DOI: 10.1002/adsc.200606033

Direct Coupling Reactions of Alkynylsilanes Catalyzed by Palladium(II) Chloride and a Di(2-pyridyl)methylamine-Derived Palladium(II) Chloride Complex in Water and in NMP

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Received: January 31, 2006; Accepted: July 6, 2006

Abstract: Symmetrical internal alkynes can be prepared either by diarylation of mono- and bis(trimethylsilyl)acetylene (TMSA and BTMSA) catalyzed by ligand-less palladium(II) chloride or by a di(2-pyridyl)methylamine-derived palladium(II) chloride complex **1** (typical 0.1–1 mol% of Pd loading) in water using pyrrolidine as base and tetra-*n*-butylammonium bromide as additive. Alternatively, this same process is performed in NMP in the presence of tetra-*n*-butylammonium acetate (TBAA) as base with even lower Pd loadings (0.001–1 mol% Pd). The same reaction conditions are applied to the synthesis of unsymmetrical internal alkynes by monoarylation of silylated terminal alkynes. Aryl iodides can be coupled with TMSA, BTMSA and silylated terminal alkynes under heating or at room temperature, whereas for aryl bromides couplings are performed under water reflux or at 110 °C in the case of NMP. Complex **1** can be reused during several cycles either in water or in NMP without loss of catalytic activity. These simple reaction conditions allow the preparation of internal alkynes without secondary products, most probably by succesive protiodesilylation-Sonogashira coupling.

Keywords: alkynylation; aryl halides; diarylalkynes; dipyridyl ligands; palladium; trimethylsilylacetylenes

Introduction

Symmetrical and unsymmetrical internal alkynes play an important role as building blocks in many synthetic transformations and are common units of natural products and new materials such as conjugated oligomers and polymers, liquid crystals, non-linear materials, molecular wires, and other engineering materials.[1] The most important strategies for the synthesis of diarylalkynes are based on palladium-catalyzed cross-coupling reactions.[2] In the case of symmetrical alkynes the diarylation of acetylene with aryl iodides under typical Sonogashira conditions (with CuI as co-catalyst) was described.[3] In order to avoid the use of toxic acetylene, which is also difficult to handle in exact amounts, mono- and bis(trimethylsilyl)acetylene (TMSA and BTMSA) are used as acetylene equivalents in the so-called sila-Sonogashira reaction.[4] In this type of sila-Sonogashira reaction a transmetalation from silicon to copper has been proposed when using CuCl as co-catalyst.[5] A sequential Sonogashira reaction with TMSA followed by addition of 40 mol% of water and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) has been recently described by Grieco et al. for the straightforward one-pot synthesis of unsymmetrical alkynes.[6] Oxime-derived palladacycles have been used as catalysts in our group to promote the diarylation of TMSA and BTMSA in the presence of CuI or tetra-*n*-butylammonium bromide (TBAB) as co-catalysts.[7] Copper-free sila-Sonogashira diarylation of TMSA with aryl iodides in the presence of MeONa in methanol has been performed with Pd-$(PPh_3)_4$ as catalyst.[8]

The main advantage of the use of trimethylsilyl-protected terminal alkynes instead of unprotected acetylenes (Sonogashira *versus* sila-Sonogashira reaction) is to suppress the formation of by-products from alkynes, such as diynes and enynes. In addition, the deprotection step can be avoided, thus making the introduction of an alkyne during a synthetic process more simple. There are some protocols for the synthesis of unsymmetrical alkynes from silylated terminal acetylenes with aryl iodides and triflates under copper-free conditions by using other promotes, such as fluorides,[9] and or silver salts.[10] Yang and Nolan have described an efficient coupling of aryl bromides and alkynylsilanes with *in situ* generated palladium carbenes from $Pd(OAc)_2$ (3 mol%) and an imidazoli-

um salt in *N,N*-dimethylacetamide (DMAc) at 80 °C.[11] The same type of coupling has been carried out under microwave heating using $Pd(OAc)_2$ (5 mol %) and tri(*o*-tolyl)phosphine as catalyst in the presence of tetra-*n*-butylammonium chloride (TBAC) in DMF at 100 °C.[12] However, this type of direct coupling with alkynylsilanes has not been performed in neat water.

We have recently described that $PdCl_2$ and the di(2-pyridyl)methylamine-based palladium(II) chloride complexes **1**[13] and **2**[14] (Figure 1) showed high

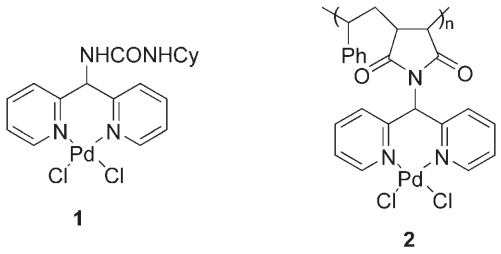


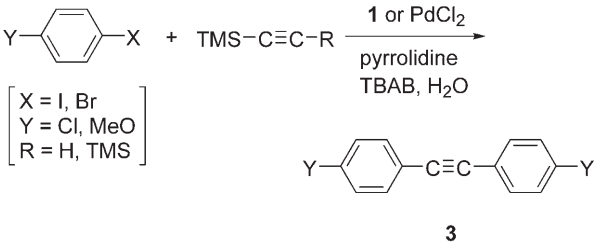
Figure 1. Di(2-pyridyl)methylamine-derived palladium dichloride catalysts.

catalytic activity in Heck, Suzuki, and Sonogashira reactions in water[13,14] and in NMP.[13] In this contribution we report that the palladium complex **1** and also ligand-less $PdCl_2$ can be efficient catalysts in the direct coupling reaction of alkynylsilanes either in water or in NMP for the synthesis of symmetrical and unsymmetrical diarylalkynes.

Results and Discussion

Di- and Monoarylation of Silylated Acetylenes in Water

Symmetrically substituted diarylacetylenes were prepared in a single step by using TMSA and BTMSA as synthetic equivalents of acetylene. For the implementation of this diarylation process in water as solvent, the same reaction conditions established for the arylation of terminal alkynes,[13c] pyrrolidine as base and TBAB as additive, were used. Either TMSA or BTMSA were coupled with representative activated and deactivated aryl iodides and bromides under water reflux by using 1 mol % of di(2-pyridyl)methylamine-derived complex **1** or $PdCl_2$ as catalysts (Scheme 1 and Table 1). Initial studies for the coupling of 4-chloroiodobenzene and TMSA needed 2.5 equivs. of pyrrolidine and 6 h for full conversion (Table 1, entries 1–3), whereas in the case of BTMSA the diarylation took place faster (2 h) with only 1.5 equivs. of pyrrolidine (Table 1, entries 4 and 5) to



Scheme 1. Diarylation of TMSA and BTMSA.

Table 1. Diarylation of TMSA and BTMSA in H_2O.[a]

Entry	X	Y	R	Cat [mol % Pd]	Pyrrolidine [equivs.]	*T* [°C]	Time	No.	Yield [%][b]
1	I	Cl	H	**1** (1)	1.5	100	23 h	**3aa**	81
2	I	Cl	H	**1** (1)	2.5	100	6 h	**3aa**	100 (94)
3	I	Cl	H	$PdCl_2$ (1)	2.5	100	6 h	**3aa**	100
4	I	Cl	TMS	**1** (1)	1.5	100	2 h	**3aa**	83 (76)
5	I	Cl	TMS	$PdCl_2$ (1)	1.5	100	2 h	**3aa**	86
6	I	Cl	TMS	**1** (4)	1.5	25	5 d	**3aa**	74
7	I	Cl	TMS	$PdCl_2$ (4)	1.5	25	5 d	**3aa**	94 (89)
8	I	OMe	H	**1** (1)	2.5	100	5 h	**3bb**	100 (90)
9	I	OMe	H	$PdCl_2$ (1)	2.5	100	8.5 h	**3bb**	100
10	I	OMe	TMS	**1** (1)	1.5	100	6 h	**3bb**	100
11	I	OMe	TMS	$PdCl_2$ (1)	1.5	100	3.5 h	**3bb**	100
12	Br	Cl	TMS	**1** (1)	1.5	100	8.5	**3aa**	80
13	Br	Cl	TMS	$PdCl_2$ (1)	1.5	100	7 h	**3aa**	100[c]
14	Br	OMe	TMS	**1** (1)	1.5	100	8 h	**3bb**	100[c]
15	Br	OMe	TMS	$PdCl_2$ (1)	1.5	100	8 h	**3bb**	100[c]

[a] *Reaction conditions:* aryl halide (1 mmol), TMSA or BTMSA (1.2 mmol), pyrrolidine, TBAB (0.5 mmol), Pd catalyst (see column), H_2O (2 mL), 100 or 25 °C.

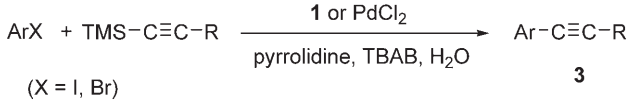
[b] Yield determined by GC based on aryl halide using decane as internal standard. In brackets, isolated yield of compound **3** after flash chromatography.

[c] A 3/1 mixture of compound **3** and silylated alkyne was obtained.

give internal alkyne **3aa** in good yields. Alternatively, the last process could be carried out at room temperature in 5 d by increasing to 4 mol% the loading of Pd (Table 1, entries 6 and 7). When the couplings between 4-chloroiodobenzene and BTMSA (Table 1, entries 4 and 5) were carried out under microwave irradiation at 110 °C (80 W)[15] with both catalysts irreproducible mixtures of diarylated product **3aa** and monoarylated silylated compound were obtained. The use of polymer-supported complex **2** (1 mol% Pd) as catalyst for the reaction between 4-chloroiodobenzene with TMSA and BTMSA (under the same reaction conditions as indicated in Table 1, entries 2 and 4) gave quantitative yields of compound **3aa** in 9 and 7 h, respectively.

Diarylation of TMSA and BTMSA with deactivated 4-methoxyiodobenzene could be performed under similar reaction conditions to activated 4-chloroiodobenzene to provide symmetrical alkyne **3bb** (Table 1, entries 8–11). The experiments were followed by GC showing that the mono- and diarylation were competitive processes. 4-Chloro- and 4-methoxybromobenzene reacted with BTMSA to give mixtures of **3aa** and **3bb**, respectively but also monoarylated silylated alkynes in a *ca.* 3/1 ratio (Table 1, entries 12–15). On the other hand, 4-chlorobromobenzene gave exclusively compound **3aa** when complex **1** was used as catalyst. It can be concluded that BTMSA is a better acetylene equivalent than TMSA for the diarylation reaction in water.

For the synthesis of unsymmetrical internal alkynes in water, different silylated terminal alkynes were arylated under the above-mentioned reaction conditions (Scheme 2 and Table 2). The arylation of 1-phenyl-2-(trimethylsilyl)acetylene with 4-chloroiodobenzene in



Scheme 2. Arylation of silylated terminal alkynes in H_2O.

refluxing water catalyzed by complex **1** or $PdCl_2$ could be accomplished with 1 to 0.01 mol% of Pd achieving 2300 or 1450 turnover number per hour (TOF), respectively, to afford the internal alkyne **3ac** (Table 2, entries 1–5). Alternatively, the reaction could be performed at room temperature in 1 day with 1 mol% loading of catalyst (Table 2, entries 6 and 7). A quantitative yield was also obtained after 1 h by using the polymer-supported complex **2** (0.1 mol% Pd) as catalyst under the reaction conditions indicated in Table 2, entry 3. When this reaction was

Table 2. Arylation of silylated terminal alkynes in H_2O.[a]

Entry	ArX	R	Cat [mol% Pd]	*T* [°C]	Time	No.	Yield [%][b]
1	4-ClC_6H_4I	Ph	**1** (1)	100	1 h	**3ac**	100 (92)
2			$PdCl_2$ (1)	100	1 h	**3ac**	95
3			**1** (0.1)	100	1 h	**3ac**	95
4			**1** (0.01)	100	4 h	**3ac**	92
5			$PdCl_2$ (0.01)	100	6 h	**3ac**	87
6			**1** (1)	25	1 d	**3ac**	96
7			$PdCl_2$ (1)	25	1 d	**3ac**	92
8			**1** (0.5)	110	30 min[c]	**3ac**	85
9		3-Pyridyl	**1** (0.1)	100	4 h	**3ad**	100 (93)
10			$PdCl_2$ (0.1)	100	4 h	**3ad**	100
11		2-Thienyl	**1** (0.1)	100	1.5 h	**3ae**	99 (89)
12			$PdCl_2$ (0.1)	100	1.5 h	**3ae**	88
13		*n*-C_3H_7	**1** (0.1)	100	5.5 h	**3af**	21
14			$PdCl_2$ (0.1)	100	5.5 h	**3af**	19
15			**1** (1)	25	1 d	**3af**	92
16			$PdCl_2$ (1)	25	1 d	**3af**	6
17	4-$MeOC_6H_4I$	Ph	**1** (0.1)	100	2 h	**3bc**	97 (85)
18			$PdCl_2$ (0.1)	100	3 h	**3bc**	94
19	4-ClC_6H_4Br	Ph	**1** (1)	100	3 h	**3ac**	79
20			$PdCl_2$ (1)	100	2 h	**3ac**	66
21	4-$MeOC_6H_4Br$	Ph	**1** (1)	100	8 h	**3bc**	90
22			$PdCl_2$ (1)	100	8 h	**3bc**	71

[a] *Reaction conditions:* aryl halide (1 mmol), silylated alkyne (1.2 mmol), pyrrolidine (1.5 mmol), TBAB (0.5 mmol), Pd catalyst (see column), H_2O (2 mL), 100 or 25 °C.

[b] Yield determined by GC based on aryl halide using decane as internal standard. In brackets, isolated yield of compound **3** after flash chromatography.

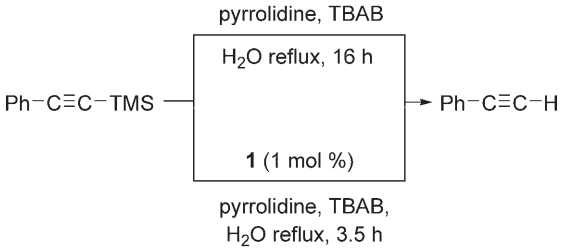
[c] The reaction was performed under microwave irradiation conditions (80 W).

performed under microwave irradiation at 110 °C (80 W)[15] with complex **1** (0.5 mol %), product **3ac** was obtained in 85 % yield after 30 min (Table 2, entry 8).

Other silylated terminal alkynes, such as 3-pyridyl- and 2-thienylacetylene were arylated in similar way with 4-chloroiodobenzene to provide compounds **3ad** and **3ae** in good yields (Table 2, entries 9–12). However, 1-(trimethylsilyl)pent-1-yne gave poor conversions in refluxing water, probably due to protiodesilylation and evaporation of the *in situ* formed pent-1-yne (see below). This problem could be avoided by performing the reaction at room temperature during 1 day with complex **1** as catalyst, affording a 92 % yield of 1-(4-chlorophenyl)pent-1-yne (**3af**), whereas $PdCl_2$ gave only 6 % yield (Table 2, entries 13–16). In the case of the arylation of 1-phenyl-2-(trimethylsilyl)acetylene with deactivated 4-methoxyiodobenzene, product **3bc** was obtained in good yield with both catalysts (Table 2, entries 17 and 18). For the couplings between 1-phenyl-2-(trimethylsilyl)acetylene and 4-chloro- or 4-methoxybromobenzene the loading of Pd was increased to 1 mol % to get compounds **3ac** and **3bc**, respectively, in good yields, complex **1** being a superior catalyst than $PdCl_2$ (Table 2, entries 19–22).

The catalytic activity of complex **1** (1 mol %) was maintained during 4 cycles by succesive addition of the reagents to the reaction, according to the conditions of entry 1 in Table 2 (Scheme 3). After 1 h reaction time each cycle occurred in higher than 95 % yield, with no deactivation of complex **1**.

In order to get a further insight into the reaction mechanism, 1-phenyl-2-(trimethylsilyl)acetylene was treated with 1.5 equivs. of pyrrolidine under water reflux, and the desilylation process took place in 16 h (Scheme 4). However, in the presence of complex **1** (1 mol %) quantitative formation of phenylacetylene was observed after 3.5 h in refluxing water. This observation indicates that the process takes place mainly through a protiodesilylation reaction followed by Sonogashira-type coupling. In order to rule out the transmetalation from silicon to copper, ICP-MS analyses of both reaction media were performed. Traces of copper were found in he Pd desilylation reaction. In the case of catalyst **1** 2.903×10^{-5} mg of copper per mg of complex were found and 2.397×10^{-4} mg of copper in the case of $PdCl_2$. For that reason, a com-



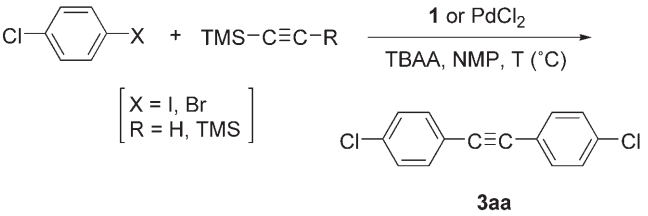
Scheme 4. Desilylation of 1-phenyl-2-(trimethylsilyl)acetylene in H_2O.

petitive process through a transmetalation reaction from silicon to copper cannot be ruled out.

The direct coupling of alkynylsilanes can be performed under water reflux or at room temperature either by using complex **1** or ligand-less $PdCl_2$ as catalysts and pyrrolidine as base in the presence of TBAB as additive by using aryl iodides or bromides in good yields. This methodology allows the synthesis of symmetrical and unsymmetrical internal alkynes.

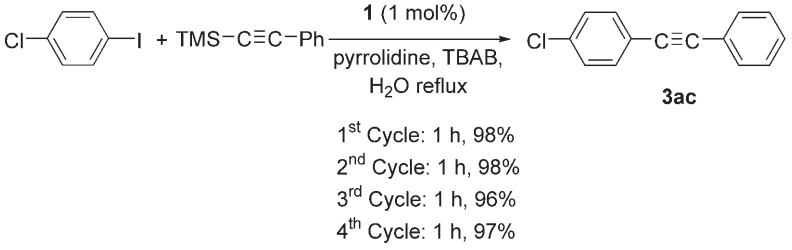
Di- and Monoarylation of Silylated Acetylenes in NMP

Initial studies on the diarylation of TMSA and BTMSA were performed with 4-chloroiodobenzene and complex **1** or $PdCl_2$ as catalysts using TBAA as base in NMP (Scheme 5 and Table 3). These reaction



Scheme 5. Diarylation of TMSA and BTMSA in NMP.

conditions were found to be the most appropriate for the Sonogashira couplings.[7,13c] The diarylation of TMSA was performed with 0.1 mol % of Pd at different temperatures, such as 110, 60 and 40 °C. Full conversion was obtained only at 110 °C with both cata-



Scheme 3. Efficiency of catalyst **1** in the arylation of 1-phenyl-2-(trimethylsilyl)acetylene in H_2O.

Table 3. Diarylation of TMSA and BTMSA with 4-chloroiodobenzene in NMP.[a]

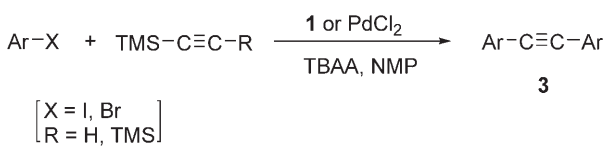
Entry	R	Cat [mol% Pd]	T [°C]	Time	Yield [%][b]	TON	TOF [h^{-1}]
1	H	**1** (0.1)	110	0.5 h	100 (89)	10^3	2×10^3
2	H	$PdCl_2$ (0.1)	110	0.5 h	100	10^3	2×10^3
3	H	**1** (0.1)	60	8 h	60	600	75
4	H	**1** (0.1)	40	8.5 h	13	130	15
5	H	**1** (1)	25	45 h	93	93	2
6	H	$PdCl_2$ (1)	25	17 h	100 (90)	100	6
7	TMS	**1** (0.1)	110	1.5 h	100	10^3	666
8	TMS	$PdCl_2$ (0.1)	110	1.5 h	100	10^3	666
9	TMS	**1** (0.1)	60	8 h	58	580	73
10	TMS	**1** (0.1)	40	8.5 h	20	200	24
11	TMS	**1** (4)	25	48 h	100 (88)	25	0.5
12	TMS	$PdCl_2$ (4)	25	8 h	100	25	3
13	TMS	**1** (0.01)	110	23 h	72	7200	313
14	TMS	$PdCl_2$ (0.01)	110	33 h	5	500	15

[a] *Reaction conditions:* aryl halide (1 mmol), TMSA or BTMSA (1.2 mmol), TBAA (1.5 mmol), Pd catalyst (see column), NMP (2 mL).

[b] Yield determined by GC based on aryl halide using decane as internal standard. In parenthesis, isolated yield of compound **3aa** after flash chromatography.

lysts in 30 min with TOF up to 2000 h^{-1} (Table 3, entries 1–4). For room temperature reactions using complex **1** and $PdCl_2$ as catalysts, the loading of Pd was increased to 1 mol% to get high yields in 45 and 17 h, respectively (Table 3, entries 5 and 6). When these experiments were performed with BTMSA, similar results were obtained although in lower TOFs than with TMSA (Table 3, entries 7–12). The loading of Pd was decreased to 0.01 mol%, complex **1** was the only active species under these reaction conditions to provide compound **3aa** in 72% yield (TOF = 313 h^{-1}) (Table 3, entries 13 and 14).

Diarylation of TMSA and BTMSA was performed with different aryl iodides and bromides in NMP with complex **1** and $PdCl_2$ as catalysts and TBAA as base (Scheme 6 and Table 4). The diarylation with 4-chloroiodobenzene, 4-methoxyiodobenzene, and 1-iodonaphthalene took place more efficiently in the case of TMSA than BTMSA (Table 4, entries 1–14). Both catalysts showed similar efficiency at 110 °C, but at room temperature $PdCl_2$ was more efficient than complex **1**. When the related aryl bromides were allowed to react with TMSA and BTMSA in NMP at 110 °C, a similar loading of Pd (0.1 mol%) was used to that for iodides, but longer reaction times were needed for good conversions (Table 4, entries 15–22). In these couplings TMSA gave also better results than BTMSA.



Scheme 6. Synthesis of symmetrical alkynes by diarylation of TMSA and BTMSA in NMP.

The stability of catalyst **1** in this diarylation reaction was studied for the coupling between 4-chloroiodobenzene and TMSA in NMP at 110 °C with 0.1 mol% of Pd (Scheme 7). The efficiency of complex **1** was maintained during five consecutive cycles of 30 min to give product **3aa** in quantitative yield.

Reaction conditions studies for the arylation of silylated terminal alkynes were performed with silylated phenylacetylene and 4-chloroiodobenzene with complex **1** and $PdCl_2$ as catalysts (Scheme 8 and Table 5). The reaction could be carried out in good yields by using 0.1 mol% of complex **1** at 40, 60 or 110 °C (Table 5, entries 1–3). At 110 °C both catalysts (0.1 mol%) gave full conversion after 15 min with a TOF of 4000 h^{-1} (Table 5, entries 3 and 4). At this temperature, the loading of Pd could be decreased to 0.001 mol% while still getting good yields of product **3ac** in 1 d with a TOF up to 37,500 h^{-1} (Table 5, entries 5 and 6). For the couplings at room temperature increasing the loading of Pd to 1 mol% was necessary in order to perform the reaction in 1 d (Table 5, entries 7–9).

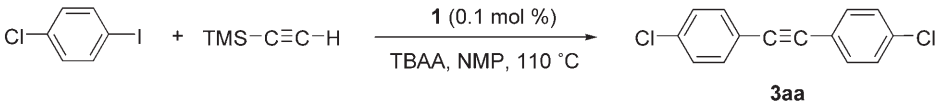
The syntheses of unsymmetrical internal alkynes **3** in NMP were performed with representative activated and deactivated aryl iodides and bromides with different silylated terminal alkynes at 110 °C and with a loading of 0.1 mol% of catalysts (Scheme 9 and Table 6). In the case of 4-chloroiodobenzene, the arylation of different silylated alkynes such as phenylacetylene, 3-pyridylacetylene, 2-thienylacetylene, and pent-1-yne afforded very good yields in short reaction times (15 min to 3.5 h) (Table 6, entries 1–8). Similar behaviour was observed in the couplings of 4-meth-

Table 4. Diarylation of TMSA and BTMSA in NMP.[a]

Entry	ArX	R	Cat [mol% Pd]	*T* [°C]	Time	No.	Yield [%][b]
1	4-ClC_6H_4I	H	**1** (0.1)	110	0.5 h	**3aa**	100 (89)
2		H	$PdCl_2$ (0.1)	110	0.6 h	**3aa**	100
3		H	**1** (1)	25	45 h	**3aa**	93
4		H	$PdCl_2$ (1)	25	17 h	**3aa**	100 (90)
5		TMS	**1** (0.1)	110	1.5 h	**3aa**	100
6		TMS	$PdCl_2$ (1)	110	1.5 h	**3aa**	100
7		TMS	**1** (4)	25	48 h	**3aa**	100 (88)
8		TMS	$PdCl_2$ (4)	25	8 h	**3aa**	100
9	4-$MeOC_6H_4I$	H	**1** (0.1)	110	2 h	**3bb**	90 (79)
10		H	$PdCl_2$ (0.1)	110	2 h	**3bb**	100
11		TMS	**1** (0.1)	110	4 h	**3bb**	100
12		TMS	$PdCl_2$ (0.1)	110	4 h	**3bb**	100
13	1-Iodonaphthalene	H	**1** (0.1)	110	3.5 h	**3cc**	98 (79)
14		TMS	**1** (0.1)	110	1 h	**3cc**	92
15	4-ClC_6H_4Br	H	**1** (0.1)	110	10 h	**3aa**	96
16		H	$PdCl_2$ (0.1)	110	7 h	**3aa**	96
17		TMS	**1** (0.1)	110	5 h	**3aa**	77
18		TMS	$PdCl_2$ (0.1)	110	4 h	**3aa**	60
19	4-$MeOC_6H_4$	H	**1** (0.1)	110	48 h	**3bb**	67 (53)
20		TMS	**1** (0.1)	110	48 h	**3bb**	20
21	1-Bromonaphthalene	H	**1** (0.1)	110	4 h	**3cc**	97
22		TMS	**1** (0.1)	110	4 h	**3cc**	89

[a] *Reaction conditions:* aryl halide (1 mmol), TMSA or BTMSA (1.2 mmol), TBAA (1.5 mmol), Pd catalyst (see column), NMP (2 mL), 110 or 25 °C.

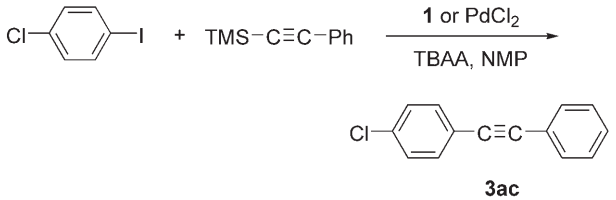
[b] Yield determined by GC based on aryl halide using decane as internal standard. In parenthesis, isolated yield of compound **3** after flash chromatography.



3aa

1st Cycle: 0.5 h, 100%
2nd Cycle: 0.5 h, 100%
3rd Cycle: 0.5 h, 100%
4th Cycle: 0.5 h, 100%
5th Cycle: 0.5 h, 100%

Scheme 7. Efficiency of catalyst **1** in the diarylation reaction of TMSA in NMP.



3ac

Scheme 8. Arylation of 1-phenyl-2-(trimethylsilyl)acetylene in NMP.

oxyiodobenzene with silylated phenyl-, 3-pyridyl-, and 2-thienylacetylenes (Table 6, entries 9–11). With respect to 4-chlorobromobenzene, the reaction with silylated phenylacetylene and pent-1-yne took place under 0.1 mol% loading of both catalysts in good yields and 45 min to 6.5 h reaction times (Table 6, entries 12–15). However, the coupling between 4-methoxybromobenzene and 1-phenyl-2-(trimethylsilyl)-acetylene proceeded in a modest 28% yield (Table 6, entry 16).

The catalytic activity of complex **1** was evaluated by performing the arylation of 1-phenyl-2-(trimethylsilyl)acetylene with 4-chloroiodobenzene in NMP at 110 °C (Scheme 10). The same efficiency was observed after addition of the reagents to the reaction during 5 consecutive cycles of 15 min.

The mechanism of the coupling reaction of alkynylsilanes in NMP was studied by treatment of 1-phenyl-2-(trimethylsilyl)acetylene with TBAA at 110 °C in the absence and in the presence of complex **1** (Scheme 11). Under both reaction conditions the protiodesilylation took place in 15 min, much faster than

Table 5. Arylation of 1-phenyl-2-(trimethylsilyl)acetylene with 4-chloroiodobenzene in NMP.[a]

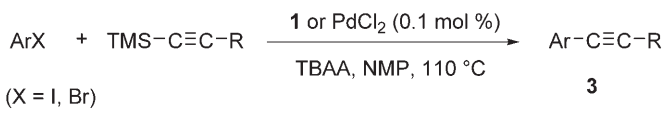
Entry	Cat [mol% Pd]	T [°C]	Time	Yield [%][b]	TON	TOF [h^{-1}]
1	**1** (0.1)	40	5.5 h	88	880	160
2	**1** (0.1)	60	0.5 h	84	840	1680
3	**1** (0.1)	110	15 min	100 (94)	1000	4000
4	$PdCl_2$ (0.1)	110	15 min	100	1000	4000
5	**1** (0.001)	110	24 h	90	9×10^5	37,500
6	$PdCl_2$ (0.001)	110	24 h	87	8.7×10^5	36,250
7	**1** (0.1)	25	13 d	96	960	3
8	**1** (1)	25	23 h	91	91	4
9	$PdCl_2$ (1)	25	23 h	88	88	4

[a] *Reaction conditions:* aryl halide (1 mmol), 1-phenyl-2-(trimethylsilyl)acetylene (1.2 mmol), TBAA (1.5 mmol), Pd catalyst (see column), NMP (2 mL).
[b] Yield determined by GC based on aryl halide using decane as internal standard. In parenthesis, isolated yield of compound **3ac** after flash chromatography.

Table 6. Synthesis of unsymmetrical internal alkynes in NMP.[a]

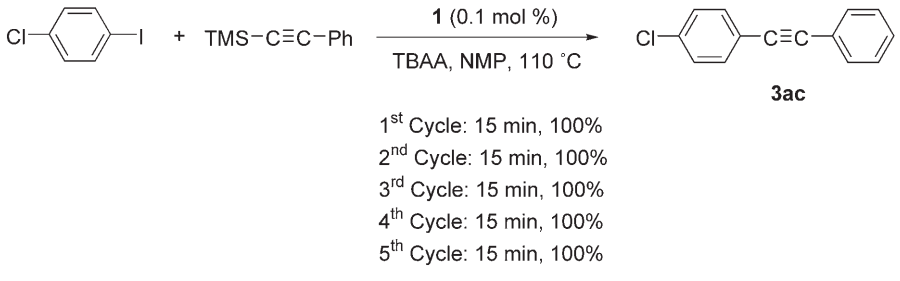
Entry	ArX	R	Cat [mol% Pd]	Time	No.	Yield [%][b]
1	4-ClC_6H_4I	Ph	**1** (0.1)	15 min	**3ac**	100 (94)
2		Ph	$PdCl_2$ (0.1)	15 min	**3ac**	100
3		3-Pyridyl	**1** (0.1)	3.5 h	**3ad**	87 (85)
4			$PdCl_2$ (0.1)	2.5 h	**3ad**	97
5		2-Thienyl	**1** (0.1)	2 h	**3ae**	100 (89)
6			$PdCl_2$ (0.1)	3.5 h	**3ae**	97
7		n-C_3H_7	**1** (0.1)	0.5 h	**3af**	100 (84)
8			$PdCl_2$ (0.1)	1 h	**3af**	97
9	4-$MeOC_6H_4I$	Ph	**1** (0.1)	15 min	**3bc**	98 (91)
10		3-Pyridyl	**1** (0.1)	3.5 h	**3bd**	74 (62)
11		2-Thienyl	**1** (0.1)	2.5 h	**3be**	80
12	4-ClC_6H_4Br	Ph	**1** (0.1)	45 min	**3ac**	72 (63)
13			$PdCl_2$ (0.1)	3 h	**3ac**	37
14		n-C_3H_7	**1** (0.1)	6.5 h[c]	**3af**	31
15			$PdCl_2$ (0.1)	3 h[c]	**3af**	87
16	4-$MeOC_6H_4Br$	Ph	**1** (0.1)	7.5 h	**3bc**	28

[a] *Reaction conditions:* aryl halide (1 mmol), silylated acetylene (1.2 mmol), TBAA (1.5 mmol), Pd catalyst (see column), NMP (2 mL) at 110 °C.
[b] Yield determined by GC based on aryl halide using decane as internal standard. In parenthesis, isolated yield of compound **3** after flash chromatography.
[c] The reaction was performed in a pressure tube.

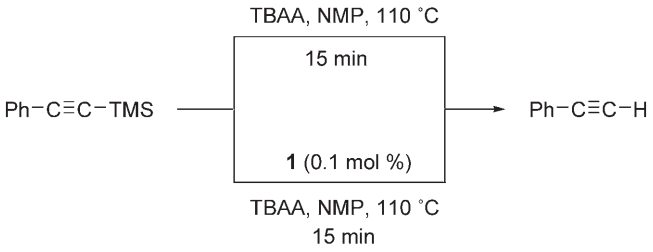


Scheme 9. Arylation of silylated terminal alkynes in NMP.

under water reflux (Scheme 4). It seems that the acetate anion in NMP is a stronger base than the hydroxide generated in water by the presence of pyrrolidine for the desilylation process. This fast desilylation reaction means that the reaction takes place mainly by ar-



Scheme 10. Efficiency of catalyst **1** in the arylation reaction of 1-phenyl-2-(trimethylsilyl)acetylene in NMP.



Scheme 11. Desilylation of 1-phenyl-2-(trimethylsilyl)acetylene in NMP.

ylation of the *in situ* generated deprotected terminal alkyne. Although, a competitive transmetalation from silicon to traces of copper (see above) cannot be ruled out.

The direct coupling reaction with alkynylsilanes can be performed in NMP either at 110 °C or at room temperature by using either complex **1** or ligand-less $PdCl_2$ as catalysts and TBAA as base using aryl iodides or bromides in good yields and with higher TOFs than in water. This methodology allows the synthesis of symmetrical and unsymmetrical internal alkynes.

Conclusions

We can conclude that the di(2-pyridyl)methylamine-derived complex **1** and $PdCl_2$ are efficient pre-catalysts for the direct di- and monoarylation of silylated alkynes either in water or in NMP as solvents using pyrrolidine or TBAA as bases, respectively. The synthesis of symmetrical and unsymmetrical internal alkynes can be carried out with activated and deactivated aryl iodides and bromides. Couplings with aryl iodides can be carried out under heating or at room temperature. For the diarylation in neat water BTMSA was the best acetylene equivalent, whereas TMSA is the reagent of choice in NMP. In general, a lower catalyst loading was necessary for the couplings performed in NMP than in water and normal heating gave better results than microwave irradiation. These types of direct couplings with alkynylsilanes gave internal alkynes with higher purity than the Sonogashira reaction previously described by us.[13c] The very high efficiency and stability of complex **1** was maintained in both media, being suitable for reuse during several catalytic cycles. Under these very simple reaction conditions a protiodesilylation-Sonogashira type coupling instead of transmetalation from silicon to traces of copper seems to be the major reaction pathway.

Experimental Section

General Remarks

The reagents and solvents were obtained from commercial sources and were generally used without further purification. Flash chromatography was performed on silica gel 60 (0.040–0.063 mm, Merck). Thin layer chromatography was perfomed on Polygram® SIL G/UV_{254} plates. Melting points were determined on a Reicher Thermovar apparatus. Gas chromatographic analyses were performed on a HP-6890 instrument equipped with a WCOT HP-1 fused silica capillary column. IR data were collected on a Nicolet Impact-400D-FT spectrophometer in cm^{-1}. ^1H NMR spectra were recorded on Bruker AC-300 (300 MHz) and when specified on a Bruker Advance-DRX-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm using tetramethylsilane (TMS, $\delta = 0.00$) as internal standards. ^{13}C NMR spectra were recorded at 75 MHz with $CDCl_3$ as the internal reference. EI-MS were measured on a Mass Selective Detector G2579 A from Agilent Technologies 5973N in *m/z* (rel. intensity in % of base peak). ICP-MS analyses were performed in a Thermo Elemental VG PQ-Excell spectometer. The catalysts were weighed up in an electronic microscale (Sartorius, XM1000P) with a precision of 1 μg. Microwave reactions were performed with a CEM Discover Synthesis Unit in glass vessels (10 mL) sealed with a septum under magnetic stirring.

Typical Procedure for the Palladium-Catalyzed Direct Coupling of Alkynylsilanes in Water

A mixture of aryl halide (1 mmol), alkyne (1.2 mmol), tetra-*n*-butylammonium bromide (161 mg, 0.5 mmol), pyrrolidine (0.205 mL, 2.5 mmol, only for trimethysilylacetylene and 0.123 mL, 1.5 mmol, for the rest of the reactions), complex **1** or $PdCl_2$ (see Tables) was stirred in water (2 mL) under reflux or at room temperature and the reaction progress analysed by GC. After the reaction was completed or stopped, the mixture was extracted with EtOAc (3×15 mL). The organic phases were dried ($MgSO_4$) and evaporated under vacuum. The subsequent residue was purified by flash chromatography on silica gel.

Typical Procedure for the Palladium-Catalyzed Direct Coupling of Alkynylsilanes in NMP

A solution of aryl halide (1 mmol), alkyne (1.2 mmol), tetra-*n*-butylammonium acetate (452 mg, 1.5 mmol), complex **1** or $PdCl_2$ (see Tables) in NMP (2 mL) was heated at 110 °C or at the temperature indicated in the Tables. The conversion of the reaction was followed by GC. Subsequently the cooled reaction was extracted with EtOAc (3×15 mL) and water and the organic phase was dried ($MgSO_4$) and evaporated under vacuum. The crude product was purified by flash chromatography on silica gel.

Compounds **3aa**, **3bb**, **3ac**, **3ad**, and **3bc** are commercially available and compounds **3cc**,[6] **3ae**,[6] **3af**,[7] and **3bd**[16] have been previously reported and were characterized by comparison with their reported data. Physical, analytical and spectroscopic data of the newly synthesized compound is gevine below.

1-(4-Methoxyphenyl)-2-thienylacetylene (3be): mp 55 °C; R_f = 0.15 (hexane); ^{1}H NMR ($CDCl_3$): δ = 7.44 (d, 2H, J = 8.4 Hz), 7.25–7.24 (m, 2H), 6.99–6.98 (m, 1H), 6.83 (d, 2H, J = 8.4 Hz), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 159.7, 132.9, 131.4, 127.0, 126.8, 123.6, 114.9, 114.0, 93.0, 81.2, 55.2; HR-MS: m/z = 214.0453, calcd for $C_{13}H_{10}OS$: 214.0452.

Acknowledgements

We thank DGES of the Spanish Ministerio de Educación y Ciencia (MEC) (grants: BQU2001–0724-CO2–01, CTQ2004–00808/BQU), the Generalitat Valenciana (grants: GRUPOS05/11) and the University of Alicante for financial support. J. G.-M. thanks the MEC for a predoctoral fellowship.

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[15] Microwave reactions were performed with a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC) with a continuous focused microwave power delivery system in glass vessels (10 mL) sealed with a septum under magnetic stirring. The temperature of the reaction mixture inside the vessel was monitored using a calibrated infrared temperature control under the reaction vessel.

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