

THE PALLADIUM-CATALYSED CROSS COUPLING REACTION OF ACETYLENIC COMPOUNDS WITH ARYL HALIDES AND RELATED COMPOUNDS

Paulo T. de Sousa Jr.

Programa de Pós-Graduação em Saúde e Ambiente - Instituto de Saúde Coletiva - UFMT

Recebido em 17/7/95; aceito em 22/3/96

The palladium-catalysed cross coupling reactions of acetylenic compounds with aryl halides and related compounds is reviewed; more than one hundred references are given.

Keywords: palladium-coupling; Sonogashira; acetylenic compounds.

1. GENERAL

The coupling reactions of organic halides with organometallic compounds to make a new C-C bond can be done by a number of different ways¹. However, the use of an organotransition metal salt or complex catalysed coupling is by far the most elegant and practical way of doing these reactions².

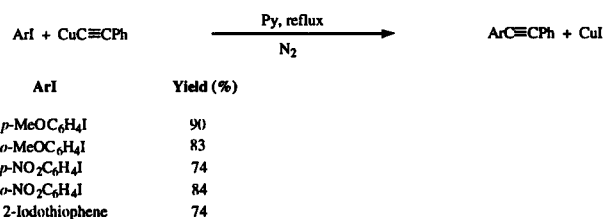
Until the middle 1970's, the most widely used method for the obtaining of aryl and heteroaryl acetylenes was the reaction of copper acetylides with aryl and heteroaryl halides, known as the Stephens-Castro reaction³. This reaction can be carried out with activated or deactivated aryl and heteroaryl⁴ halides, and aryl or alkyl copper acetylides (Schemes 1 and 2)^{3,4}. Although the products can be obtained in fairly good yields, only cyclised products are obtained when the aryl halide bears an *ortho*, non-alkylated, nucleophilic substituent (Scheme 2), imposing a serious limitation to the scope of the reaction. Apart from this, the use of pyridine or DMF⁵ in drastic conditions (reflux, from six to sixteen hours in general) and the need to prepare and handle large amounts of the explosive copper acetylides⁶ also imposes serious restrictions to the process.

The palladium catalysed cross-coupling⁷ of monosubstituted acetylenes with aromatic-, heteroaromatic-, vinylic-compounds, enol triflates and vinyl boron derivatives to produce a disubstituted acetylenic compound can be performed in two ways:

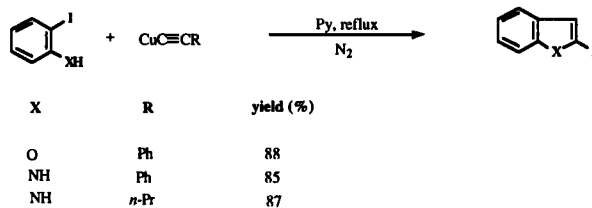
1. Acetylenes and acetylenic organometallics (e.g, Grignard, Zn, Al, Sn and Si reagents) reacting directly with aryl-, vinyl-, heteroarylhalides or triflates in the presence of a suitable Pd catalyst (silicon reagents need fluoride activation⁸).
2. Pd-catalysed reaction of alkynyl halides with Grignard, zinc or boron derivatives of aryl-, vinyl- or heteroarylcompounds.

The first of these possibilities is by far the most common and will be the subject of this review.

Initially⁹, these reactions were carried out using rather drastic conditions (100 °C), as illustrated in table 1, for Pd-catalysed reactions of phenylhalides and non-metallated terminal acetylenes.



Scheme 1



Scheme 2

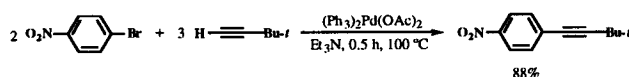
Thus, when iodobenzene was allowed to react with phenylacetylene, the product was obtained in 57-73% yield, after 1.5h at 100 °C in triethylamine (entry 1). The same reaction took 2.5 h to afford the product in 51% yield when the less reactive compound bromobenzene was employed (entry 4). The fact that the reaction with phenylacetylene proceeded smoothly in triethylamine (entry 1), while the reaction with 1-hexyne failed in triethylamine (entry 2) but worked when a stronger base (piperidine-entry 3) was used, indicated that the acidity of the acetylenic protons seems to be an important factor to consider when one wants to establish the reaction parameters in these coupling reactions.

The dramatic effect of electron withdrawing substituents in these Pd-catalysed reactions of aryl halides with terminal acetylenes can be seen by the excellent yield obtained after

Table 1. Pd-catalysed cross-coupling reactions: yields as a function of the reactivity of the substrates.

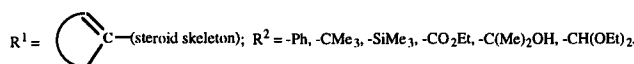
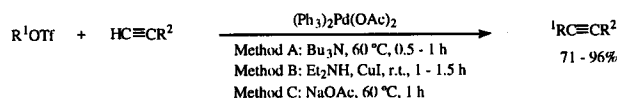
Entry	X	R	$\text{PhX} + \text{HC}\equiv\text{CR} \xrightarrow[100\text{ }^\circ\text{C}]{(\text{PPh}_3)_2\text{Pd}(\text{OAc})_2, 2\text{ mol}\%} \text{PhC}\equiv\text{CR}$				Yield (%)
			PhX/HC≡CR	Base	t (h)		
1	I	Ph	1 / 1.3	Et ₃ N	1.5	57 - 73	
2	I	C ₄ H ₉	1 / 2.0	Et ₃ N	not reported	0	
3	I	C ₄ H ₉	1 / 2.0	piperidine	1.0	62	
4	Br	Ph	1 / 2.0	Et ₃ N	2.5	51	

only 30 minutes of reaction⁹ between 4-bromonitrobenzene and the bulky *t*-butylacetylene, even in the presence of a weak base (Scheme 3).



Scheme 3

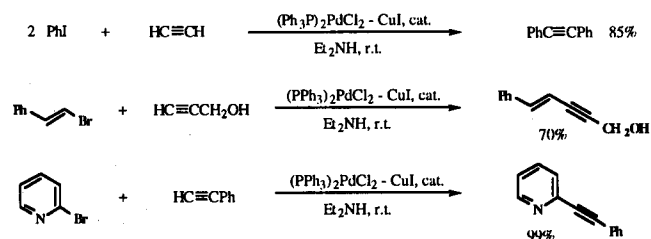
Enol triflates are also reported to couple with alkynyl derivatives, under several experimental conditions, giving good yields of the coupled products¹⁰ (Scheme 4).



Scheme 4

2. THE SONOGASHIRA COUPLING REACTION OF TERMINAL ACETYLENES WITH ARYL HALIDES AND RELATED COMPOUNDS

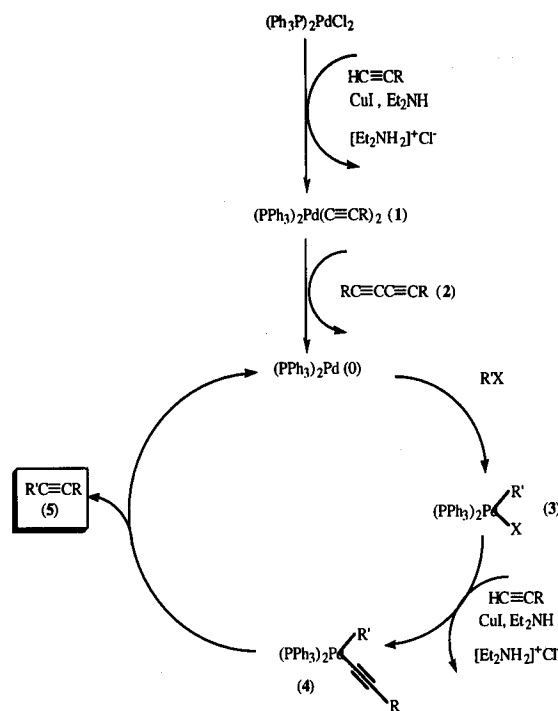
In 1975, Sonogashira *et al*¹¹ found that these coupling reactions could be carried out under milder conditions if cuprous iodide was used as co-catalyst. Several disubstituted acetylenic compounds were obtained by reacting vinyl-, aryl- or heteroaryl halides with acetylene or propargyl alcohol, at room temperature, using bis(triphenylphosphine)palladium(II) dichloride and cuprous iodide as catalysts. The products were obtained in high yields, regardless of the relatively low reactivity of the substrates (Scheme 5).



Scheme 5

The proposed¹¹ mechanism for these reactions (Scheme 6) involves firstly alkynylation of (Ph₃P)₂PdCl₂ by two alkyne molecules, producing bis-(triphenylphosphine)dialkynyl palladium (II) (1), which upon reductive elimination of a diyne unit (2) produces (PPh₃)₂Pd(0). Subsequent oxidative addition of aryl or vinyl halide (R'X) to (PPh₃)₂Pd(0) leading to (3) and alkynylation of (3), produces an aryl- or vinyl- bis-(triphenylphosphine) palladium (II) derivative (4), which is an unstable species and regenerates (PPh₃)₂Pd(0) through reductive elimination of the coupled product (5). The authors¹¹ also speculated that the role of CuI in these reactions would be to facilitate the halide-alkyne substitution in (PPh₃)₂PdCl₂.

The most used catalysts for these reactions (being now popularised as "Sonogashira Coupling"^{12a-j}) are bis-(triphenylphosphine) palladium(II) dichloride and bis-(triphenylphosphine) palladium(0). In most situations they can

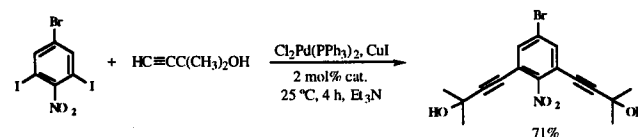


Scheme 6

be used interchangeably, but the fact that the former is more stable and cheaper than the latter, makes it the preferred catalyst. However, more recent literature presents some seemingly attractive alternatives. Guzmán¹³ *et al*, claim to have obtained good yields when coupling a series of aryl bromides with terminal acetylenes using a mixture of 4 mol% of palladium (as 10% palladium on charcoal), 16 mol% of triphenylphosphine and 4 mol% of CuI as catalyst; the authors also collected experimental evidence that suggested that this is an *in situ*^{14a-d} source of Pd(PPh₃)₄. Sometimes, the combination Pd(dba)₂/CuI or Pd(dba)₂/PPh₃/CuI can also be used in catalytic amounts, affording the coupled products in good yields¹⁵⁻¹⁷. It has been demonstrated that, in some situations, the use of CuI as a co-catalyst can lead to the formation of Clases-type dimeric acetylenic compounds as the major products¹⁸. In another paper¹⁹, Weatherford *et al* described the preparation and use of soluble and recoverable polymer-bound palladium(0) and palladium(II) catalysts.

A common problem encountered in these reactions, when unreactive halides (*e.g.* thienyl and furyl bromides) are used, is the formation of metallic palladium, with the consequent interruption of the reaction. Brandsma²⁰ and co-workers reported that this could be avoided by the addition of triphenylphosphine [10 mol% of excess related to Pd(PPh₃)₄] to the reaction mixture.

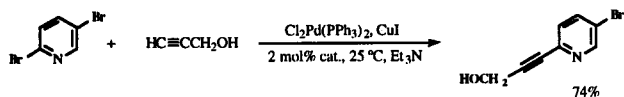
The preferential displacement of iodine²¹⁻²² over the other halides is sometimes used to regioselectively displace one of the halides in a polyhalogenated molecule²³ (Scheme 7).



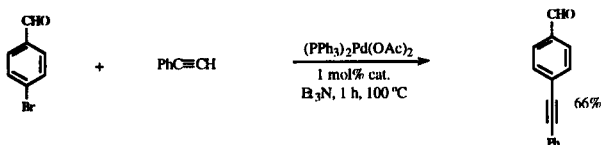
Scheme 7

Regioselectivity was also observed in the palladium-copper catalysed reaction of 2,5-dibromopyridine with terminal acetylenes²⁴ (Scheme 8). Other functional groups such as aldehydes can be tolerated, even under more drastic conditions,

as in the selective displacement of bromine in the Pd-catalysed reaction of *p*-bromobenzaldehyde with phenylacetylene⁹ (Scheme 9). It should be pointed out that the more drastic conditions employed in the latter reaction (Scheme 9) are necessary due the non-utilisation of a copper salt as co-catalyst.

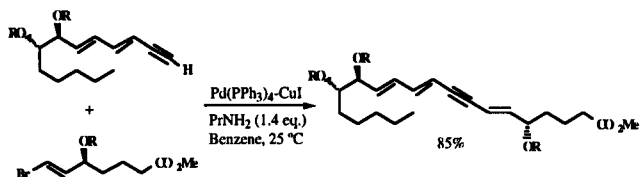


Scheme 8



Scheme 9

Another remarkable feature of this reaction is the stereoselectivity. In fact, this characteristic makes this reaction extremely useful in the synthesis of natural products, where olefins of precisely defined geometry are often required²⁵ (Scheme 10).



Scheme 10

Table 2 shows a brief survey of the conditions usually employed in these reactions. Amines are often used as bases and solvents (entry 1). However, in specific situations it is found that the reaction can give rise to the products in better yields if it is carried out in other organic solvents (e.g., DMF, benzene, CHCl₃), with a slight stoichiometric excess of amines

as bases (entries 2, 3 and 4). Inorganic bases can also be used, under phase transfer conditions^{25,28} (entry 5).

Sometimes, the choice of a proper base is crucial. Thus, in the reaction of enol triflates with ethyl propionate, it was reported¹⁰ that the use of amines as bases failed to afford any enyne. However, good results were obtained by substituting sodium acetate for the amine, while the use of sodium hydrogencarbonate and tetrabutylammonium chloride gave only modest yields. Taylor and Sousa^{29,26} found more reproducible results (and cleaner reactions) using diisopropylamine instead of triethylamine in the coupling reaction of 2-(1-hydroxyonyl)-5-iodothiophene (6) and methyl-5-hydroxyhept-6-ynoate (7) (Table 3). Recently³⁰, it has been shown the critical importance of the nature of the amine in the Pd-catalysed reaction of vinyl and aryl halides or triflates with 1-alkynes.

3. THE Pd-COUPLING REACTIONS OF METALLATED ACETYLENES WITH ARYL HALIDES AND RELATED COMPOUNDS

The coupling of tin-alkyne derivatives with vinylic iodides occurs under extremely mild conditions, where neither base nor CuI are necessary. In fact, this excellent reactivity of organotin compounds in Pd-coupling reactions has been dramatically demonstrated in the literature^{31a-i}. These tin reactions are also highly stereoselective^{31h} (Schemes 11 and 12) and the "ligandless catalyst" (MeCN)₂PdCl₂ seems to be the most appropriate one for this class of reactions. The combination of Pd catalyst and AsPh₃ can also lead to good yields of coupled products³².

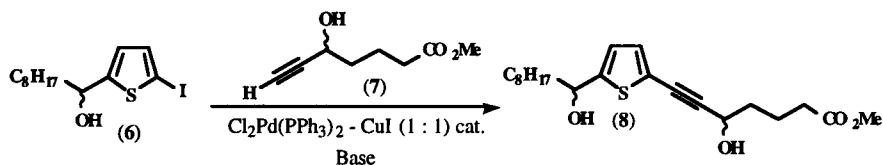
As already mentioned before, many kinds of different organometallic derivatives of alkynes can be employed. Thus, Italian researchers³³ reported the stereospecific reaction of compounds of the type R¹-M (R¹ = alkyl, aryl, 1-alkynyl, PhS; M = -MgX, -Cu, -ZnCl, -SnBu₃) with (*E*)-1-bromo-1-alkenes in the presence of the corresponding (*Z*)-stereoisomers (Scheme 13). This stereoselectivity can be used as a convenient way to prepare pure (*E*) alkenes from a diastereomeric mixture.

The production of enynes, with high stereospecificity, via organozinc Pd-coupling reactions³⁴ is said to be advantageous over Pd-coupling reactions using other alkynyl metal derivatives³⁵. Furthermore, apart from their greater stability, some functional groups not compatible with other alkynyl metal derivatives can be tolerated by alkynylzinc compounds. Pd(0) can

Table 2. Pd-Cu catalyzed cross-coupling reactions: a brief survey of the conditions usually employed.

Entry	Substrates	Solvent	Base	Catalyst	T(°C)	Ref.
1		<i>i</i> -Pr ₂ NH	<i>i</i> -Pr ₂ NH	(PPh ₃) ₂ PdCl ₂ , CuI	25	26
2		DMF	Et ₂ NH	(PPh ₃) ₂ PdCl ₂ , CuI	25	11
3		benzene	<i>i</i> -Pr ₂ NH	Pd(PPh ₃) ₄ , CuI	25	25
4		CHCl ₃	Et ₃ N	IPhPd(PPh ₃) ₂ , CuI Et ₃ NH ⁺ X ⁻	25	27
5		benzene	NaOH	Pd(PPh ₃) ₄ , CuI BnEt ₃ N ⁺ Cl ⁻	25	28

Table 3. Pd-Cu catalysed reaction of (6) and (7): influence of the solvent /base.

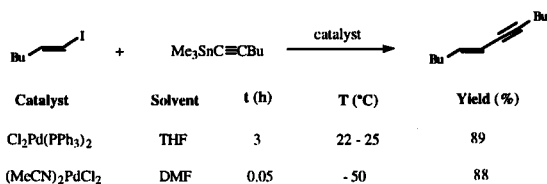


Entry ^a	Solvent ^b	(6) / (7) (mmol)	Temp. (°C) / Time (h.)	% Yield ^c (8)
1	Et ₃ N	0.14 / 0.15	25 / 4 and 60 / 2	78
2	Et ₃ N	1.50 / 1.55	60 / 96	49 (68)
3	Et ₃ N	2.55 / 2.58	25 / 20	36 (49)
4	<i>i</i> -Pr ₂ NH	0.21 / 0.22	25 / 3	74 (84)
5	<i>i</i> -Pr ₂ NH	0.84 / 0.88	25 / 4	62 (88)
6	<i>i</i> -Pr ₂ NH	1.14 / 1.15	25 / 17	69 (97)

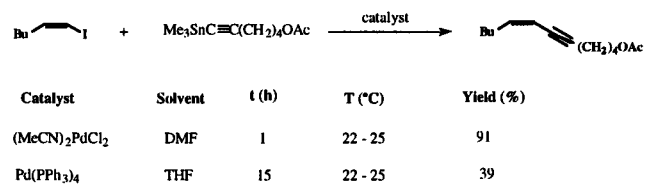
a: Amount of catalysts: entries 1, 3, 6 = 3 mmol%; entries 4, 5 = 2 mmol%; entry 6 = 3 + 1.5 + 1.5 mmols, in successive additions.

b: Amount of solvent = 3 mL / mmol.

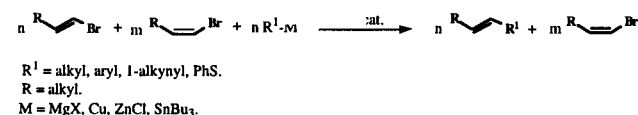
c: The numbers in brackets refer to yields based on recovered starting material.



Scheme 11



Scheme 12



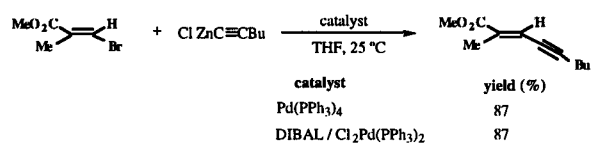
Scheme 13

be either directly used as catalyst or generated *in situ* from Pd(II) and DIBAL (Scheme 14). The use of the catalyst Cl₂Pd(dppf)₂, where the bidentate ligand diphenylphosphineferrocene (dppf) replaces two monodentate triphenylphosphines, was shown to be advantageous³⁶⁻³⁷ in the reactions of 1-alkynylzinc compounds with 1,2-dihaloalkenes (Scheme 15).

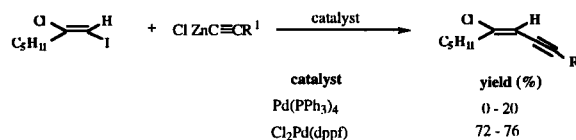
Recently, it was found³⁷ that good results could be obtained using a cheaper and more stable catalyst, consisting of a mixture of 10% Pd/C [or Pd(OAc)₂] and the soft ligand AsPh₃ (Scheme 16).

There are several examples of Pd coupling reactions using Grignard salts of acetylenic compounds^{28b,38}. Thus, Carpita *et al.*³⁸ reported obtaining 2-ethynylthiophene in 83% overall yield, by coupling 2-iodothiophene with trimethylsilyl ethynylmagnesium bromide followed by deprotection of the acetylenic moiety (Scheme 17).

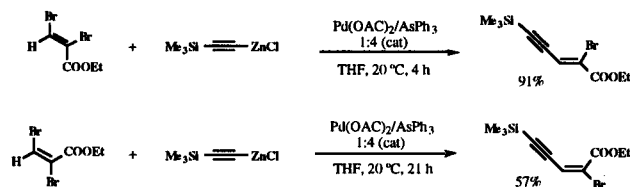
Silicon-protected acetylenes can also be allowed to couple directly with enol and aryl triflates in the presence of Pd(0) catalyst and fluoride ion^{8,39} (Scheme 18), affording good yields



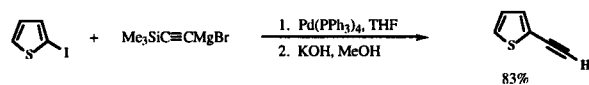
Scheme 14



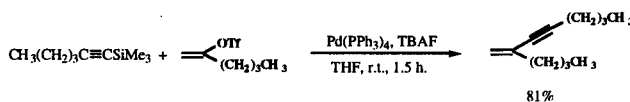
Scheme 15



Scheme 16

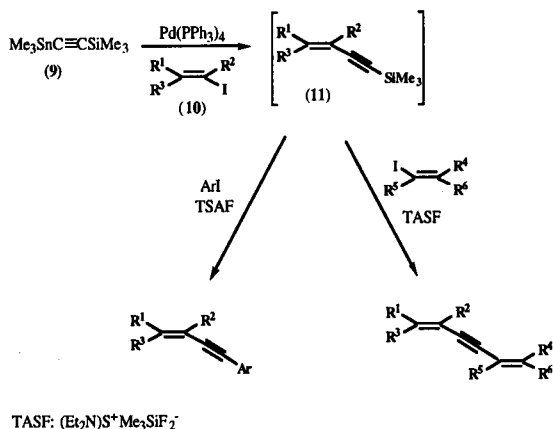


Scheme 17



Scheme 18

of coupled products. Another interesting application⁴⁰ of this fluoride induced reaction is shown in Scheme 19. In this case, the carbon-tin moiety of trimethylstannyl(trimethylsilyl)ethyne (9) was allowed to react with an alkenyl iodide (10), generating the silylated intermediate (11), which was then activated by fluoride ion, before it was allowed to react with another alkenyl- or aryl iodide, in the presence of the same palladium catalyst, affording good yields of disubstituted acetylenes.



Scheme 19

4. FINAL CONSIDERATIONS

The wide applicability of these mild and powerful reactions can be easily verified in the recent synthetic organic chemistry literature, where it has been extensively used in the synthesis of medicines (e.g. nucleosides^{41,42}, enediyne-based anti-tumor drugs⁴³⁻⁵⁵, and others⁵⁶⁻⁶¹), polymers and macromolecules⁶⁰⁻⁷², heterocycles⁷³⁻⁷⁶, natural products⁷⁷⁻⁷⁹ and analogues⁸⁰, to mention only a few recent applications. In fact, it has been hard to see an issue of any respectable magazine that does not bring at least one mention of these reactions. In addition, their increasing industrial importance was highlighted in a review⁸¹ entitled "Expanding Industrial Applications of Palladium Catalysts".

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