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Lewis Base-Catalyzed Additions of Alkynes Using Trialkoxysilylalkynes

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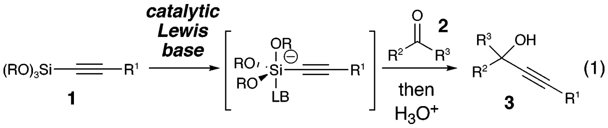
ABSTRACT

The Lewis base-catalyzed additions of alkynyl nucleophiles to aldehydes, ketones, and imines is described. Mechanistic studies strongly indicate that the use of new triethoxysilylalkynes facilitates access of a reactive hypervalent silicate intermediate. This activated carbon nucleophile subsequently undergoes rapid addition to carbonyl compounds and imines, thus affording the secondary and tertiary propargyl systems in moderate to high yield.

Chemical reactions catalyzed by nucleophilic species (Lewis bases) possess significant potential for new bond-forming strategies. Over the past decade, many advances in Lewis base-catalyzed processes have been realized, including asymmetric acylations,[1] aldol reactions,[2] and the enantioselective synthesis of β-lactams and β-lactones.[3] However, Lewis base-catalyzed reactions have not been explored to the same extent as Lewis acid or transition-metal-promoted processes, and consequently, these organocatalytic nucleophilic manifolds possess considerable promise. Many Lewis base-catalyzed reactions involve the judicious incorporation of a silyl group that can facilitate access to a hypervalent silicate species which ultimately undergoes delivery of a nucleophile.[4] Based on this principle, we reasoned that the mild and general addition of an alkynyl unit to various electrophiles might be accomplished employing Lewis base catalysts. In this paper, we report that trialkoxysilylalkynes (**1**) are novel alkynyl nucleophiles in the presence of catalytic Lewis bases and undergo mild and efficient addition to aldehydes and ketones (**2**) to cleanly afford propargyl alcohols (**3**, eq 1).



Many highly stereoselective metal-promoted additions of alkynes to aldehydes have been reported, most notably by Carreira and co-workers,[5] However, there are fewer general strategies for the addition of alkynes to both aldehydes and ketones under mild catalytic conditions.[6] Inspired by the silicon-based allyl additions,[7] carbonyl reductions,[8] that are catalyzed by Lewis bases, we envisioned that appropriately

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[1] (a) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412−420. (b) Vedejs, E.; Daugulis, O.; MacKay, J. A.; Rozners, E. *Synlett* **2001**, 1499−1505.

[2] (a) Denmark, S. E.; Stavenger, R. A.; Su, X. P.; Wong, K. T.; Nishigaichi, Y. *Pure Appl. Chem.* **1998**, *70*, 1469−1476. (b) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432−440.

[3] (a) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*, 4245−4255. (b) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166−168 and references therein. (c) Orr, R. K.; Calter, M. A. *Tetrahedron* **2003**, *59*, 3545−3565.

[4] (a) Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *Chem. Rev.* **1993**, *93*, 1371−1448. (b) Holmes, R. R. *Chem. Rev.* **1996**, *96*, 927−950. (c) Brook, M. A. *Silicon in Organic, Organometallic, and Polymer Chemistry*; Wiley-Interscience: New York, 1999.

[5] (a) Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806−1807. (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687−9688. (c) Pu, L. *Tetrahedron* **2003**, *59*, 9873−9886 and references therein. (d) Li, X. S.; Lu, G.; Kwok, W. H.; Chan, A. S. C. *J. Am. Chem. Soc.* **2002**, *124*, 12636−12637.

[6] (a) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2895−2898. For specific asymmetric alkynyl additions to acetophenone derivatives, see: (b) Lu, G.; Li, X. S.; Jia, X.; Chan, W. L.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5057−5058. (c) Saito, B.; Katsuki, T. *Synlett* **2004**, 1557−1560.

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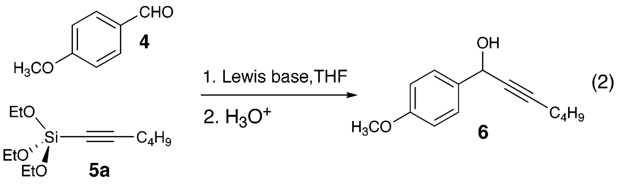
functionalized alkynes might productively interact with an electron-rich catalyst to generate a reactive nucleophilic species.[9,10]

To test this hypothesis, electron-deficient trialkoxysilylalkynes (such as **5a**) were easily accessed from the corresponding terminal alkynes[11] and subjected to various nucleophilic species in the presence of an aldehyde (**4**, Table 1, eq 2). The alkoxy substitutents were placed on the silicon to induce significant hypervalency in the presence of a Lewis base catalyst while maintaining ease of synthetic accessibility.[12] Fluoride sources were initially surveyed as potential catalysts, but stoichiometric quantities of various salts resulted in limited success (entry 1). Prompted by the strong Si−O bond strength, we examined simple alkoxides with various counterions. Interestingly, while LiOMe afforded no product (entry 2), the use of alkoxides with more electropositive counterions (Na and K) cleanly provided the desired propargyl alcohol **6**, with KOEt affording a significant rate enhancement over NaOMe (entries 3 and 4). During these early investigations, we noticed product decomposition as a function of increasing reaction time and Lewis base concentration. Gratifyingly, catalytic reaction conditions with only 10 mol % of KOEt at 0 °C generated alcohol **6** in good yield (entry 5). In addition, sterically hindered tertiary and secondary alkoxides can also be employed as catalysts (entries 6 and 7).[13]

Table 1. Lewis Base-Catalyzed Additions of Alkynes[a]

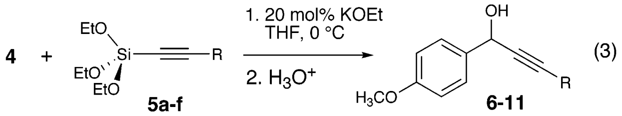


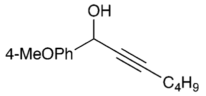
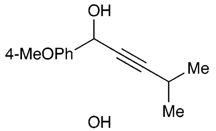
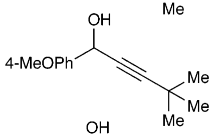
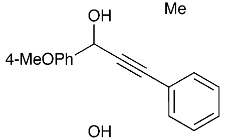
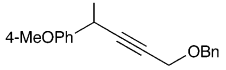
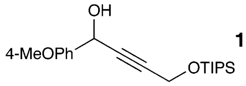
entry	Lewis base	equiv	time (h) ((T (°C))[b]	yield[c] (%)
1	n-Bu$_4$N·F$_2$SiPh$_3$	1.0	16 (23)	50
2	LiOMe	1.0	24 (23)	NR[d]
3	NaOMe	1.0	19 (23)	50
4	KOEt	1.0	1 (23)	57
5	KOEt	0.1	2 (0)	84
6	KO-t-Bu	0.2	2 (0)	75
7	(±)-KOCH(CH$_3$)Ph	0.2	2 (0)	75

[a] All reactions were performed under inert atmosphere at 0.2 M. [b] Reactions halted after 100% conversion. [c] Isolated yields after purification. [d] No reaction.

With catalytic conditions identified for this process, the structure of the alkyne nucleophile was varied (Table 2, eq 3). The reaction is facile at 0 °C, and the alkyne can accommodate linear or branched alkyl groups (entries 1−3) as well as aryl substitution (entry 4). Propargyl systems employing benzyl and triisopropylsilyl protecting groups smoothly afford the desired carbinols in good yields.

Table 2. Scope of Alkyne Addition



entry	alkyne	R	product		yield (%)
1	**5a**	n-butyl		**6**	84
2	**5b**	i-Pr		**7**	75
3	**5c**	t-Bu		**8**	73
4	**5d**	Ph		**9**	77
5	**5e**	CH$_2$OBn		**10**	76
6	**5f**	CH$_2$OTIPS		**11**	76

Under Lewis base-catalyzed conditions (10 mol % of KOEt), triethoxysilylalkyne **5a** undergoes facile addition to various aldehydes in good yields (eq 4, Table 3). The reaction is high yielding with numerous electron-rich and electron-deficient aromatic aldehydes, is mild enough to accommodate enolizable aldehydes (entries 9 and 10), and notably affords selective additions in the presence of esters (entry 11).[14]

A distinctive and important attribute of this process is the capability of this new alkynyl nucleophilic reagent to undergo

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(7) (a) Kobayashi, S.; Nishio, K. *Tetrahedron Lett.* **1993**, *34*, 3453−3456. (b) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419−6420. (c) Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron* **1999**, *55*, 977−988. (d) Denmark, S. E.; Fu, J. P. *J. Am. Chem. Soc.* **2001**, *123*, 9488−9489 and references therein.

(8) (a) Kobayashi, S.; Yasuda, M.; Hachiya, I. *Chem. Lett.* **1996**, 407−408. (b) Schiffers, R.; Kagan, H. B. *Synlett* **1997**, 1175−1178. (c) LaRonde, F. J.; Brook, M. A. *Tetrahedron Lett.* **1999**, *40*, 3507−3510. (d) Iwasaki, F.; Onomura, O.; Mishima, K.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **1999**, *40*, 7507−7511. (e) Nishikori, H.; Yoshihara, R.; Hosomi, A. *Synlett* **2003**, 561−563.

(9) For early contributions in this area, see: (a) Nakamura, E.; Kuwajima, I. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 498−499. (b) Kuwajima, I.; Nakamura, E.; Hasimoto, K. *Tetrahedron* **1983**, *39*, 975−982.

(10) With trialkylsilylalkynes, see: (a) Busch-Petersen, J.; Bo, Y.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 2065−2068. (b) Baldwin, J. E.; Pritchard, G. J.; Rathmell, R. E. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2906−2908. (c) Kraus, G. A.; Bae, J. *Tetrahedron Lett.* **2003**, *44*, 5505−5506.

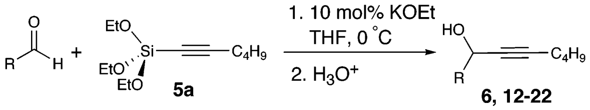
(11) See the Supporting Information for details.

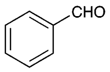
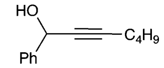
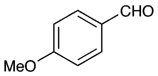
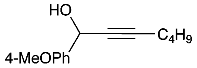
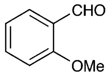
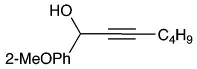
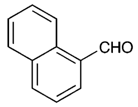
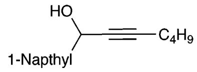
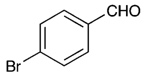
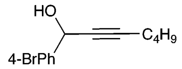
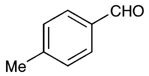
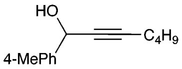
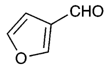
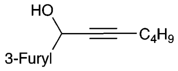
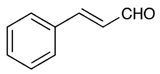
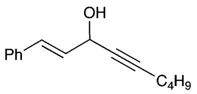
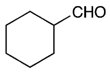
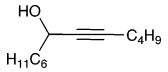
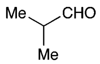
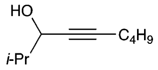
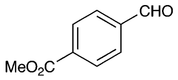
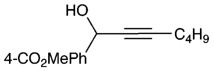
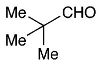
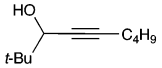
(12) The use of trialkylsilylalkynes with KOEt afforded minimal amounts of alkynyl addition products with aldehydes and was not pursued.

(13) The control experiment with 1-hexyne, KOEt, and aldehyde does not produce desired propragyl alcohol under the reaction conditions. The addition of Si(OEt)$_4$ in this system yields no product either. See the Supporting Information for details.

(14) In contrast, the lithium alkyne addition to methyl 4-formylbenzoate affords a complex mixture from the addition to both carbonyl carbons.

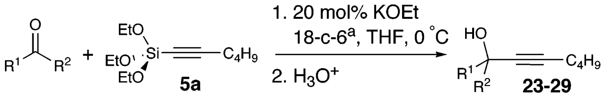
Table 3. Triethoxysilylhexyne (**5a**) Additions to Aldehydes


(4)

entry	RCHO	product		yield (%)[a]
1			**12**	74
2			**6**	84
3			**13**	82
4			**14**	76
5			**15**	76
6			**16**	80
7			**17**	85
8[b]			**18**	59
9			**19**	56
10			**20**	58
11			**21**	78
12			**22**	93

[a] Isolated yields after chromatography. [b] >95% (*E*)-cinnamaldehyde.

Table 4. Triethoxysilylhexyne (**5a**) Additions to Ketones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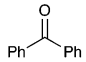
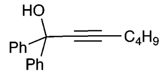
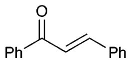
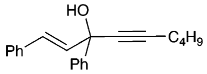
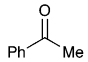
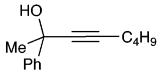
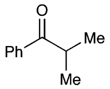
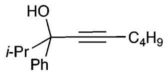
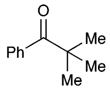
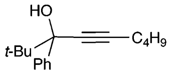
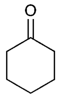
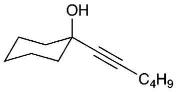
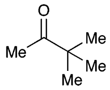
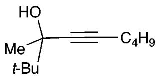
entry	ketone	product		yield (%)[b]
1			**23**	73
2[c]			**24**	54[d]
3			**25**	54
4			**26**	71
5			**27**	85
6			**28**	64
7			**29**	73

[a] 20 mol % of 18-crown-6. [b] Isolated yields after chromatography. [c] >95% (*E*)-chalcone. [d] Only 1,2-addition product observed.

addition to ketones (Table 4, eq 5). The conditions that afford the best yields employ a higher catalyst loading (20 mol %) and a crown ether (18-crown-6).[15] By utilizing these Lewis basic conditions, undesired aldol products are not observed with enolizable ketones as substrates, indicating that the basicity of these new reagents is attenuated relative to standard alkynyl organometallic reagents.

Our preliminary investigations of this process have provided important clues about the operative reaction mechanism. We propose that the active alkynyl nucleophile is a hypervalent silicate intermediate resulting from reversible addition of alkoxide. Evidence for this species was obtained by the low-temperature ^{29}Si NMR experiment of combining trialkoxysilylalkyne **5a**, 1.0 equiv of KOEt, and 1.0 equiv of 18-crown-6 (Figure 1). A new and distinct signal at −126 ppm is similar to previously studied pentavalent silicate intermediates such as $(EtO)_4SiPh{\cdot}K$ (−117 ppm).[16]

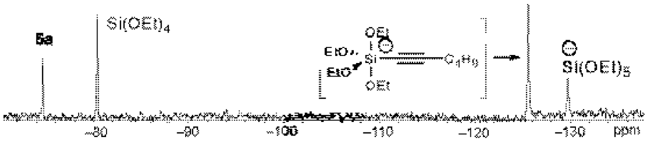


Figure 1. ^{29}Si NMR (−60 °C) of **5a**, KOEt, and 18-crown-6 (1:1:1).

An intriguing aspect of the reaction is that the propargyl product is initially an alkoxide and may well activate the

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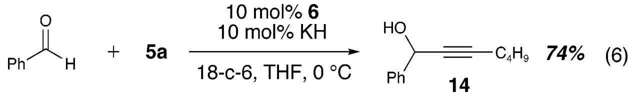
(15) The addition of 18-crown-6 allows for catalytic KOEt to be used and presumably promotes turnover of the nucleophilic alkoxide product. See the Supporting Information for details.

(16) Swamy, K. C. K.; Chandrasekhar, V.; Harland, J. J.; Holmes, J. M.; Day, R. O.; Holmes, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 2341−2348.

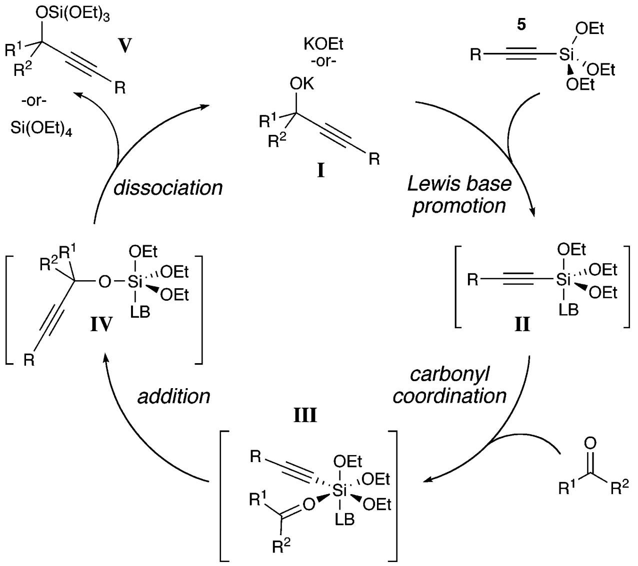
trialkoxysilylalkyne in a manner similar to KOEt. To probe this product-activation possibility, the potassium salt of propargyl alcohol **6** was added (10 mol %) to silylalkyne **5a** and benzaldehyde (Scheme 1). Interestingly, propargyl alcohol **14** is isolated in good yield after aqueous workup (74%).

Scheme 1



Drawing from the data observed in both Figure 1 and Scheme 1, we propose a plausible mechanistic description of this reaction involving Lewis base initiation of an autocatalytic cycle (Scheme 2). The addition of a Lewis base to **5** would lead to formation of a pentavalent silicon intermediate **II**, which could mediate the transfer of an alkynyl nucleophile via hexacoordinate organization (**III**).

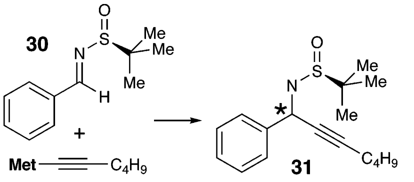
Scheme 2



The resulting silated alkyne-addition product (**IV**) could dissociate, leading to generation of alkoxide base **I**, thereby perpetuating the reaction. Further evidence for self-promotion was the direct observation of **V** by gas chromotography under catalytic reaction conditions.[17] A mechanism involving self-promotion is also supported by the necessity of crown ether for catalytic turnover in the addition to ketones, where a more sterically congested tertiary propargyl alkoxide (**I**) is generated.[15]

The unique properties and synthetic potential of these trialkoxysilylalkynes can be observed in the formation of secondary propargylamines[18] (Scheme 3). The combination of **5a** and *tert*-butylsulfinyl imine **30**[19] affords alkyne **31** in exceptional yield (95%) with high selectivity (20:1) favoring the (S_S,R) diastereomer. Surprisingly, alternative alkynyl organometallic nucleophiles are either less selective (Met = K) or prefer the *opposite* stereoisomer (Met = Li or MgEt).[11]

Scheme 3



Met	dr (*R:S*)	yield
MgEt	1:3	74%
Li	1:7	99%
K	2:1	30%
Si(OEt)$_3$	**20:1**	**95%**

In conclusion, we have reported an efficient nucleophile-catalyzed addition reaction of alkynes. This new strategy utilizes trialkoxysilylalkynes as stable nucleophile precursors with preliminary mechanistic data implicating a hypervalent organosilane as the active reagent. The new alkynyl species accessed by the addition of a Lewis base possess reactivity to undergo smooth, and in some cases highly selective, additions to aldehydes, ketones, and imines. Mechanistic investigations and applications of this Lewis base-catalyzed strategy based on trialkoxyorganosilane activation are currently underway.

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

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[17] Generation of **V** is not observed in the presence of stoichiometric amounts of potassium ethoxide.

[18] Asymmetric alkyne additions to imines: (a) Gommermann, N.; Knochel, P. *Chem. Commun.* **2004**, 2324−2325. (b) Fassler, R.; Frantz, D. E.; Oetiker, J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3054−3056. (c) Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 3273−3275.

[19] Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984−995.