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Palladium mediated direct coupling of silylated arylalkynes with propargylic chlorides: an efficient access to functionalized conjugated allenynes

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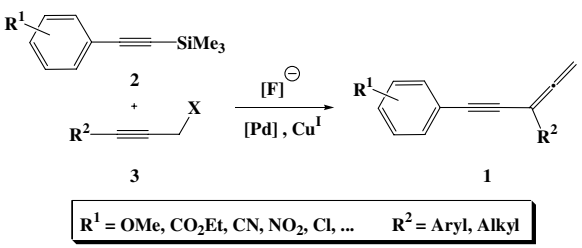
Abstract—Pd/Cu-catalyzed one-pot reaction of 1-trimethylsilyl-2-arylalkynes with propargylic chlorides in the presence of TBAF is described. The present new procedure is applicable to a wide range of silylated arylalkynes with both electron-withdrawing and electron-donating substituents. Functionalized allenynes can thus be obtained in good yields without prior deprotection of the alkynes.

In the course of a program devoted to the stereo- and regioselective addition of metalloid hydrides to unsymmetrical alkynes including arylalkynes[1] and enynes,[2] we were interested to prepare effectively aryl allenynes **1** bearing various substituents on the aromatic ring. A survey of the literature revealed that few methods for the preparation of this class of compounds have been developed. Among various routes,[3] the Pd/Cu-catalyzed reaction of terminal alkynes with either allenyl bromides,[4] or propargylic species including carbonates,[5] halides, tosylates, and acetates[6] is the most popular and attractive method. However, the described procedures are only based on the coupling with available terminal alkylalkynes or with phenylacetylene. On the contrary, functionalized terminal arylalkynes have not been investigated in these Pd-catalyzed reactions, probably because their preparation required, from aryl halides, Sonogashira coupling[7] with trimethylsilylacetylene followed by a desilylation step. Moreover, such terminal alkynes are sensitive substrates when bearing an electron-withdrawing substituent (CN, NO_2, CF_3, ...) on the aromatic ring.[8] It obviously would be interesting and economical to be able to engage functionalized trimethylsilylalkynes **2** in these coupling reactions. Although the coupling of trimethylsilylalkynes with vinyl and aryl halides is well-known,[9] to our knowledge, nothing is described on their coupling with propargylic halides. We present in this communication, a mild and convenient one-pot procedure for the direct coupling of 1-trimethylsilyl-2-arylalkynes **2** with propargylic chlorides **3** to provide efficiently conjugated allenynes **1** (Scheme 1).

We have studied the reaction of arylalkyne **2a** as a model substrate with propargylic species **3** and the results are summarized in Table 1. Preliminary experiments have been carried out using Linstrumelle's method,[6] with silylated alkyne **2a** (1.2 equiv), propargylic chloride **3** (1 equiv), TEA (1.5 equiv), and TBAF (1 equiv) in DMF at room temperature. Under these conditions, the reaction afforded moderate yields of allenyne **1a**



Scheme 1.

Keywords: Palladium; Coupling; Allenynes; Silylated alkynes; Propargylic chlorides.
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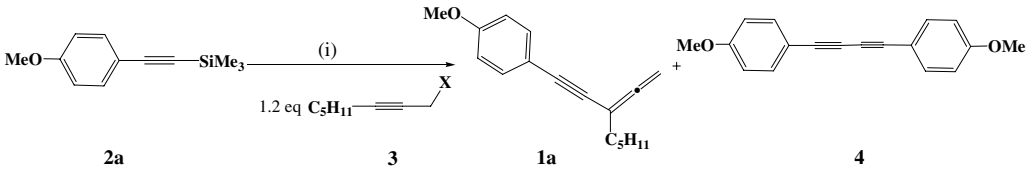
Table 1. Pd/Cu-catalyzed coupling reaction of silylated arylalkyne **2a** with propargylic compounds **3**: synthesis of **1a**



2a **3** **1a** **4**

(i) 0.05 eq [Pd], 1 eq [Cu^I], 1 eq [F^-], Base, DMF, 20 °C, time

Entry	Base	[F^-]	[Pd]	[Cu^I]	X	Time (h)	Conv.[a] (%)	**1a/4**	Yield[b] of **1a** (%)
1	TEA	TBAF	$PdCl_2(PPh_3)_2$	CuI	Cl	3	100	72/28	44
2	K_2CO_3	TBAF	$PdCl_2(PPh_3)_2$	CuI	Cl	2	100	70/30	48
3	TBAF	CsF	$PdCl_2(PPh_3)_2$	CuI	Cl	6	66	75/25	nd
4	TBAF	KF	$PdCl_2(PPh_3)_2$	CuI	Cl	72	72	29/71	nd
5	TBAF	LiF	$PdCl_2(PPh_3)_2$	CuI	Cl	96	50	0/100	0
6	None	TBAF	$PdCl_2(PPh_3)_2$	CuI[c]	Cl	1	100	91/9	66
7	None	TBAF	$Pd(PPh_3)_4$	CuI	Cl	1	100	90/10	58
8	None	TBAF	$Pd(dba)_2 + 2PPh_3$	CuI	Cl	1	100	56/44	26
9	None	TBAF	$PdCl_2(PPh_3)_2$	CuCl	Cl	24	100	55/45	23
10	None	TBAF	$PdCl_2(PPh_3)_2$	CuBr	Cl	24	75	33/67	nd
11	None	TBAF	$PdCl_2(PPh_3)_2$	CuCN	Cl	5	13	66/34	nd
12	None	TBAF	$PdCl_2(PPh_3)_2$	CuTC[d]	Cl	1	100	45/55	19
13	None	TBAF	$PdCl_2(PPh_3)_2$	CuI	OAc	3.5	100	0/100	0
14	None	TBAF	$PdCl_2(PPh_3)_2$	CuI	$OPO(OEt)_2$	2	67	86/14	nd
15	None	TBAF	$PdCl_2(PPh_3)_2$	CuI	OTs	1.75	100	80/20	45
16	None	TBAF	$PdCl_2(PPh_3)_2$	CuI	Br	1.5	95	80/20	nd

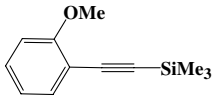
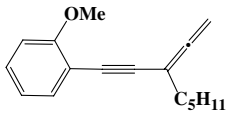
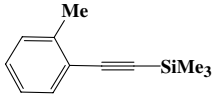
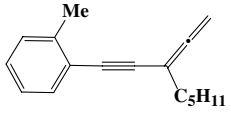
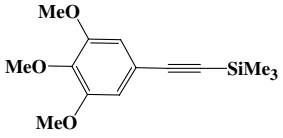
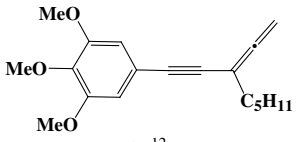
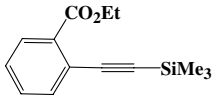
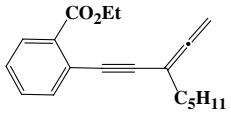
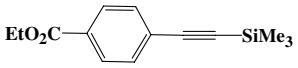
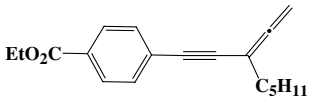
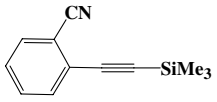
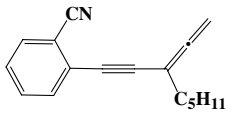
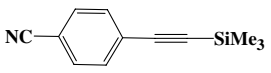
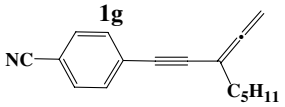
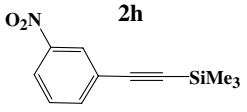
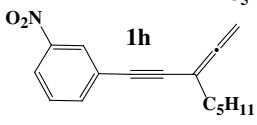
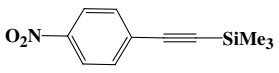
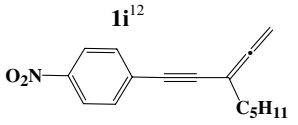
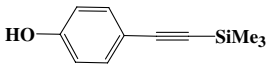
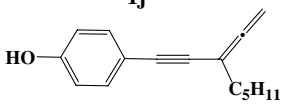
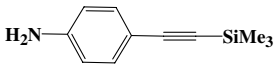
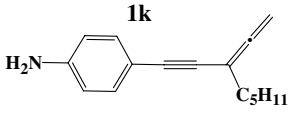
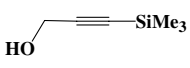
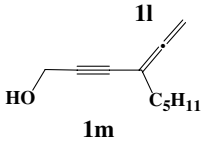
[a] The conversion was measured by ^1H NMR analysis and is based on terminal alkyne.
[b] Isolated yield.
[c] When the reaction was carried out for 1 h with 0.1 equiv of CuI a mixture of terminal alkyne/**1a/4** was obtained in the ratio 44/19/37. With 1.5 equiv of CuI, the ratio became 14/79/7.
[d] Copper(I) thiophene-2-carboxylate.

together with significant amounts of the homocoupling diyne **4**[10] easily separated by flash column chromatography. The ratio **2a/3** was examined to decrease the yield of by-product **4** and after optimization it was reversed and fixed to 1/1.2. Accordingly, the coupling reaction afforded a mixture of **1a/4** in a 72/28 ratio (entry 1). Replacing TEA by a mineral base (K_2CO_3), resulted in a similar ratio but in a shorter reaction time (2 h, entry 2). The nature of the fluorine source was next investigated and we found that CsF too was effective but less reactive than TBAF (entry 3). On the contrary, the reaction provided poor yields with KF and it failed completely with LiF (entries 4 and 5). Seeing that the nature of the base had apparently no effect, we have carried out an attempt without any base and we were pleased to observe a complete conversion of the starting material **2a** within 1 h and allenyne **1a** was isolated in a 66% yield (entry 6). Under these experimental conditions no skipped diyne resulting from a formal S_N2 was observed. In order to avoid the formation of the diyne by-product **4**, Pd(0) catalysts ($Pd(PPh_3)_4$, $Pd(dba)_2 + 2PPh_3$) were evaluated in this coupling but did not give better results (entries 7 and 8) indicating that diyne **4** did not result only from the reduction of the catalyst (Pd(II)→Pd(0)). Because Pd(0) catalysts had to be stored under argon and are more expensive than $PdCl_2(PPh_3)_2$ we have carried on this study with this catalyst and tested the influence of various Cu(I) salts (entries 9–12). Unfortunately, longer reaction times, by comparison with CuI, were required and as a probable consequence, the quantity of by-product diyne **4** was increased (entries 9–12). The role of the leaving group on the propargylic partner was examined in the next set of experiments. Under the previous experimental conditions, propargylic acetate was unreactive (entry 13). Otherwise, tosylate, bromide and phosphonate were effective substrates for the synthesis of **1a** but the reaction proceeded slowly without improvement in the ratio allenyne **1a** versus diyne **4** (entries 14–16). Finally, a number of solvents were investigated in this reaction (dioxane, EtOAc, NMP, toluene, and MeCN), but DMF was found to be the best solvent with regard to reaction time and minimizing the yield of homocoupled by-product **4**.

To demonstrate the versatility of the method, this one-pot reaction was then applied to various substituted arylalkynes and propargylic chlorides. Thus, we screened various substituted silylated arylalkynes **2b–l** and alkynol **2m** for their Pd/Cu-catalyzed coupling with propargylic chlorides and the results are shown in Table 2.

Performing the reaction with variously substituted arylalkynes resulted in the formation of allenynes **1** in good yields. Electron-donating and electron-withdrawing substituents on the aromatic ring did not interfere with the outcome of the present reaction and similar yields were obtained (entries 1–11). Similarly, the results in Table 2 showed that changing the substituent's position on the aromatic ring from para to ortho (entries 4, 5 and 6, 7) or meta to para (entries 8 and 9) did not affect the

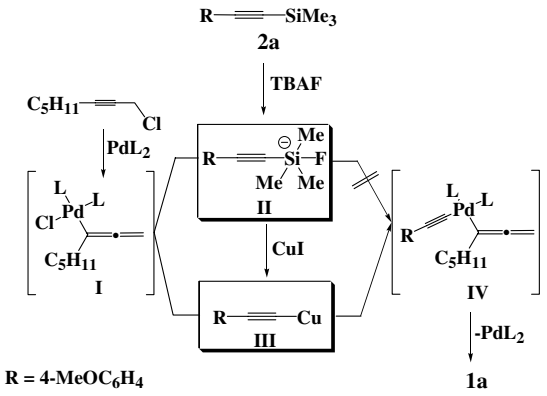
Table 2. Coupling of trimethylsilyl-1-alkynes with propargylic chlorides: synthesis of allenynes **1**

Entry	Alkynes **2**	Allenynes **1**[11]	Yield[a] (%)
1	 **2b**	 **1b**	64
2	 **2c**	 **1c**	67
3	 **2d**	 **1d**[12]	63
4	 **2e**	 **1e**	61
5	 **2f**	 **1f**	59
6	 **2g**	 **1g**	57
7	 **2h**	 **1h**	53
8	 **2i**	 **1i**[12]	60
9	 **2j**	 **1j**[12]	60
10	 **2k**	 **1k**	51
11	 **2l**	 **1l**	53
12	 **2m**	 **1m**	64[b]

Compounds **1d**, **1i**, and **1j**: Ref. 12.

[a] Isolated yield.

[b] Not optimized yield.



Scheme 2.

yield of the reaction. The presence of a free hydroxyl or amino group did not impart the efficiency of this coupling as demonstrated by the coupling of **2k** and **2l** with propargylic chloride **3** (entries 10 and 11). Finally, one cross coupling was successfully attempted between 1-chloro-2-octyne and silylated propargylic alcohol **2m** leading, as expected, to the corresponding allenyne **1m** with a 64% unoptimized isolated yield (entry 12). Thus this result revealed that aliphatic silylated alkynes can also be utilized with yields as good as those from their aromatic counterparts.

From a mechanistic point of view, it is reasonable to think that the reaction proceeded firstly via a σ-allenic palladium complex **I**,[13] which resulted from the oxidative addition of the propargylic chloride to the catalyst (Scheme 2). At this stage, two nucleophilic species could enter the Pd catalytic cycle: a pentacoordinated fluorosilicate **II**[14] resulting from the activation of the silane **2a** by TBAF or, in the presence of CuI, a trans metallated copper acetylide **III**. To define as well as possible the nature of the reactive Nu^- species, we have achieved an experiment without copper iodide. After stirring for 1 h,[15] only 26% of allenyne **1a** was isolated indicating clearly that CuI remarkably improved the reactivity of Nu^-. Consequently, species **IV** certainly resulted through the nucleophilic copper acetylide **III**.

In summary, the Pd/Cu-catalyzed coupling reaction of propargylic chlorides with various silylated alkynes has been achieved in a one-pot procedure in the presence of TBAF. This methodology opens a useful and direct route to a series of allenynes **1** bearing various substituents on the aromatic ring, particularly on the *ortho* position. A variety of substituted aryl allenynes **1** have been prepared according to this very simple procedure and metal-catalyzed hydrometallation of substituted allenynes **1** are currently under progress.

Typical procedure: Under a nitrogen atmosphere, alkyne **2a** (106 mg; 0.52 mmol) was added dropwise at room temperature to a suspension of $PdCl_2(PPh_3)_2$ (18.3 mg; 0.026 mmol), CuI (99 mg; 0.52 mmol), 1-chloro-2-octyne (90 mg; 0.62 mmol), and TBAF (1 N in THF 520 μL; 0.52 mmol) in degassed DMF (2 mL). The initially slightly yellow solution gradually darkened. After 1 h, diethyl ether (5 mL) was added to the reaction mixture, which was filtered over a pad of Celite. The organic layer was washed successively with a saturated NH_4Cl solution twice and with water. After drying over sodium sulfate, filtration, and solvent evaporation, a yellow oil was obtained. Flash chromatography over neutral aluminium oxide provided pure product **1a**[16] as a colorless oil (82 mg; 0.34 mmol; 66%).

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11. Allenynes **1** are sensitive substrates and must be stored under argon at −20 °C.
12. All new compounds allenynes **1** were characterized by ^1H NMR (300 MHz), ^{13}C NMR (75 MHz), and elemental analyses.

Selected data for allenynes: Compound **1d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, $J = 7.0$ Hz), 1.30–1.40 (m, 4H), 1.50–1.60 (m, 2H), 2.15–2.25 (m, 2H), 3.83 (s, 9H), 4.97 (t, 2H, $J = 2.8$ Hz), 6.66 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (CH_3), 22.4 (CH_2), 27.5 (CH_2), 31.1 (CH_2), 33.3 (CH_2), 56.2 (2, OCH_3), 60.9 (OCH_3), 76.8 (CH_2), 83.6 (C), 89.9 (C), 91.4 (C), 108.7 (2CH), 118.6 (C), 138.7 (C), 153.0 (2C), 213.7 (C).

Compound **1i**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 3H, $J = 7.0$ Hz), 1.30–1.40 (m, 4H), 1.50–1.65 (m, 2H), 2.15–2.25 (m, 2H), 5.02 (t, 2H, $J = 2.8$ Hz), 7.47 (t, 1H, $J = 7.8$ Hz), 7.71 (dt, 1H, $J = 7.8$ Hz, $J = 0.9$ Hz), 8.10–8.15 (m, 1H), 8.26 (t, 1H, $J = 1.8$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (CH_3), 22.4 (CH_2), 27.5 (CH_2), 31.1 (CH_2), 33.0 (CH_2), 77.1 (CH_2), 87.6 (C), 88.8 (C), 89.4 (C), 122.6 (CH), 125.4 (C), 126.2 (CH), 129.2 (CH), 137.0 (CH), 148.1 (C), 214.0 (C).

Compound **1j**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 3H, $J = 7.0$ Hz), 1.28–1.40 (m, 4H), 1.50–1.60 (m, 2H), 2.15–2.25 (m, 2H), 5.03 (t, 2H, $J = 2.8$ Hz), 7.55 (d, 2H, $J = 9.0$ Hz), 8.17 (d, 2H, $J = 9.0$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (CH_3), 22.4 (CH_2), 27.5 (CH_2), 31.0 (CH_2), 33.0 (CH_2), 77.2 (CH_2), 89.5 (C), 89.6 (C), 90.5 (C), 123.5 (2CH), 130.5 (C), 132.0 (2CH), 146.8 (C), 214.1 (C).

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15. Without CuI and after stirring for 25 h, the conversion yield based on terminal alkyne was estimated at 45%.
16. Compound **1a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, $J = 6.8$ Hz), 1.30–1.60 (m, 6H), 2.15–2.20 (m, 2H), 3.80 (s, 3H), 4.96 (t, 2H, $J = 3.0$ Hz), 6.83 (d, 2H, $J = 8.8$ Hz), 7.37 (d, 2H, $J = 8.8$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.4 (CH_2), 27.5 (CH_2), 31.1 (CH_2), 33.4 (CH_2), 55.3 (OCH_3), 76.6 (CH_2), 83.1 (C), 90.1 (C), 91.4 (C), 113.9 (2CH), 115.7 (C), 132.8 (2CH), 159.4 (C), 213.6 (C).