Percy, J. M.; Wilkes, R. D. *J. Org. Chem.* **1996**, *61*, 166. (b) Kedar, T. E.; Miller, M. W.; Hegedus, L. S. *J. Org. Chem.* **1996**, *61*, 6121. (c) Tobe, Y.; Nakagawa, N.; Naemura, K.; Wakabayashi, T.; Shida, T.; Achiba, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4544. (d) Auner, N.; Grasmann, M. *J. Organomet. Chem.* **2001**, *621*, 10.

(6) (a) Mori, A.; Hishida, T.; Soga, Y.; Kawakami, Y. *Chem. Lett.* **1995**, 107. (b) Mori, A.; Sato, H.; Mizuno, K.; Hiyama, T.; Shintani, K.; Kawakami, Y. *Chem. Lett.* **1996**, 517. (c) Hirabayashi, K.; Takahisa, E.; Nishihara, Y.; Mori, A. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2409.

(7) Bourgeois, P.; Lucrece, J.; Dunogues, J. *J. Heterocycl. Chem.* **1978**, 1543.

(8) For the moderately yielding synthesis of trimethylsilyl acetylene via sodium-mediated silylation of ethyne with TMSCl, see: Schmidbauer, H.; Ebenhoch, J. *Z. Naturforsch.* **1988**, *43b*, 49.

(9) Sugita, H.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1995**, *36*, 2769.

(10) Maeorg, U.; Viirlaid, S.; Hagu, H.; Verkruijsse, H. D.; Brandsma, L. *J. Organomet. Chem.* **2000**, *601*, 341.

Tin acetylenes can be conveniently synthesized through the direct stannation of terminal alkynes with amino-[12] or alkoxystannanes.[13] Although an analogous noncatalyzed reaction with silicon analogues is unfeasible, we found that this transformation is achievable in the presence of zinc halides. Thus, heating phenylacetylene (**1a**) with *N*-TMS-diethylamine (TMSDEA) (**2a**) in the presence of 1.2 equiv[14] of zinc chloride in dichloromethane[15] afforded silylalkyne **3a** in 70% yield (Table 1, entry 1). Solvent optimization

Table 1. Optimization of the Lewis Acid-Mediated Silylation of Alkynes

entry	aminosilane **2**	Lewis acid	solvent	yield, %[a]
1	*N*-TMS-diethylamine (**2a**)	ZnCl$_2$	CH$_2$Cl$_2$	70[b]
2	**2a**	ZnCl$_2$	DMF	27[b]
3	**2a**	ZnCl$_2$	toluene	88[b]
4	**2a**	ZnCl$_2$	THF	>99[b]
5	**2a**	ZnCl$_2$	1,4-dioxane	94[b]
6	*N*-TMS-dimethylamine (**2b**)	ZnCl$_2$	1,4-dioxane	92[c]
7	**2a**	ZnBr$_2$	1,4-dioxane	>99[b]
8	**2a**	ZnI$_2$	1,4-dioxane	>99[b]
9	**2a**	Zn(OTf)$_2$	1,4-dioxane	49[b]
10	*N*-TMS-imidazole (**2c**)	ZnCl$_2$	1,4-dioxane	0[c]
11	*N*-TMS-acetamide (**2d**)	ZnCl$_2$	1,4-dioxane	0[c]
12	HMDS (**2e**)	ZnCl$_2$	1,4-dioxane	0[c]
13	*N*-TMS-benzylamine (**2f**)	ZnCl$_2$	1,4-dioxane	54[c]
14	*N*-TMS-piperidine (**2g**)	ZnCl$_2$	1,4-dioxane	90[c]
15	*N*-TMS-morpholine (**2h**)	ZnCl$_2$	1,4-dioxane	86[c]

[a] Isolated yield. [b] Method A: reactions were performed in 1.0-mmol scale. [c] Method B: reactions were performed in 100-mmol scale.

indicated that this reaction proceeded most readily in THF and 1,4-dioxane (entries 4 and 5). A 100-mmol-scale silyla-tion at ambient pressure proceeded smoothly to give **3a** in equally high yield (entry 6). Other zinc halides tested pro-vided virtually quantitative yields of the product (entries 7 and 8). Substitution of zinc halides with zinc triflate caused the reaction to proceed sluggishly and resulted in a moderate yield of **3a** (entry 9). Interestingly, other commonly used *N*-based silylating agents, such as *N*-TMS-imidazole (**2c**), *N*-TMS-acetamide (**2d**), and HMDS (**2e**), appeared to be completely ineffective in this reaction (entries 10−12). *N*-TMS-benzylamine (**2f**) was moderately effective (entry

(11) A wide variety of aminosilanes are commercially available and reasonably inexpensive.

(12) (a) Logue, M. W.; Teng, K. *J. Org. Chem.* **1982**, *47*, 2549. (b) Djeghaba, Z.; Jousseaume, B.; Ratier, M.; Dunoudin, J. G. *J. Organomet. Chem.* **1986**, *304*, 115.

(13) (a) Wrackmeyer, B.; Bihlmayer, C. *J. Organomet. Chem.* **1984**, *266*, 33. (b) Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc.* **1987**, *109*, 2138. (c) Williamson, B. L.; Stang, P. J. *Synlett* **1992**, 199. (d) Godt, A. *J. Org. Chem.* **1997**, *62*, 7471.

(14) Attempts to employ catalytic amounts of zinc halides caused a dramatic decrease of yields of the silylated products.

(15) Initial experiments were performed in Wheaton minivials equipped with Mininert valves.

13) whereas *N*-TMS-piperidine (**2g**) and *N*-TMS-morpholine (**2h**) exhibited silylating efficiency comparable to that for *N*-TMS-diethylamine (entries 14 and 15). Next, the optimized conditions (Table 1, entries 5 and 6)[16] were applied to the direct silylation of different alkynes **3a−l** (Table 2). It was

**Table 2.** ZnCl$_2$-Mediated Silylation of Terminal Alkynes

entry	alkyne **1**	product	yield, %[a]
1		**3 a**	95[b]
2		**3 b**	91[b]
3		**3 c**	95[b]
4		**3 d**	91[b]
5		**3 e**	97[b]
6		**3 f**	86[b]
7		**3 g**	82[c,d]
8		**3 h**	79[c]
9		**3 i**	77[c]
10		**3 j**	78[c]
11		**3 k**	75[c]
12		**3 l**	68[c,e]

[a] Isolated yield. [b] Method A. [c] Method B. [d] ZnBr$_2$ was used. [e] Yield of bis-silylated product.

found that various aryl alkynes underwent smooth silylation with TMSDEA to give silylalkynes **3a−f** in very high yield (entries 1−6). Silylation of 1-octyne (**1g**), benzyl propargyl ether (**1h**), and various propargyl esters (**1i−l**) proceeded uneventfully as well (entries 7−12). Remarkably, silylation under these conditions proceeded equally well in both small (1 mmol) and multigram (100 mmol) scale. Furthermore, a variety of functional groups were tolerated and no traces of reduced products were detected (Table 2).

Further experiments demonstrated that other aminosilanes **4**, possessing nonsterically demanding silyl groups, can also serve as silylating agents in this reaction. Thus, phenylacety-lene, under the standard reaction conditions, readily under-went silylation with diethylaminoarylsilanes **4a,b** to give the corresponding silylalkynes **5a,b** in excellent yields (Scheme

(16) Although employment of ZnBr$_2$ and ZnI$_2$ provided slightly higher yields, cheaper and more easily handled ZnCl$_2$ was chosen for use in further experiments.

Scheme 1

| SiR₃	yield, %
(**a**) SiPhMe₂	90
(**b**) Si(C₆H₄-CF₃-*p*)Me₂	96
(**c**) SiEt₃	74
(**d**) SiMe₂Bu*ᵗ*	NR
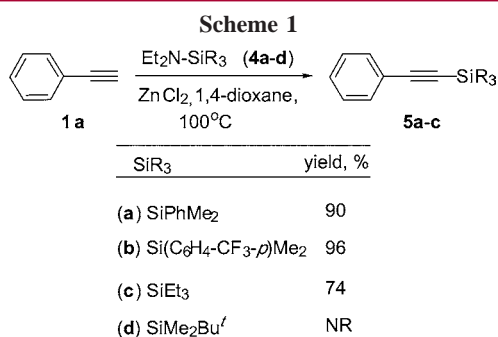
1). Installation of the larger triethylsilyl group with this method was reasonably successful (74%), whereas attempts to silylate **1a** with the bulkier TBS group failed.

Naturally, we were interested in elucidating the mechanism of this novel Lewis acid-mediated silylation of alkynes. Despite some apparent differences,[17] we thought that Carreira's direct zinc triflate-catalyzed nucleophilic addition of terminal alkynes to carbonyl compounds[18] could serve as a prototype for our silylation reaction. According to the nucleophilic pathway (path A, Scheme 2), aminosilane-assisted deprotonation of alkyne **6**, activated by the Lewis acid, would produce zinc acetylide **7** which, upon quenching with silyl electrophile **2**, would give product **3**. In light of the following observations, however, the nucleophilic mechanism (path A) involving zinc acetylide species **7**[19] seems very unlikely. Presuming that deprotonation of **1** occurs at the rate-limiting step, electron-withdrawing substituents at the para position of arylalkyne **1** (R) should facilitate the reaction, whereas electron-releasing groups should suppress it.[20] To test the

above proposal, we performed comparative kinetic studies[21] of silylation of differently para-substituted phenylalkynes **1** with **2a** in the presence of 2 equiv of ZnCl₂ (Scheme 3). The results revealed an apparent electronic effect opposite to that expected for the nucleophilic path A: electron-releasing groups (Me, OMe) facilitated the reaction, whereas electron-withdrawing substituents (CF₃, NO₂) suppressed it (Scheme 3). Furthermore, our test experiments revealed that zinc acetylide **7**, prepared by an independent method,[22] did not react with **2**, providing further evidence against the potential involvement of **7** in our silylation reaction. It is believed that the obtained kinetic data (Scheme 3) strongly support the electrophilic character of this transformation. We suggest two possible pathways for this silylation reaction. According to the first path (B), electrophilic attack of ZnX₂ at the alkyne produces zwitterionic species **9**, which, upon transmetalation, transforms into vinyl cation **10**.[23]

Alternatively, direct addition of the silylium species[24] across the triple bond would form **10** directly (path C). Finally, aminozincate-assisted deprotonation of **10** would give alkynylsilane **3**. The basicity of amide in the aminozincate is probably crucial for this deprotonation step, as supported by the failure of silylation with less basic aminosilanes **2c−e** (Table 1, entries 10−12). It should be mentioned that in the case of acetylenes possessing α-hydrogen atoms, **3g−l**, the regiochemistry of deprotonation could have become an issue, potentially leading to isomeric allenylsilanes. However, formation of the latter was never observed,[25] most likely due to thermodynamic reasons.[27]

In summary, we have developed a novel selective one-step method for the synthesis of silylalkynes, which proceeds via zinc halide-mediated silylation of terminal alkynes with
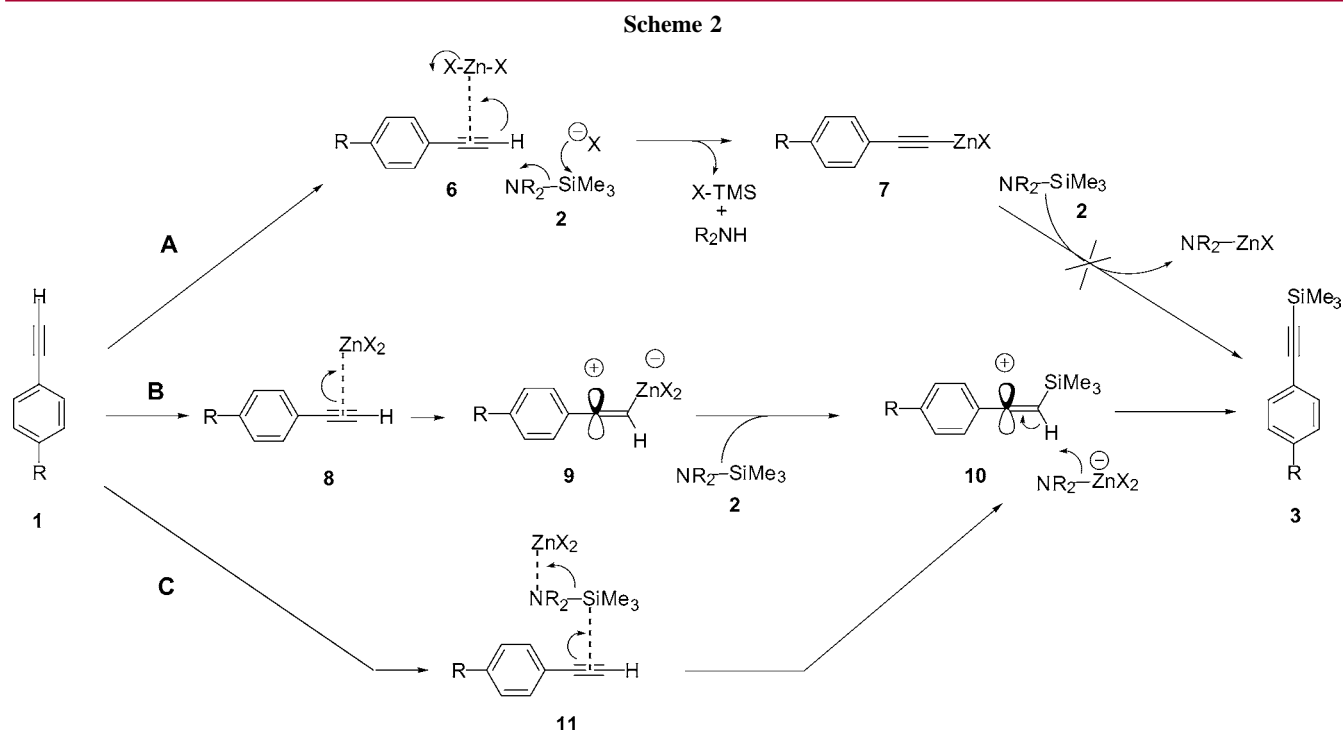
Scheme 2

Scheme 3
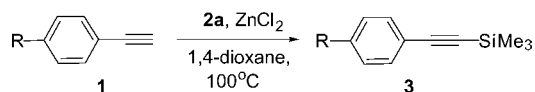
R	R/H
(**d**) Me	1.52
(**e**) OMe	1.48
(**a**) H	1.00
(**c**) CF$_3$	0.49
(**m**) NO$_2$	0.38

aminosilanes. The procedure is very straightforward and the reaction is high yielding and easily scaled up. We believe this method has high potential in synthesis, complementing the existing nucleophilic methods for the synthesis of silylalkynes, as a wide range of nucleophile-sensitive func-

tionalities are tolerated under these direct silylation conditions. Further studies to establish the scope and to elucidate a precise mechanism for this novel silylation are underway in our laboratories.

Supporting Information Available: Detailed experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) As mentioned above (Table 1, entry 9), in our reactions zinc triflate was the less efficient Lewis acid among the other zinc salts tested. Furthermore, attempts to apply Carreira's standard conditions for the silylation of alkynes with TMSCl in the presence of Et$_3$N resulted in negligible yields of the products. See the Supporting Information for details.

(18) See, for example: Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806.

(19) For involvement of zinc acetylide species in the zinc triflate-catalyzed addition of alkynes to aldehydes, see: Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245.

(20) Terekhova, M. I.; Petrov, E. S.; Vasilevskii, S. F.; Ivanov, V. F.; Shvartsberg, M. S. *Izv. Akad. Nauk SSSR*, *Ser. Khim.* **1984**, 923.

(21) See the Supporting Information for details.

(22) See, for example: (a) Ramos Tombo, G. M.; Didier, E.; Loubinoux, B. *Synlett* **1990**, 547. (b) Ruitenberg, K.; Kleijn, H.; Westmijze, H.; Meijer, J.; Vermeer, P. *Recl. J. R. Neth. Chem. Soc.* **1982**, *101*, 405. (c) Bumagin, N. A.; Ponomarev, A. B.; Beletskaya, I. P. *Zh. Org. Khim.* **1987**, *23*, 1345.

(23) Sudo, T.; Asao, N.; Gevorgyan, V.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 2494.

(24) (a) Lambert, J. B.; Zhao, Y.; Wu, H. *J. Org. Chem.* **1999**, *64*, 2729. (b) Rubin, M.; Schwier, T.; Gevorgyan, V. *J. Org. Chem.* **2002**, *67*, 1936. (c) Imamura, K.; Yoshikawa, E.; Gevorgyan, V.; Sudo, T.; Asao, N.; Yamamoto, Y. *Can. J. Chem.* **2001**, *79*, 1624.

(25) Likewise, formation of isomeric allenes has never been observed in earlier reported electrophilic hydrosilylation[24c] and hydrostannation[26] of alkynes, proceeding via intermediates analogous to **10**.

(26) Gevorgyan, V.; Liu, J.-X.; Yamamoto, Y. *J. Chem. Soc.*, *Chem. Commun.* **1998**, 37.

(27) Our ab initio calculations (6-31G*) indicated that 1-trimethylsilyl-1-butyne is ca. 9 kcal/mol more stable than its allenic isomer 1-trimethylsilyl-1,2-butadiene. Thus, even if allenylsilane, a potential kinetic product of the deprotonation of **10**, is initially formed, it should undergo complete isomerization to its thermodynamically more stable alkynyl counterpart under the reaction conditions.