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Copper-free Oxime Palladacycle-Catalyzed Sonogashira Alkynylation of Deactivated Aryl Bromides and Chlorides in water under Microwave Irradiation

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Keywords: Sonogashira Reaction / Palladium / Water / Aryl Halide / Alkyne

The palladium-catalyzed Heck alkynylation cross-coupling reactions between terminal alkynes and deactivated aryl chlorides and aryl bromides can be carried out in the absence of copper cocatalyst using water as solvent at 130 ºC under microwave irradiation. Oxime-derived chloro-bridged palladacycle **1a**, is an efficient pre-catalyst to perform this transformation using XPhos as ancillary ligand, pyrrolidine as base, and SBDS as surfactant. All the reactions can be performed under air and employing reagent-grade chemicals under low loading conditions (0.1-1 mol% Pd).

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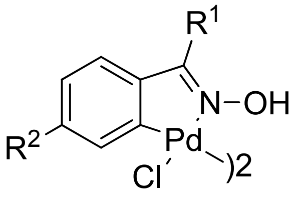
Introduction

Palladium-catalyzed reactions for carbon-carbon and carbon-heteroatom bond formation have gained a predominant place in the arsenal of synthetic chemists.[1] In organic synthesis, among the leading "name" Pd-catalyzed reactions, the Sonogashira-Hagihara coupling[2] is one of the most important and widely used methods for preparing aryl- and alkylacetylenes as well as conjugated enynes, which are precursors for natural products, pharmaceuticals, as well as optical and electronic materials.[2,3] Given the relevance of the Sonogashira reaction, the design of sustainable protocols to perform green aqueous couplings[4] is nowadays considered of high practical value, especially when deactivated electrophiles such as aryl chlorides[5] and hydroxyarene derivatives[6] are involved in the process. The use of water as a solvent in Pd-catalyzed reactions has gained increasing attention during last years[7] due to the environmental and economic benefits of replacing organic solvents by water as well as its interesting chemical properties, including high polarity and strong hydrogen-bonding ability, among others. However, using water as solvent, mostly aryl iodides[8] and bromides[9] have been used as coupling partners and only a few reports can be found in the literature on the successful coupling of activated aryl chlorides.[5,10] In recent years, we have demonstrated the high activity of oxime palladacycles[11] **1** (Figure 1) in a wide variety of cross-coupling reactions using organic and aqueous solvents.[12] Specially interesting has resulted those couplings performed using neat water as solvent and deactivated electrophiles such as aryl chlorides (Suzuki reaction[13]) and aryl imidazolylsulfonates (Suzuki[14] and Sonogashira[6] reactions) in the presence of surfactants.7h,7l In continuation of our exploration on the application of oxime palladacycles under green conditions, we herein describe the Sonogashira coupling reaction of deactivated aryl bromides and chlorides in water under microwave irradiation.



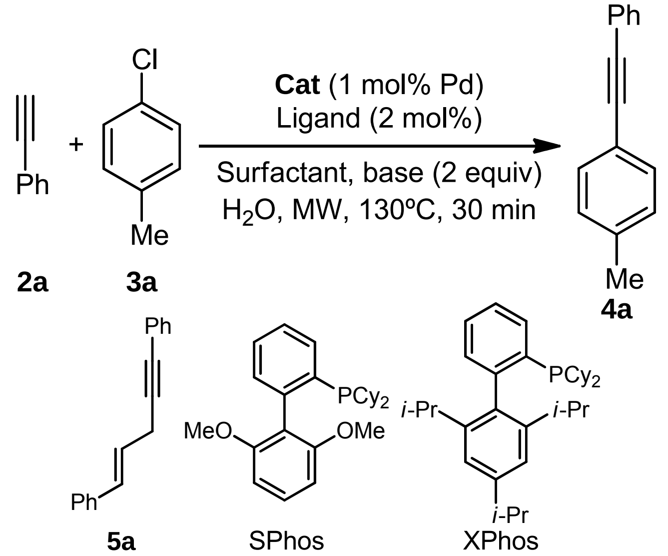
1a, R^1 = 4-ClC_6H_4, R^2 = Cl
1b, R^1 = Me, R^2 = OH

Figure 1. Oxime Palladacycle Catalysts

Results and Discussion

Deactivated aryl chlorides are good indicators of optimal catalyst performance. Thus, we initially investigated the microwave-promoted Sonogashira coupling of phenylacetylene (**2a**, 1.2 equiv) with 4-chlorotoluene (**3a**, 1 equiv) in water in the presence of hexadecyltrimethylammonium bromide (CTAB, 0.4 equiv) as additive and TEA (2 equiv) as base (Table 1). With an initial microwave irradiation of 40 W, the reaction temperature was maintained at 130 ºC for 30 min. As catalyst, oxime palladacycle **1a** (1 mol% Pd) in the presence of 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos, 2 mol%) was selected due to the high activity of this catalytic system for the alkynylation of aryl imidazolylsulfonates in water.[6,15] Unfortunately, under these conditions (Table 1, entry 1), the reaction afforded 1-methyl-4-(phenylethynyl)benzene (**4a**) in a 14% isolated yield together with the enyne (*E*)-but-1-en-3-yne-1,4-diyldibenzene (**5a**) in a 7% yield. The formation of compound **5a** has been previously detected in Heck alkynylations of deactivated aryl chlorides and it is postulated to occur via a Pd-catalyzed head-to-head dimerization of phenylacetylene.[16] Indeed, the formation of linear enynes from terminal alkynes, that is, head to head coupled products, has been previously achieved employing a range of metal catalysis.[17] Then, an optimization of the reaction conditions was carried out in order to improve the yield and especially the selectivity of the process (Table 1). When the reaction was performed under the same reaction conditions, but using oxime catalyst **1a** (1 mol% Pd), negligible amounts of **5a** were observed in the crude reaction mixture, but still a low 21% reaction conversion to **4a** was detected (Table 1, entry 2). A 77% conversion was obtained when pyrrolidine was used as base regardless of the amount of surfactant used (Table 1, entries 3 and 4).

Table 1. Sonogashira alkynylation of 4-chlorotoluene with phenylacetylene. Reaction conditions optimization.



Entry	Pd Cat.	Ligand[a]	Surfactant (equiv)[b]	Base	Yield (%)[c]
1	**1b**	Sphos	CTAB (0.4)	TEA	50 (14)[d]
2	**1a**	Sphos	CTAB (0.4)	TEA	21
3	**1a**	Sphos	CTAB (0.4)	Pyrrolidine	77
4	**1a**	Sphos	CTAB (1)	Pyrrolidine	77
5	**1a**	Xphos	CTAB (0.4)	Pyrrolidine	84 (54)
6	**1a**	Xphos	CTAB (1)	Pyrrolidine	90 (60)
7	**1a**	Xphos	PTS (1)	Pyrrolidine	95 (40)
8	**1a**	Xphos	Brij 35 (1)	Pyrrolidine	>95 (73)
9	**1a**	Xphos	Brij C10 (1)	Pyrrolidine	>95 (73)
10	**1a**	Xphos	SDBS (1)	Pyrrolidine	>95 (76)
11	**1a**	Xphos	TBAB (1)	Pyrrolidine	65
12	**1a**	Xphos	SDBS (1)	TEA	54
13	**1a**	Xphos	SDBS (1)	*i*-Pr_2EtN	50
14	**1a**	Xphos	SDBS (1)	Cy_2NH	87 (54)
15	**1a**	Xphos	SDBS (1)	Piperidine	89 (63)
16	**1a**	Xphos	SDBS (1)	K_2CO_3	90 (63)
17	**1b**	Xphos	SDBS (1)	Pyrrolidine	>95 (24)
18	[e]	Xphos	SDBS (1)	Pyrrolidine	80 (40)
19	[f]	Xphos	SDBS (1)	Pyrrolidine	90 (68)
20	**1a**	Xphos	SDBS (1)	Pyrrolidine	(24)[g]

[a] Xphos: 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; Sphos: 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl. [b] CTAB: hexadecyltrimethyl ammonium bromide; PTS: polyoxyethanyl-α-tocopheryl sebacate; Brij 35: polyoxyethylene lauryl ether, Brij C10: polyethylene glycol hexadecyl ether; SDBS: sodium dodecyl benzene sulphonate; TBAB: tetrabutylammonium bromide. [c] Conversion determined by GC analysis. In parenthesis, isolated yield after preparative thin layer chromatography. [d] A 7% yield of (*E*)-but-1-en-3-yne-1,4-diyldibenzene (**5a**) was also obtained. [e] $Pd_2(dba)_3$ (1 mol% Pd) was used as catalyst. [f] $Pd(OAc)_2$ (1 mol% Pd) was used as catalyst. [g] Isolated yield when the reaction was performed under conventional thermal conditions (130 ºC, 24 h).

Then, using the most chemoselective catalyst and base, **1a** and pyrrolidine, a ligand study was carried out (see SI) which showed 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (Xphos) as the most effective ligand being **4a** obtained in a 60% isolated yield when 1 equivalent of CTAB was used (Table 1, entry 6). Xphos has been shown by Lipshutz as the most effective for the palladium-catalyzed Sonogashira coupling of aryl bromides in water at room temperature using PTS as surfactant.[9c] Then, the effect of the surfactant on the activity of the catalytic system was studied (Table 1, entries 7-11). Non-ionic surfactants such as the polyethers polyoxyethylene lauryl ether (Brij35), and polyethylene glycol hexadecyl ether (BrijC10) as well as the anionic sodium dodecyl benzene sulphonate (SDBS) afforded good yields of **4a**, being the latter the highest (76%, entry 10).

Significant sensitivity to base was also noted (Table 1, entries 12-16). Thus, good isolated yields were obtained with other organic (dicyclohexylamine and piperidine) and inorganic bases (K_2CO_3), though these experiments did not improve the ability of pyrrolidine in this process.[18]

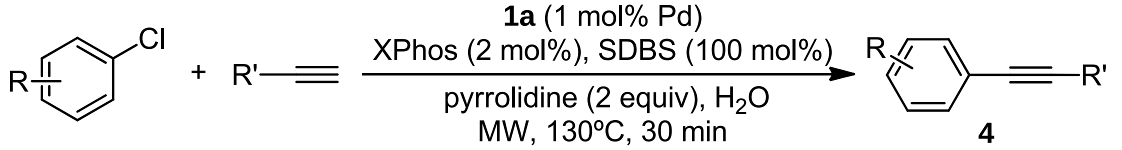
Regarding the catalyst, a 24% yield of 11-methyl-4-(phenylethynyl)benzene (**4a**) was obtained under the optimized reaction conditions when oxime-derived palladacycle **1b** (1 mol% Pd) was employed as catalyst (Table 1, entry 17). Other Pd sources such as $Pd_2(dba)_3$ and $Pd(OAc)_2$ were also less effective than **1a** affording lower yields of **4a** as shown in entries 18 and 19.

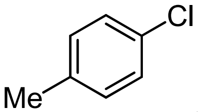
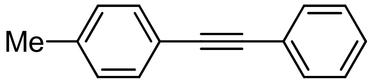
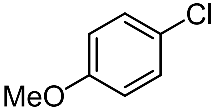
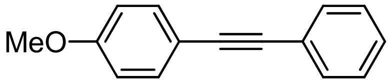
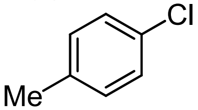
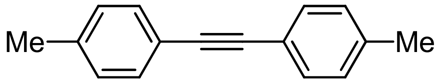
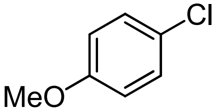
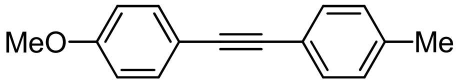
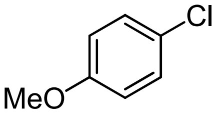
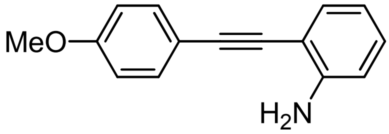
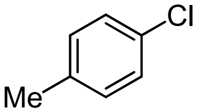
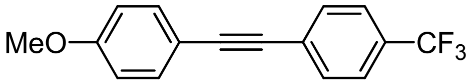
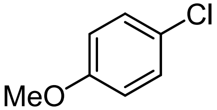
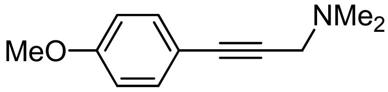
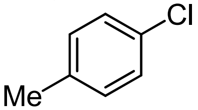
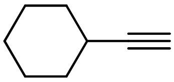
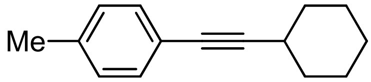
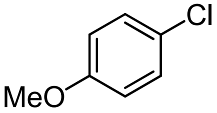
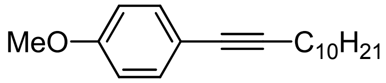
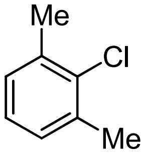
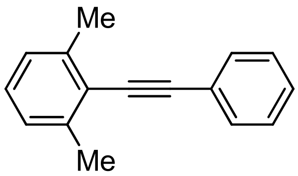
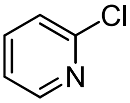
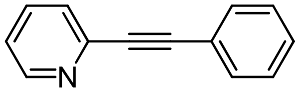
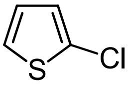
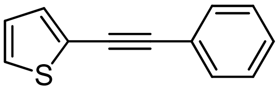
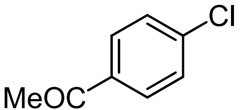
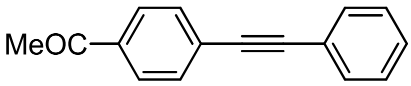
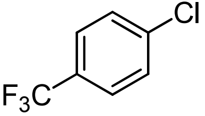
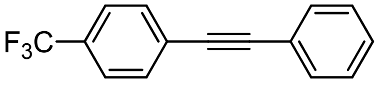
Finally, the efficiency of the microwave irradiation was demonstrated since only a 24% reaction yield was obtained when the reaction was performed under conventional thermal conditions (130 ºC, 24 h, Table 1, entry 20).

To test the effectiveness of the optimized catalytic system in the Pd-catalyzed Sonogashira coupling in water, a range of aryl- and alkyl-substituted terminal alkynes were examined in the reaction with different aryl chlorides (Table 2). As previously described for 4-chlorotoluene, deactivated 4-chloroanisole was coupled with phenylacetylene to afford 4-methoxytolane in a 80% yield (Table 2, entry 2). The coupling of these two deactivated aryl chlorides with electron-rich terminal alkynes, such as (4-methoxyphenyl)acetylene, (4-methyphenyl)acetylene, and (2-aminophenyl)acetylene led to the corresponding 1,2-diarylalkynes **4c** and **4d** in moderate to good yields (47-63%, Table 1, entries 3-5). A 40% yield of the donor-acceptor tolane derivative with potential optoelectronic properties **4e**[19] was obtained when 4-chlorotoluene was coupled with the electron-poor 4-(trifluoromethyl)phenylacetylene, result which is in accordance with the low reactivity in Sonogashira reactions of alkynes bearing electron-withdrawing groups (entry 6). The scope of this coupling was extended to other alkynes such as *N*,*N*-dimethyl-2-propynylamine, cyclohexylacetylene, and 1-dodecyne, which after coupling with 4-chloroanisole and 4-chlorotoluene afforded disubstituted alkynes **4f**, **4g**, and **4h** in a 50, 20, and 20% yield, respectively (Table 2, entries 7-9). Hindered 2-chloro-1,3-dimethylbenzene underwent the coupling with phenylacetylene to produce the desired alkyne **4i** in a 63% isolated yield (Table 2, entry 10). The coupling of heterocyclic 2-chloropyridine and 2-chlorothiophene with phenylacetylene, afforded the Sonogashira derivatives **4j** and **4k** in 87 and 53% yield, respectively (Table 2, entries 11 and 12). Finally, the reaction of activated 4-acetylchlorobenzene and 4-(trifluoromethyl)benzene with phenylacetylene afforded compounds **4l** and **4m** in a 89 and 80% isolated yield, respectively (Table 2, entries 13 and 14).

Under the optimized reaction conditions for the Sonogashira coupling of aryl chlorides, we also evaluated the alkynylation of aryl bromides in water (Table 3). After a catalyst, temperature, and catalyst loading study (see SI), we demonstrated that for these more active electrophiles oxime palladacycle **1a** was the most active palladium source and that the palladium loading could be reduced to 0.1 mol%. As expected 4-bromotoluene and 4-bromoanisole afforded the desired products in high isolated yields after reaction with phenylacetylene and electron-rich alkynes such

Table 2. Sonogashira alkynylation of aryl chlorides.

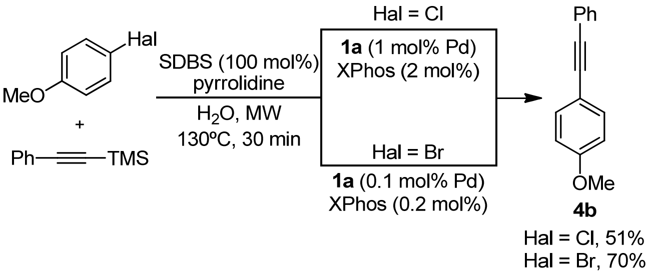


Entry	ArCl	R'—≡	Product	**No.**	Yield (%)[a)]
1		Ph—≡		**4a**	76
2		Ph—≡		**4b**	80
3		4-MeOC$_6$H$_4$—≡		**4c**	47
4		4-MeC$_6$H$_4$—≡		**4c**	63
5		2-H$_2$NC$_6$H$_4$—≡		**4d**	51
6		4-F$_3$CC$_6$H$_4$—≡		**4e**	40
7		Me$_2$NCH$_2$—≡		**4f**	50
8				**4g**	20
9		C$_{10}$H$_{21}$—≡		**4h**	20
10		Ph—≡		**4i**	63
11		Ph—≡		**4j**	87
12		Ph—≡		**4k**	53
13		Ph—≡		**4l**	89
14		Ph—≡		**4m**	80

a) Isolated yield after preparative thin layer chromatography.

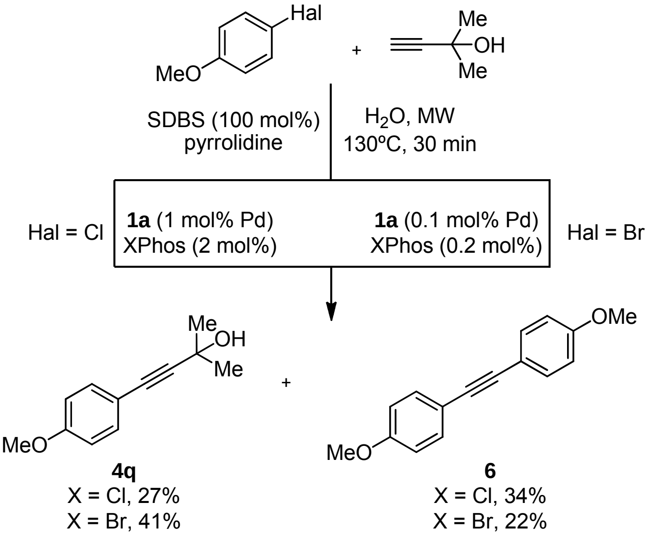
as, (4-methoxyphenyl)acetylene and 4-tolylacetylene respectively (Table 3, entries 1-2 and 4-5). Lower yields were observed when using electron-poor nucleophiles, as found in the reaction between 4-chloroanisole and (4-trifluoromethylphenyl)acetylene, coupling which led to the tolane derivative **4e** in a 51% isolated yield (Table 3, entry 6). A terminal alkyne with an alkene functionality, such as 1-ethynylcyclohexene, underwent Sonogashira coupling with 4-bromoanisole to afford the conjugated enyne **4n** in 49% yield (Table 3, entry 7). In a similar fashion, we next examined aliphatic alkynes as a coupling partner with 4-bromotoluene and 4-bromoanisole. Again, we observed that in general, aliphatic alkynes showed lower reactivities as compared to arylalkynes. The coupling reaction of 4-bromotoluene and 4-bromoanisole with cyclohexylacetylene afforded disubstituted alkynes **4g** and **4o** in a 40 and 37% yield, respectively (Table 3, entries 3 and 9). A 61% yield of the semicarbazide-sensitive amine oxidase (SSAO) inhibitor[20] **4f** was obtained when 4-bromoanisole reacted with *N*,*N*-dimethyl-2-propynylamine under the optimized conditions (Table 3, entry 8). A low 30% yield of alkyne **4h** was obtained by reaction of 4-bromoanisole with 1-dodecyne (Table 3, entry 10). The alkynylation of the sterically hindered 2-bromo-1,3-dimethylbenzene with phenylacetylene and 4-tolylacetylene afforded compounds **4i** and **4p** in 69 and 61% yield, respectively. Good isolated yields were also obtained for the coupling of 2-bromopyridine and 2-bromothiophene with phenylacetylene, reactions which led to the Sonogashira coupling products **4j** and **4k** in 91 and 63% yield, respectively (Table 3, entries 13 and 14). Finally, the reaction between activated 4-acetylbromobenzene and phenylacetylene afforded compound **4l** in an 87% isolated yield (Table 3, entry 15).

We then decided to carry out an investigation of the catalytic activity of complex **1a** in the cross-coupling reaction between deactivated aryl bromides and chlorides and other alkynes. Firstly, we studied the coupling with silylated alkynes. As depicted in Scheme 1, the reaction of 4-chloro- and 4-bromoanisole with 1-phenyl-2-(trimethylsilyl)acetylene afforded 4-methoxytolane (**4b**) in a 51 and 70% yield, respectively, under the optimized reaction conditions through a desilylation/cross-coupling sequence.[21]



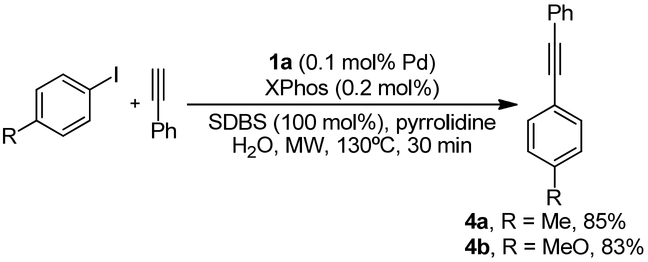
Scheme 1. Sonogashira coupling with 1-phenyl-2-(trimethylsilyl)acetylene.

On the other hand, the reaction of 4-chloro- and 4-bromoanisole with 2-methylbut-3-yn-2-ol afforded a mixture of compounds **4q** and **6**, as a consequence of the mono- or double alkynylation reaction with the acetylenic nucleophile (Scheme 2).



Scheme 2. Sonogashira coupling with 2-methylbut-3-yn-2-ol.

Finally, we also studied the reactivity of deactivated aryl iodides in the Sonogashira reaction in water under the optimized reaction conditions. Using the catalyst loading employed for aryl bromides, good isolated yields were obtained for the coupling of 4-iodotoluene and 4-iodoanisole with phenylacetylene, as depicted in Scheme 3.



Scheme 3. Sonogashira coupling of deactivated aryl iodides in water

Conclusions

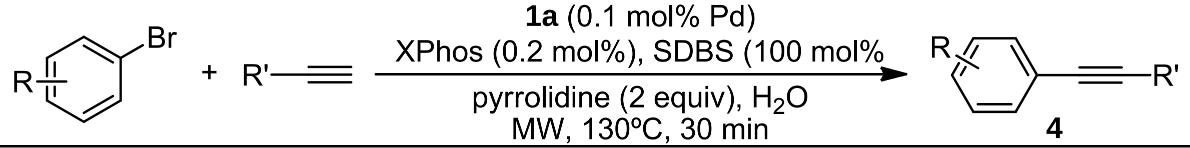
We have disclosed a copper-free oxime palladacycle-catalyzed Sonogashira cross-coupling reaction of deactivated aryl chlorides and aryl bromides with aryl- and alkyl-substituted terminal alkynes using water as solvent under microwave irradiation. This reaction is carried out in the presence of XPhos as ligand (0.2-2 mol%), SDBS as surfactant, and the bench stable oxime palladacycle **1a** as precatalyst under low loading conditions (0.1-1 mol% Pd).

Experimental Section

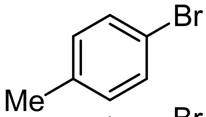
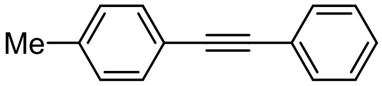
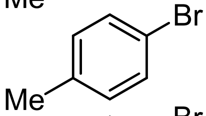
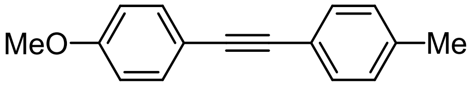
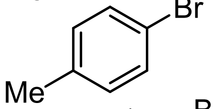
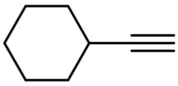
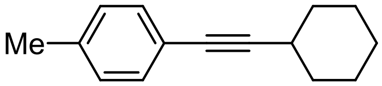
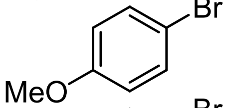
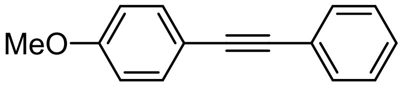
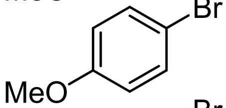
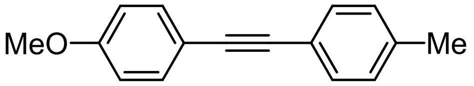
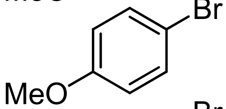
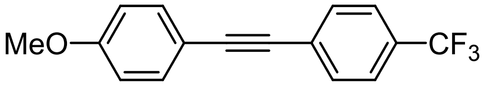
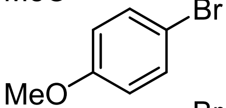
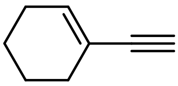
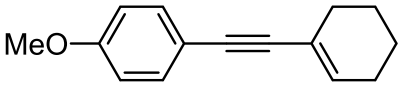
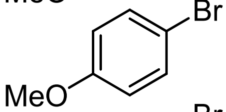
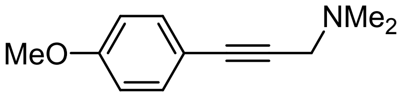
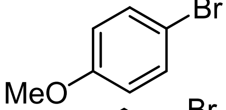
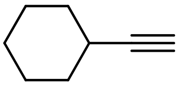
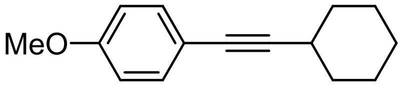
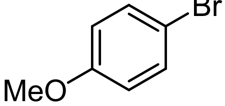
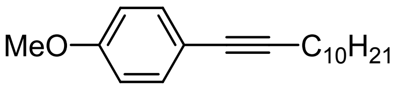
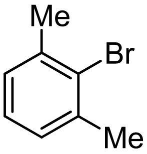
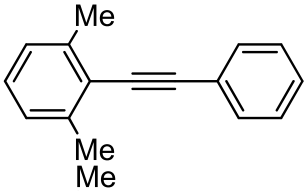
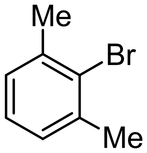
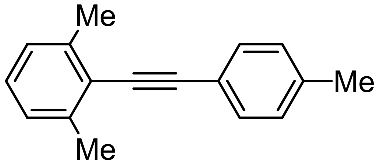
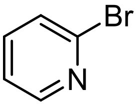
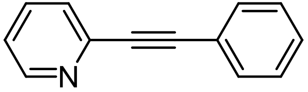
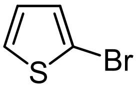
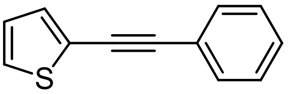
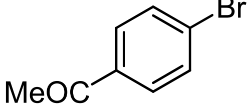
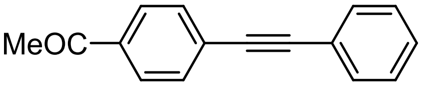
Typical Procedure for the Sonogashira Coupling under MW Irradiation Conditions. A 10 mL MW vessel was charged with 4-chlorotoluene (0.038 g, 0.3 mmol, 1 equiv), phenylacetylene (0.040 mL, 0.36 mmol, 1.2 equiv), pyrrolidine (0.050 mL, 0.6 mmol, 2 equiv), sodium dodecylbenzenesulfonate (0.1045 g, 0.3 mmol, 100 mol%), catalyst **1a** (0.0012 g, 1 mol% Pd), XPhos (0.0029 g, 2 mol%) and H_2O (1.5 mL). The vessel was sealed with a pressure lock, and the mixture was heated at 130 ºC for 30 min with the aid of an initial 40 W MW irradiation in a CEM Discover MW reactor. After this time, the reaction mixture was extracted with EtOAc (3 × 10 mL), and the organic layers were washed with H_2O (3 × 10 mL), dried over $MgSO_4$, filtered over Celite, and concentrated under reduced pressure. The crude residue was purified by preparative layer chromatography (hexane) to obtain 0.044 g of the corresponding pure coupling compound (76% yield).

Supporting Information (see footnote on the first page of this article): Experimental procedures for the cross-coupling reactions as well as spectroscopic data for all the synthesized products.

Table 3. Sonogashira alkynylation of aryl bromides.



4

Entry	ArBr	R'—≡	Product	No.	Yield (%)[a)]
1		Ph—≡		**4a**	94
2		4-$MeOC_6H_4$—≡		**4c**	91
3				**4g**	40
4		Ph—≡		**4b**	82
5		4-MeC_6H_4—≡		**4c**	72
6		4-$F_3CC_6H_4$—≡		**4e**	51
7				**4n**	49
8		Me_2NCH_2—≡		**4f**	61
9				**4o**	37
10		$C_{10}H_{21}$—≡		**4h**	30
11		Ph—≡		**4i**	69
12		4-MeC_6H_4—≡		**4p**	61
13		Ph—≡		**4j**	91
14		Ph—≡		**4k**	63
15		Ph—≡		**4l**	85

a) Isolated yield after preparative thin layer chromatography.

Acknowledgments

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[18] At this point, and considering that the ligand study had been done with CTAB as additive (see SI), we performed a new study using SDBS as surfactant, which did not lead to any improvement of the yield of the reaction (see SI).

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[21] Under the reaction conditions but in the absence of electrophile, 1-phenyl-2-(trimethylsilyl)acetylene was fully converted to phenylacetylene.

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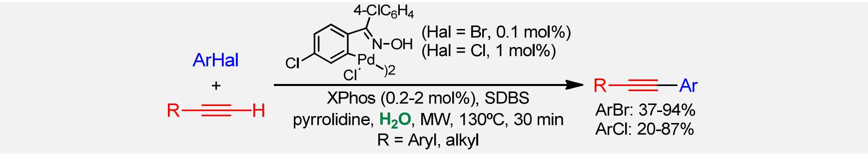

Deactivated and hindered aryl bromides and chlorides are cross-coupled with terminal alkynes using low catalyst loadings of an oxime palladacycle, pyrrolidine as base, SBDS as surfactant, water as solvent, and microwave irradiation (40 W) at 130 ºC. Under these reaction conditions a wide array of tolane derivatives have been prepared in moderate to good yields.

((Key Topic))

Eduardo Buxaderas, Diego A. Alonso, and Carmen Nájera.…….... Page No. – Page No.

Copper-free Palladacycle-Catalyzed Heck Alkynylation of Deactivated Aryl Bromides and Chlorides in water under Microwave Irradiation

Keywords: Sonogashira Reaction / Palladium / Water / Aryl Halide / Alkyne