# Mild Pd/Cu-Catalyzed Sila-Sonogashira Coupling of (Hetero)aryl Bromides with (Hetero)arylethynylsilanes under PTC Conditions

Fabio Bellina,\* Marco Lessi

Dipartimento di Chimica e Chimica Industriale, University of Pisa, Via Risorgimento 35, 56126 Pisa, Italy Fax +39(050)2219260; E-mail: bellina@dcci.unipi.it *Received 26 December 2011* 

**Abstract:** The palladium/copper cocatalyzed sila-Sonogashira reaction of (hetero)arylethynysilanes with (hetero)aryl bromides in toluene and water at 40 °C under PTC conditions gave the required di(hetero)arylethynes in moderate to high yields. Activated, deactivated and *ortho*-substituted (hetero)aryl bromides are well tolerated. This protocol also allowed the preparation of symmetrical diarylethynes by double arylation of 1,2-bis(trimethylsilyl)ethyne.

Key words: Sonogashira reaction, palladium, alkynylsilanes, diarylethynes, copper, phase-transfer catalysis

Symmetrical and unsymmetrical di(hetero)arylethynes represent important scaffolds for the assembly of new materials such as molecular electronic devices,<sup>1</sup> dendrimers,<sup>2</sup> foldamers,<sup>3</sup> or polymers.<sup>4</sup> The most important synthetic strategies for the preparation of this class of molecules are undoubtedly based on the palladium/copper cocatalyzed cross-coupling reactions of (hetero)aryl halides or pseudohalides with terminal alkynes in the presence of a base (Sonogashira reaction).<sup>5</sup> The original protocol published by Sonogashira, Tohda, and Hagihara in 1975,<sup>6</sup> which required a Pd/Cu(I) catalyst system for the Csp-Csp<sup>2</sup> coupling, has been repeatedly modified and improved to overcome several drawbacks.7 In particular, copper-free (Cassar-Heck alkynylation),<sup>8,9</sup> silver<sup>10</sup> or zinc<sup>11</sup> cocatalyzed, the use of palladacycles as precatalysts,<sup>12</sup> the use of ionic liquids as reaction media,<sup>13</sup> or microwave heating<sup>14</sup> have been reported to increase the efficiency of this reaction by limiting the undesired formation of alkyne homocoupling Glaser-type products.<sup>15</sup> However, despite these improvements the use of Sonogashira reactions to prepare di(hetero)aryl alkynes often requires systematic silane protection-deprotection to afford the terminal alkyne coupling partner, and this stage generally precedes the cross-coupling step.<sup>5,7</sup> In order to overcome the necessity of protecting-group removal and to avoid the use of acetylene, trimethylsilylalkynes and silylated acetylene equivalents such as ethynyltrimethylsilane (ETS) or 1,2-bis(trimethylsilyl)ethyne (BTSE) have been directly used as nucleophilic partners in the so-called sila-Sonogashira reaction.<sup>16,17</sup> A further distinct advantage of the use of TMS-protected alkynes instead of unprotected terminal alkynes resides in the suppression of the formation of diynes and enynes, which, as stated

SYNLETT 2012, 23, 773–777 Advanced online publication: 28.02.2012 DOI: 10.1055/s-0031-1290601; Art ID: D80911ST © Georg Thieme Verlag Stuttgart · New York above, are typical byproducts of classical Sonogashira protocols.<sup>7,15</sup> However, these methods are generally limited to the use of (hetero)aryl iodides<sup>16a-c,f-j,m,n</sup> or activated (hetero)aryl bromides<sup>16i</sup> as coupling partners and require high reaction temperatures,<sup>16b,d,e,j-m</sup> or the use of commercially unavailable palladium precatalysts.<sup>16j-k</sup>

In this paper, we report a mild protocol for the Pd/Cu cocatalyzed sila-Sonogashira cross-coupling reaction of (hetero)arylethynylsilanes and BTSE with a variety of activated and deactivated (hetero)aryl bromides in a mixture of toluene and water in the presence of benzyl(tri-*n*butyl)ammoniun chloride which acts as a phase-transfer catalyst (PTC).<sup>18</sup> Our need for an efficient synthesis of di(hetero)arylethynes was dictated by our very recent interest in preparing new organic fluorophores for nonlinear optical (NLO) materials.

At the onset of our studies, we tested a diverse array of bases as promoters for the sila-Sonogashira coupling reaction of trimethyl(phenylethynyl)silane (1a) with 2-bromothiophene (2a, 1.1 equiv) in the presence of  $PdCl_2(PhCN)_2$  (5 mol%), CuI (10 mol%) as the cocatalyst, *t*-Bu<sub>3</sub>PHBF<sub>4</sub> (10 mol%) as the palladium ligand, and Bn(*n*-Bu)<sub>3</sub>NCl (20 mol%) as the phase-transfer catalyst in a mixture of toluene and water (Scheme 1).





The choice of these specific reaction conditions deserves comment. In particular, we decided to perform the reaction in a biphasic system because we guessed that the high temperatures frequently reported in the literature for similar sila-Sonogashira reactions may be, at least in part, a result of the poor solubility of inorganic bases in common organic solvents. Moreover, t-Bu<sub>3</sub>P (as its air-stable phosphonium tetrafluoroborate salt) was selected because it has been reported to be an effective ligand for palladium when aryl bromides are employed as electrophiles in classical Sonogashira reactions.<sup>19</sup>

As shown in Table 1, the use of three equivalents of KF or  $K_2CO_3$  did not gave any of the required 2-(phenylethy-nyl)thiophene (**3a**, Table 1, entries 1 and 2), and even af-

ter four days at 80 °C the GLC yields of **3a** were unsatisfactory (Table 1, entries 3 and 4). No reaction was also observed when the amount of KF or  $K_2CO_3$  was increased to ten equivalents (Table 1, entries 5 and 6). It is worth mentioning that **1a** was quantitatively recovered from the crude reaction mixtures when KF or  $K_2CO_3$  were employed at 40 °C (Table 1, entries 1, 2, 5, and 6), even though these bases have been routinely used for the deprotection of trimethylsilylalkynes in organic solvents.<sup>20</sup> In contrast, when three equivalents of NaOH were used to promote the coupling of **1a** with **2a**, compound **3a** was obtained in 47% GC yield (Table 1, entry 7). We were then pleased to find that when ten equivalents of NaOH were used, the coupling of **1a** with **2a** afforded **3a** in a satisfactory 88% isolated yield (Table 1, entry 8).

Interestingly, when the reaction was carried out without copper, no reaction was observed, and only ethynylbenzene was detected in the crude reaction mixture (Table 1, entry 9).

Entry <sup>a</sup>	Base (equiv)	Temp (°C)	Time (h)	Yield of $3a (\%)^b$
1	KF (3)	40	48	0 <sup>c</sup>
2	$K_{2}CO_{3}(3)$	40	24	0 <sup>c</sup>
3	KF (3)	80	96	20
4	$K_{2}CO_{3}(3)$	80	96	38
5	KF (10)	40	48	0 <sup>c</sup>
6	K <sub>2</sub> CO <sub>3</sub> (10)	40	48	0 <sup>c</sup>
7	NaOH (3)	40	24	47
8	NaOH (10)	40	17	93 (88)
9 <sup>d</sup>	NaOH (10)	40	17	0 <sup>e</sup>

<sup>a</sup> Unless otherwise mentioned, the reactions were carried out using **1a** (1.0 mmol), **2a** (1.1 equiv),  $PdCl_2(PhCN)_2$  (5 mol%), *t*-Bu<sub>3</sub>PHBF<sub>4</sub> (10 mol%), CuI (10 mol%), Bn(*n*-Bu)<sub>3</sub>NCl (20 mol%), toluene/H<sub>2</sub>O (1:1, 8 mL).

<sup>b</sup> GC yield. Isolated yield is given in parentheses.

<sup>c</sup> Trimethyl(phenylethynyl)silane (**1a**) was quantitatively recovered from the crude reaction mixture.

<sup>d</sup> This reaction was carried out in the absence of CuI.

<sup>e</sup> Only ethynylbenzene was detected by GC and GC–MS analyses of the crude reaction mixture.

Taking into account these results and previous reports in the literature,<sup>16</sup> we proposed that the mechanism should feature an in situ NaOH-promoted protiodesilylation,<sup>21</sup> affording reactive silicon-free alkyne intermediates in low concentrations and thus suppressing the formation of Glaser-type dimerization byproducts. This step should then be followed by a classical Pd/Cu-cocatalyzed Sonogashira-type coupling. However, from our data, a direct silicon-to-copper transmetalation promoted by NaOH, in analogy to that suggested by Halbes and Pale for their Pd/Ag cocatalyzed base-promoted sila-Sonogashira protocol,<sup>16g</sup> cannot be totally ruled out.

Having successfully demonstrated the feasibility of the Pd/Cu-catalyzed sila-Sonogashira cross-coupling under PTC conditions of **1a** with **2a**, we then tested the scope and limitations of this coupling by applying the reaction conditions of entry 8 (Table 1) to the synthesis of compounds **3** starting from (hetero)arylethynyltrimethylsilanes **1** and commercially available (hetero)aryl bromides **2** (Scheme 2).<sup>22–24</sup>



Scheme 2

The reactions involving (hetero)arylethynyltrimethylsilanes 1a-e and (hetero)aryl bromides 2a-e and 2g-lproved to be clean and, as shown in Table 2, gave the required diaryl substituted ethynes 3a-e and 3g-m in moderate to high yields (Table 2, entries 1–5 and 7–13).

In particular, yields higher than 90% were observed when activated aryl bromides were used as electrophilic partners (Table 2, entries 2 and 8), but the reaction also worked well when alkynyltrimethylsilanes 1 were coupled with unactivated or deactivated (hetero)aryl bromides (Table 2, entries 1, 3–5, 7, and 10). This system also proves to be tolerant of sterically hindered substrates and 2-substituted aryl bromides 2h and 2j smoothly reacted with TMS-protected alkynes 1c and 1e affording the desired cross-coupled products **3i** and **3k** in 63% and 64% yield, respectively (Table 2, entries 9 and 11), while a lower yield was observed when a typical deactivated ortho-substituted bromide, 2-bromoanisole (21), was used as the coupling partner (Table 2, entry 13). A low chemical yield also resulted from the coupling involving the strongly deactivated 4-bromoveratrole (2k, Table 2, entry 12). Remarkably, base-sensitive groups such as the formyl or the carboxyalkyl groups are well tolerated (Table 2, entries 7–9), and the presence of basic pyridyl or amino groups did not interfere with the outcome of the coupling (Table 2, entries 3 and 10–13). Nevertheless, the Pd/Cu cocatalyzed cross coupling of 1a with 4-bromophenol (2e) did not produce the required alkyne 1f (Table 2, entry 5); on the contrary, a small amount of the Glasertype homocoupled diyne and of ethynylbenzene were observed in the crude reaction mixture. In our opinion, this lack of reaction could be ascribed at least in part to the quantitative conversion of 2e into the corresponding sodium salt which is probably confined into the aqueous phase and is unable to give an efficient oxidative addition to the  $Pd(0)L_n$  catalyst.

Having secured good access to compounds **3**, we then turned our attention to the preparation of some typical symmetrically substituted diarylethynes **4** starting from 1,2-bistrimethylsilylethyne (BTSE). We were pleased to

2 3° Entry<sup>a</sup> 1 Ar  $Ar^2$ Time (h)<sup>b</sup> Yield of  $3 (\%)^d$ 1 **1**a Ph 2a 2-thienyl 17 3a 88 2 Ph 2b  $4-O_2NC_6H_4$ 22 3b 98 **1**a 3 1a Ph 2c 4-H<sub>2</sub>NC<sub>6</sub>H<sub>4</sub> 22 3c 65 4 1a Ph 2d 4-ClC<sub>6</sub>H<sub>4</sub> 22 3d 78 5 **1**a Ph 2e 5-acetyl-2-thienyl 22 3e 82 6 1a Ph 2f 4-HOC<sub>6</sub>H<sub>4</sub> 22 3f 0 7 1b 4-OHCC<sub>6</sub>H<sub>4</sub> 15 40 2a 2-thienyl 3g 4-MeOC<sub>6</sub>H<sub>4</sub> 4-EtOOCC<sub>6</sub>H<sub>4</sub> 22 91 8 1c 2g 3h g 1c 4-MeOC<sub>6</sub>H<sub>4</sub> 2h 2-MeOOCC<sub>6</sub>H<sub>4</sub> 22 3i 63 10 1d 4-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub> 2i 2-pyridyl 22 3j 64

Table 2 Synthesis of 1,2-Diarylethynes 3 from Arylethynyltrimethylsilanes 1 and Aryl Bromides 2

<sup>a</sup> The reactions were carried out at 40 °C (oil bath) using 1 (1.0 mmol), 2 (1.1 equiv), PdCl<sub>2</sub>(PhCN)<sub>2</sub> (5 mol%), t-Bu<sub>3</sub>PHBF<sub>4</sub> (10 mol%), CuI (10 mol%), Bn(n-Bu)<sub>3</sub>NCl (20 mol%), 2.5 M aq NaOH solution (4 mL), toluene (4 mL).

2-MeC<sub>6</sub>H<sub>4</sub>

2-MeOC<sub>6</sub>H<sub>4</sub>

3,4-(MeO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>

<sup>b</sup> Unless otherwise mentioned, the conversion of the reported reactions was quantitative after the indicated reaction times.

2j

2k

21

<sup>c</sup> All compounds gave satisfactory spectroscopic and analytical data.<sup>23</sup>

3-pyridyl

3-pyridyl

3-pyridyl

<sup>d</sup> Isolated chemical yield.

1e

1e

1e

11

12

13

<sup>e</sup> Only low amounts of ethynylbenzene and of 1.4-diphenylbuta-1.3-diyne were observed by GC-MS analysis in the crude reaction mixture after the indicated reaction time.

find that the reaction conditions of entry 8 (Table 1) also proved to be suitable for the double arylation of BTSE with aryl bromides  $2^{22}$  As shown in Scheme 3, a molar excess of representative deactivated, activated, and orthosubstituted aryl bromides was successfully reacted with BTSE under Pd/Cu cocatalysis in toluene and water at 40 °C for 22 hours, furnishing the required alkynes 4 in good yields.



#### Scheme 3

In conclusion, in this study we have demonstrated that unsymmetrical di(hetero)arylethynes can be efficiently prepared in moderate to good yields by the Pd/Cucocatalyzed cross coupling of activated and deactivated (hetero)aryl bromides with (hetero)arylethynylsilanes in the presence of  $Bn(n-Bu)_3NCl$  as the phase-transfer catalyst and NaOH in a biphasic toluene/water reaction medium. Sterically hindered bromides are tolerated, as well as base-labile functional groups such as formyl and carboxyalkyl groups. Moreover, symmetrical diarylethynes can be prepared in good isolated yields by reaction of aryl bromides with BTSE. It is proposed that the coupling proceeds by a mechanism involving a NaOH-promoted protiodesilylation and a subsequent classical Pd/Cu cocatalyzed Sonogashira coupling. Studies on the application of this simple protocol, which compares favorably with those previously described in the literature,<sup>16</sup> to the preparation of highly conjugated (hetero)arylethynes are now in progress.

22

22

22

3k

31

3m

64

32

32

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#### (22) General Procedure for the Synthesis of Di(hetero)arylethynes 3 To a mixture of alkynyltrimethylsilane 1 (1 mmol),

(hetero)aryl bromide 2 (1.1 mmol), PdCl<sub>2</sub>(PhCN)<sub>2</sub> (19.8 mg, 0.05 mmol), t-Bu<sub>3</sub>PHBF<sub>4</sub> (29.0 mg, 0.1 mmol), CuI (19.0 mg, 0.1 mmol), and Bn(n-Bu)<sub>3</sub>NCl (62.4 mg, 0.2 mmol) in toluene (8 mL) was added a 2.5 M aq solution of NaOH (10 mmol, 4 mL), and the resulting biphasic mixture was stirred under argon at 40 °C for the period of time reported in Table 2. The degree of completion of the reaction and the composition of the reaction mixture were established by GC and GC-MS analyses of a sample of the crude reaction mixture after it had been treated with a sat. aq NH<sub>4</sub>Cl solution and extracted with EtOAc. After being cooled to r.t., the reaction mixture was diluted with EtOAc (15 mL) and poured into a sat. aq NH<sub>4</sub>Cl solution (15 mL), and the resulting mixture was stirred in the open air for 0.5 h and then extracted with EtOAc ( $4 \times 10$  mL). The organic extracts were washed with  $H_2O$  (2 × 5 mL), dried and concentrated under reduced pressure, and the residue was purified by flash cromatography on silica gel. This procedure was employed to prepare di(hetero)arylethynes **3a–e,g–m** (Table 2, entries 1-5 and 7-10,). The same procedure, but employing BTSE (0.23 mL, 0.17 g, 1.0 mmol) and aryl bromide 2 (2.2 mmol), was also applied to the synthesis of symmetrically substituted diarylethynes 4a-c (Scheme 3).

(23) Representative Data for New Compounds 4-(Thiophen-2-ylethynyl)benzaldehyde (3g)

Mp 110–112 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.03 (dd, *J* = 3.7, 5.0 Hz, 1 H), 7.34 (m, 2 H), 7.63 (d, *J* = 9.0 Hz, 2 H), 7.84 (d, *J* = 9.0 Hz, 2 H), 9.99 (s, 1 H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 86.87, 92.37, 122.43, 127.40, 128.43, 129.20, 129.62 (2 C), 131.79 (2 C), 132.93, 135.40, 191.39. MS: *m*/z (%) = 212 (100) [M<sup>+</sup>], 211 (60), 183 (13), 139 (35), 91 (6). Anal. Calcd for C<sub>13</sub>H<sub>8</sub>OS (212.27): C, 73.56; H, 3.80. Found: C, 73.84; H, 3.78.

3-[(3,4-Dimethoxyphenyl)ethynyl]pyridine (3l)

Mp 53–55 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 3.89 (m,

6 H), 6.83 (d, J = 9 Hz, 1 H), 7.05 (s, 1 H), 7.16 (d, J = 6 Hz, 1 H), 7.25 (m, 1 H), 7.77 (d, J = 9 Hz, 1 H), 8.55 (s, 1 H), 8.79 (s, 1 H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta = 55.67, 55.70, 84.48, 92.75, 110.83, 113.99, 114.40, 120.57, 122.91, 124.94, 137.98, 148.06, 148.46, 149.67, 151.85. MS: <math>m/z$  (%) = 239 (100) [M<sup>+</sup>], 224 (18), 196 (16), 167 (27), 1543 (12), 127 (12). Anal. Calcd for Cl<sub>3</sub>H<sub>13</sub>NO<sub>2</sub> (239.27): C, 75.30; H, 5.48. Found: C, 75.61; H, 5.52.

(24) Recently, a classical Sonogashira cross-coupling protocol for the synthesis of compounds 3 was published: Moulton, B. E.; Whitwood, A. C.; Duhme-Klair, A. K.; Lynam, J. M.; Fairlamb, I. J. S. *J. Org. Chem.* 2011, *76*, 5320. Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.