



A new mild procedure for the direct coupling of 1-trimethylsilyl acetylenes with vinyl triflates or aryl iodide

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Abstract—1-Trimethylsilyl acetylenes can be directly coupled with vinyl triflates or aryl iodide in the presence of the appropriate amount of potassium carbonate and methanol and a catalytic amount of AgCl and Pd(PPh₃)₄. Functionalized enynes can thus be obtained in good to excellent yields without prior deprotection of the alkyne. © 2002 Elsevier Science Ltd. All rights reserved.

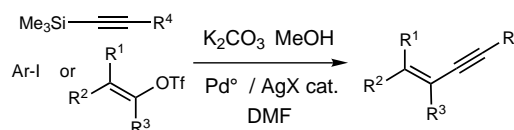
The rapid construction of a polyunsaturated system is of prime importance for material science as well as natural products chemistry. The elaboration of regular arrays of triple and double bonds is indeed often required since such units are used as core or building blocks for complex materials.^{1,2} Conjugated enyne units are often encountered in various natural products, most of them exhibiting potent biological activities.^{3,4}

Due to synthetic planning, an acetylene group often ends up in multifunctional molecules as a trimethylsilyl alkyne.⁵ Therefore, a deprotection step is required for a subsequent coupling reaction. From a practical as well as economical point of view, it would be interesting to avoid the deprotection step and to be able to directly couple 1-trimethylsilyl-1-alkynes with activated alkenes. To achieve that goal, we recently proposed a method^{6d} based on the concomitant use of *n*Bu₄NF·3H₂O and Pd(PPh₃)₄ and AgI as catalysts. However, this method cannot be applied to compounds bearing other silyl groups without deprotecting them. To circumvent this problem and enrich the panoply of synthetic tools, we developed another route to perform such direct coupling (Scheme 1).

One of the mildest methods to regenerate terminal acetylenes from trimethylsilyl acetylenes uses a mixture of potassium carbonate in methanol. In this deprotection, the cleavage of the C–Si bond probably results

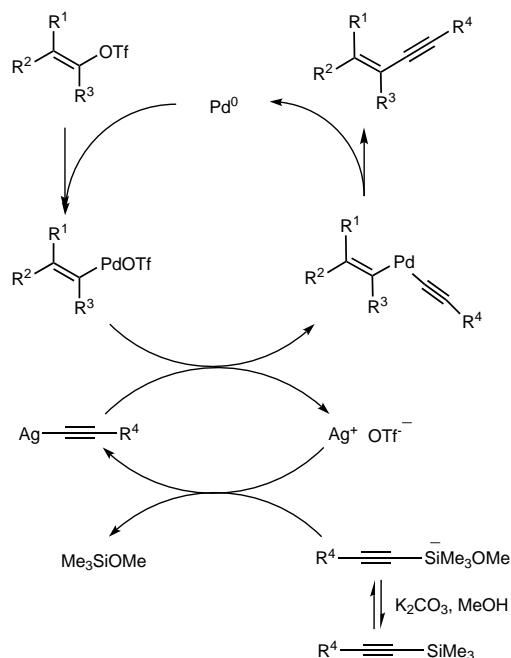
from a nucleophilic attack of in situ formed methylate ion to the silicon atom. Based on this mechanism and some of our recent results,^{6,7} we reasoned that the silicate in situ formed by addition of methylate to 1-trimethylsilyl alkynes should be displaced⁸ by the more electropositive silver ion, the release of volatile methoxytrimethylsilane would favor this process. As we demonstrated that silver acetylides are able to enter the palladium catalytic cycle,⁷ silver ion would therefore be released, allowing for another catalytic cycle, involving silver ion, to take place (Scheme 2). Since silver acetylides are efficiently prepared in protic solvents,^{7,9} and since Pd-catalyzed cross-coupling can be performed in aqueous medium,¹⁰ running the coupling reaction in methanol or in the presence of methanol would not be a problem.

In order to check the above assumptions and to find the more appropriate conditions, 4-*tert*-butylcyclohexenyl triflate **1**¹¹ and 1-trimethylsilyl hex-1-yne **2a** were first stirred in DMF together with various amounts of potassium carbonate and methanol in the presence of catalytic amounts of silver salt and tetrakis(triphenylphosphine) palladium (Scheme 3 and Table 1).

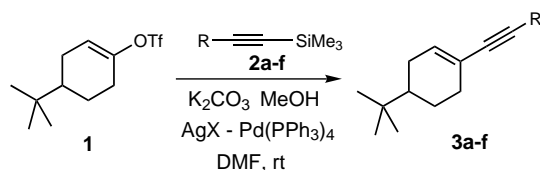


Scheme 1.

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Scheme 2. Mechanistic hypothesis for a Pd/Ag-catalyzed coupling of 1-trimethylsilylalkynes.



Scheme 3.

We were pleased to observe the formation of the expected enyne **3a**.⁶ However, the coupling yield was dramatically influenced by the amount of potassium carbonate and methanol added to the reaction mixture (Table 1, entries 1–5). Less than 4 equiv. of each reagent in DMF gave around 50% of conversion and thus a modest overall yield of the expected coupling product after purification (Table 1, entries 1–3). From some of our previous results, we anticipated an effect from the nature of silver salt and indeed, the chloride proved more effective as cocatalyst in these conditions than the iodide (entries 2 versus 1, 5 versus 4). How-

ever, the presence of silver ion is critical since no reaction was observed without silver salt whatever the amount of potassium carbonate and methanol added (entries 6, 7). Surprisingly, in the latter conditions, the starting materials were recovered intact, indicating that silver ion may play a role during the desilylation step. Running the reaction in pure methanol or in a 1 to 1 mixture of methanol and DMF was less efficient than doing it in pure DMF with just the required amount of methanol (entries 8 or 9 versus 5). In the latter conditions, **3a** was obtained in quantitative yield (entry 5).

Various representative trimethylsilylated alkynes **2b–f** were then prepared by conventional methods^{12,13} and submitted to the above conditions. The expected coupling products **3b–f** were obtained in good to excellent yields, as shown in Table 2.

The presence of a free hydroxyl group do not impart the efficiency of this coupling as demonstrated by the quantitative coupling of 5-trimethylsilyl-4-pentynol **2b** compared to the coupling of 1-trimethylsilyl-1-hexyne **2a** (entry 2 versus 1). However, if such functional group is adjacent to the triple bond, a decrease in yield is observed (entries 3, 4 versus 2). The electronic influence of this functional group may be responsible for the observed effect, and the presence of a second group which also exhibits an electronic influence proved to markedly diminish the yield (entry 4 versus 3). In the latter case, the yield is nevertheless good and comparable with those obtained through the common two-step sequence usually required. Interestingly, really conjugated 1-trimethylsilyl-1-alkynes, with or without hydroxyl group, **2f** or **2e**, respectively, gave the corresponding dienynes in very good yield (entries 5, 6).

More complex vinyl triflates can also be involved in this coupling reaction. Conjugated vinyl triflates proved to be good partners and, as an example, the triflate derived from tetralone **8** was reacted with 1-trimethylsilyl hex-1-yne **2a** and 5-trimethylsilyl-4-pentynol **2b**, providing the corresponding enynes **9a–b** in excellent yields (Scheme 4). Aryl iodide could also be engaged in this new coupling reaction. They however required a slight heating (40°C instead of rt) and a further increase of reagents (K_2CO_3 , MeOH 8 equiv. each) to undergo an efficient coupling, as illustrated with the coupling of


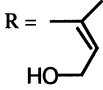
Table 1. Coupling of **1** and 1-trimethylsilyl-1-hexyne **2a** in the presence of $Pd(PPh_3)_4$ (0.1 equiv.) and AgX (0.2 equiv.)

Entry	AgX	K_2CO_3 (equiv.)	MeOH	DMF (mM)	Yield ^b of 3a
1	AgI	1.2	1.2 equiv.	33 ^a	23
2	AgCl	1.2	1.2 equiv.	33	46
3	AgCl	2	2 equiv.	33	42
4	AgI	4	4 equiv.	33	39
5	AgCl	4	4 equiv.	33	99
6	–	2	2 equiv.	33	0
7	–	4	4 equiv.	33	0
8	AgCl	4	33 mM ^a	–	72
9	AgCl	4	16.5 mM ^a	16.5 ^a	84

^a Concentration relative to the triflate.

^b Yield of isolated pure product.

Table 2. Coupling of **1** with various 1-trimethylsilyl-1-alkynes **2b–f**

Entry	Alkyne		Time (h)	Yield (%) ^a	Product
1	R = <i>n</i> Bu	2a	20	99	3a
2	R = -(CH ₂) ₃ OH	2b	19	99	3b
3	R = -C(CH ₃) ₂ OH	2c	23	78	3c
4	R = -CH(Ph)OH	2d	22	56	3d
5		2e	15	89	3e
	R = 				
6		2f	25	76	3f
	R = 				

^a Yield of isolated pure product.

phenyl iodide and **2a** or **2b** (Scheme 5). The expected 1-phenyl-1-alkynes **10a–b**¹⁴ were obtained with good yields in these conditions.

In conclusion, we demonstrated here that 1-trimethylsilyl-1-alkynes can be directly coupled to vinyl triflates or aryl iodide in the presence of potassium carbonate, methanol and with tetrakis(triphenylphosphine)-palladium and silver salt as catalysts. Various enynes have thus been conveniently obtained in good to excellent yields in a single step avoiding a preliminary deprotection step. Further works in this area are now in progress.

Typical procedure for the methylate-induced coupling reaction of 1-trimethylsilyl-1-alkynes with vinyl triflate

To a triflate (1 equiv.) solution in anhydrous and degassed DMF were successively added under argon tetrakis(triphenylphosphine) palladium (0.1 equiv.), silver chloride (0.2 equiv.), potassium carbonate (4 equiv.) The resulting mixture was then stirred for 5 min and methanol (4 equiv.) was added followed by 1-trimethylsilyl-1-alkyne (1.1 equiv.) diluted in anhydrous DMF (0.27 M). Once one of the starting materials disappeared, diethylether (10 mL) then water (10 mL) were added. After filtration over Celite and phases separation, the aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed three

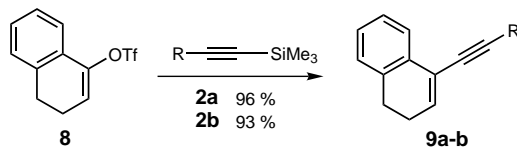
times with water to remove DMF, dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography using the appropriate mixture of hexane and ethyl acetate yielding the corresponding pure enyne.

Acknowledgements

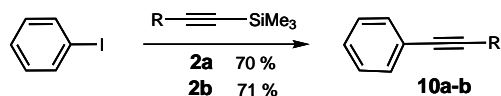
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Scheme 4. Reagents and conditions: see Table 1, entry 5.



Scheme 5. Reagents and conditions: 8 equiv. K₂CO₃, 8 equiv. MeOH, 0.1 equiv. Pd(PPh₃)₄, 0.2 equiv. AgCl, DMF, 40°C.

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