The first direct coupling of 1-trialkylsilyl-1-alkynes with vinyl triflates; a new access to enynes

Ulla Halbes, Philippe Bertus[†] and Patrick Pale*

Laboratoire de synthèse et réactivité organique, associé au CNRS, Institut Le Bel, Université L. Pasteur,
67000 Strasbourg, France

Abstract—1-Trialkylsilyl-1-alkynes can be directly coupled with vinyl triflates in the presence of TBAF, 3H₂O and a catalytic amount of AgI and Pd(PPh₃)₄. Functionalized enynes can thus be obtained in good to excellent yields without prior deprotection of the alkyne. © 2001 Published by Elsevier Science Ltd.

Enynes constitute an important class of compounds. They can be found in various living organisms, mainly higher plants, algae and sponges, and microorganisms,[1–3] where they usually play a defensive role. For example, the so-called enediyne and dienediyne antitumor antibiotics are among the most complex natural products so far isolated.[4] The enyne unit can also be found in man-made compounds designed for various applications in material science.[5]

Enynes are readily obtained either by addition of metal acetylides to aldehydes or ketones followed by elimination, or by coupling alkynes with vinyl halides or triflates, the so-called Sonogashira–Linstrumelle (S–L) reaction.[6] Due to its stereoselectivity, the latter process has gained a wide audience. For the synthesis of complex enyne molecules, the starting alkynes are usually obtained as 1-trialkylsilyl derivatives. A S–L coupling therefore requires a further deprotection step. It obviously would be interesting and economical to be able to directly engage 1-trialkylsilyl-1-alkynes in coupling reactions.

We present here a mild and really convenient method for the direct coupling of 1-trialkylsilyl-1-alkynes with vinyl triflates (Scheme 1). It is worth noting that this is the *first* method allowing the direct coupling of *any* 1-trialkylsilyl acetylenes (R₃Si = SiMe₃, SiMe₂tBu, SiPh₂tBu, SiiPr₃).

The coupling of vinyl or aryl silyl derivatives has been described. However, such reactions required an activated silyl group in order to proceed. Fluoro-, chloro- or alkoxysilyl groups have thus been used.[7] This drawback has probably hampered the development of those methods. Moreover, these reactions required a Pd^{II} source as catalyst, they are thus more related to Heck reaction rather than to S–L reaction and indeed require rather harsh conditions.

We recently showed that silver iodide and tetrakis(triphenylphosphine)palladium are efficient catalysts for the coupling of sensitive vinyl triflates and acetylenes.[8] We thought that the fluorosilicates[9] in situ formed by addition of fluoride to 1-trialkylsilyl-1-alkynes would enter the palladium catalytic cycle initiated by oxidative addition of vinyl triflate to zerovalent palladium. Silver ion would facilitate this process by displacing the fluorosilicate group, leading trialkylsilyl fluoride and silver acetylide, known to enter the Pd-catalytic
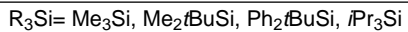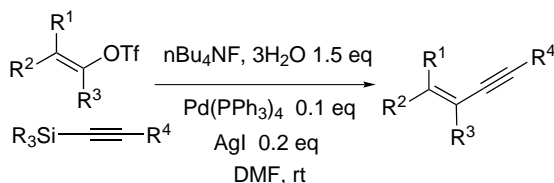
Scheme 1.

cycle.[10] Moreover, since silver acetylides can be formed in water,[11] the convenient and commercially available tetrabutyl ammonium fluoride trihydrate (TBAF, $3H_2O$) should be used without deleterious effect. Such a mechanism should also operate with any 1-trialkylsilyl-1-alkynes (Scheme 2).

We therefore investigated the coupling reaction of various 1-trialkylsilyl-1-alkynes with *tert*butylcyclohexenyl triflate **1**,[12] used as a model, in the presence of TBAF, $3H_2O$ and a catalytic amount of AgI and $Pd(PPh_3)_4$. The results obtained are collected in Tables 1–3.

1-Hexynes **2a–d** bearing a common trialkylsilyl group of increasing bulkiness were prepared by trapping 1-lithio-1-hexyne with the corresponding trialkylsilyl chloride.[13] 1-Trimethylsilyl- (TMS)-, *tert*butyldimethylsilyl (TBS)-, *tert*butyldiphenylsilyl (TBDPS)-, 1-tri*iso*propylsilyl (TIPS)-1-hexyne, **2a–d** respectively, were cleanly converted to the expected enyne **3**[8c,14] by treatment with 1.5 equivalent of TBAF, $3H_2O$, 0.2 equivalent of AgI and 0.1 equivalent of $Pd(PPh_3)_4$ in DMF. While the TMS derivative **2a** was totally consumed within a day (Table 1, entry 1 versus 2, 3, 4), the bulkier derivatives **2b–d** were not completely converted during the same period of time as reflected by lower yields and longer reaction times (prolonged reaction times did not significantly improved yields of coupling product). The bulkiness around the silyl atom thus seems to slightly affect the reaction rate.

Encouraged by these results, we prepared[13] 1-trialkylsilyl-1,3-enynes and 1-trialkylsilyl-3,4-epoxy-1-alkynes with synthetic application in mind,[15] and submitted them to the above conditions (Tables 2 and 3).
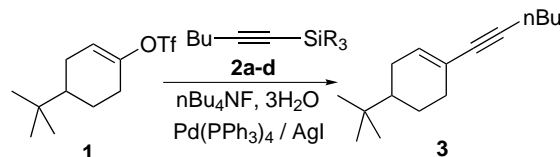
The coupling of 1-trialkylsilyl-3-methylbut-3-en-1-ynes, **4a–c**, proved to be very efficient (Table 2). The expected dienyne **5** was always isolated in quantitative yield whatever the silyl substitution.

1-Trialkylsilyl-3,4-epoxy-5-hydroxy-3-methyl-1-pentyne **6a–c**[8b,c] cleanly reacted in the above conditions, and the corresponding epoxyenyne **7**[8c,16] was isolated in fairly good yield (Table 3). As expected from our previous results,[8] such conjugated epoxyalkynes were slightly less effective in coupling reaction than less sensitive alkynes

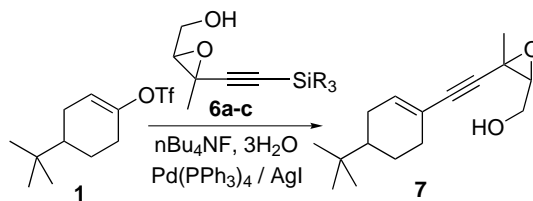**Table 1.** TBAF, $3H_2O$-promoted coupling of 1-trialkylsilyl-1-hexynes **2** in the presence of AgI

Entry		SiR_3	Time (h)	Yield (%)
1	**2a**	Me_3Si-	21	87
2	**2b**	Me_2tBuSi–	24	84
3	**2c**	Ph_2tBuSi–	24	75
4	**2d**	iPr$_3$Si–	24	75

Table 2. TBAF, $3H_2O$-promoted coupling of 1-trialkylsilyl-3-methylbut-3-en-1-ynes **4** in the presence of AgI
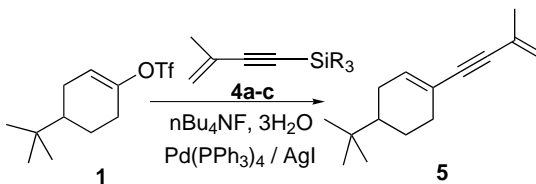
Entry		SiR_3	Time (h)	Yield (%)
1	**4a**	Me_3Si-	18	99
2	**4b**	Me_2tBuSi–	18	99
3	**4c**	Ph_2tBuSi–	18	99

Table 3. TBAF, $3H_2O$-promoted coupling of 1-trialkylsilyl-3,4-epoxy-1-alkynes **6** in the presence of AgI

Entry		SiR_3	Time (h)	Yield (%)
1	**6a**	Me_3Si-	22	78
2	**6b**	Me_2tBuSi–	22	67
3	**6c**	Ph_2tBuSi–	22	66

Scheme 2. Mechanistic hypothesis for a Pd/Ag-catalyzed coupling of 1-trialkylsilyl-1-alkynes promoted by TBAF, $3H_2O$.

(Table 3 versus Tables 1 and 2). Nevertheless, the fragile epoxyenyne moiety can easily and conveniently be obtained in high yield owing to the mildness of the present method. In this case, as in the case of **2a–d**, the bulkiness at the silyl group plays a significant role, lowering the yield of coupling product (entries 2 and 3 versus 1). It is also worth mentioning that no protecting group was required for the hydroxyl group in **6a–c**. No side reaction was detected despite the concomitant presence of a free alcohol and an acetylenic function.[16]
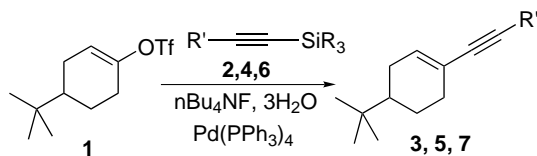
Control experiments exhibited unexpected results. Indeed, experiments run without silver cocatalyst surprisingly yielded the enynes **3**, **5** and **7** although less efficiently (Table 4). Under these conditions, the coupling efficiency is clearly related to the structure of the alkyne partner. However, the nature of the silyl group carried by the alkyne, and most probably its size, seems to be critical, dramatically reducing yields (entries 2, 4 and 6 versus 1, 3 and 5). For the sensitive trialkylsilyl-epoxyalkynes **6**, the presence of silver salt is always critical, whatever the nature of the silyl group, in order to achieve a efficient coupling (Table 4, entries 5 and 6 versus Table 3, entries 1 and 3). These preliminary results raise interesting mechanistic questions, which are now addressed.

In conclusion, functionalized enynes can be easily obtained by a new fluoride-mediated coupling reaction directly from their 1-trialkylsilyl-1-alkynes progenitors. Further synthetic developments are underway in our group.

Supplementary material

Typical procedure for the fluoride-induced coupling reaction of 1-trialkylsilyl-1-alkynes with vinyl triflate: To a triflate (1 equiv.) solution in anhydrous DMF (0.17 M) were successively added under an argon atmosphere tetrakis(triphenylphosphine)palladium (0.1 equiv.), silver iodide (0.2 equiv.) and 1-trialkylsilyl-1-alkyne (1.1 equiv.) diluted in anhydrous DMF (0.27 M). The resulting mixture was then stirred for 5 min

and a solution of tetrabutylammonium fluoride trihydrate (1.5 equiv.) in anhydrous DMF (0.15 M) was added. Once one of the starting materials disappeared, diethyl ether (10 mL) and then water (10 mL) were added. The mixture was then filtered over Celite and the phases were separated. The aqueous layer was extracted three times with diethyl ether and the combined organic layers were washed three times with water to remove DMF. The organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography yielding the expected pure enyne.

References

1. Christensen, L. P.; Lam, J. *Phytochemistry* **1991**, *30*, 11 and *Phytochemistry* **1990**, *29*, 2753.
2. (a) Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155–198; (b) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 7–55.
3. Bohlmann, F.; Burkhardt, T.; Zdero, C. *Naturally Occurring Acetylenes*; Academic Press: New York, 1973.
4. For an overview of the biological as well as chemical aspects, see: Nicolaou, K. C.; Smith, A. L. In *Modern Acetylene Chemistry*; Stang, P. J.; Diederich, F., Eds.; VCH: Weinheim, 1995; pp. 203–283. For reviews dealing with the synthesis of such enynes, see: Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453–6518; Lhermitte, H.; Grierson, D. S. Parts 1 & 2, *Contemporary Organic Synthesis* **1996**, 41–63 and 93–124.
5. *Modern Acetylene Chemistry*; Stang, P. J.; Diederich, F., Eds.; VCH: Weinheim, 1995.
6. (a) Sonogashira, K. In *Comprehensive Organic Chemistry*; Fleming, I.; Trost, B. M., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp. 521–549; (b) Farina, V. In *Comprehensive Organometallic Chemistry II*; Abel, E. W.; Stone, F. G. A.; Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, pp. 222–225.
7. (a) Horn, K. *Chem. Rev.* **1995**, *95*, 1317–1350; (b) Hiyama, T. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley: Weinheim, 1997; pp. 421–453.
8. (a) Bertus, P.; Pale, P. *Tetrahedron Lett.* **1996**, *37*, 2019–2022; (b) Bertus, P.; Pale, P. *Tetrahedron Lett.* **1997**, *38*, 8193–8196; (c) Bertus, P.; Pale, P. *J. Organomet. Chem.* **1998**, *567*, 173–180.
9. Pentacoordinated silanes bearing a vinyl or aryl group have been postulated as intermediates in a few coupling reactions. See: Kumada, M. *Tetrahedron Lett.* **1978**, *19*, 2161–2164; Hiyama, T.; Hatanaka, Y. *Pure Appl. Chem.* **1994**, *66*, 1471–1478; see also Ref. 7.

Table 4. TBAF, $3H_2O$-promoted coupling of 1-trialkylsilyl-1-alkynes without AgI

Entry	Alkyne	SiR_3	Time (h)	Yield (%)
1	**2a**	Me_3Si-	24	85
2	**2c**	$Ph_2tBuSi-$	24	26
3	**4a**	Me_3Si-	18	68
4	**4c**	$Ph_2tBuSi-$	18	31
5	**6a**	Me_3Si-	22	30
6	**6c**	$Ph_2tBuSi-$	22	15

10. Dillinger, S.; Bertus, P.; Pale, P. *Org. Lett.* **2001**, *3*, 1661–1664.
11. Davis, R. B.; Scheiber, D. H. *J. Am. Chem. Soc.* **1956**, *78*, 1675–1678.
12. Scott, W. J.; Crisp, G. T.; Stille, J. K. *Org. Synth.* **1993**, coll. vol. VIII, 97–103.
13. Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988; Winterfeldt, E. In *Modern Synthetic Methods*; Scheffold, R., Ed.; VCH: Weinheim, 1992; Vol. 6, pp. 103–226.
14. Scott, W. J.; Peña, M. R.; Swärd, K.; Stoessel, S. J.; Stille, J. K. *J. Org. Chem.* **1985**, *50*, 2302–2308.
15. The corresponding dienynes and epoxyenynes could find use, respectively, in material science and as antitumor antibiotic models.
16. Pale, P.; Chuche, J. *Eur. J. Org. Chem.* **2000**, 1019–1025.