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LETTERS

A copper- and amine-free Sonogashira-type coupling procedure catalyzed by oxime palladacycles

Diego A. Alonso, Carmen Nájera* and Mª Carmen Pacheco

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain

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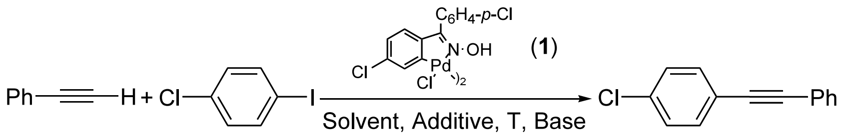
Abstract—Oxime palladacycle derived from 4,4′-dichlorobenzophenone was found to promote the Sonogashira reaction of aryl iodides and aryl bromides with terminal acetylenes using 1 equivalent of tetrabutylammonium acetate in organic solvents generally in 1 h at 110°C and in high TONs (up to 72000). © 2002 Elsevier Science Ltd. All rights reserved.

Cross-coupling reactions of acetylenes with aryl or alkenyl halides or triflates in the presence of a palladium salt or complex, copper iodide and an amine, are extensively used in organic chemistry and materials science for the preparation of internal alkynes and enynes.[1] Thus, the Sonogashira reaction is used in numerous syntheses of natural products, for instance, enediyne antibiotics,[2] as well as in the preparation of liquid crystals, conducting polymers and other engineering materials.[3] In order to simplify the Sonogashira reaction protocol, several important aspects have to be improved. First, to eliminate the use of copper(I) iodide as co-catalyst, because it induces homocoupling reactions (Glaser-type reactions) of terminal alkynes to diynes in the presence of oxygen.[4] Second to also avoid, is the use of the amine. Its presence, either as solvent or in stoichiometric amounts for the elimination of the HX formed in the reaction, seems vital but largely depends on the type of substrates to be coupled. Furthermore, and from an economical point of view, to employ lower catalyst loadings, which is a very important feature because of the high loadings (1–5 mol%) usually required when typical catalysts such as $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$ or $Pd_2(dba)_3$ are employed. Another facet to improve is the ability to perform this reaction in air using reagent-grade chemicals and solvents.

Copper-free methodologies have recently been described employing amines as solvents as in the case of palladium(0) complexes such as $Pd(PPh_3)_4$ in piperidine or pyrrolidine.[5] The only example using a palladacycle[6] in a copper-free protocol, is Herrmann′s phospha-palladacycle which is performed in triethylamine and only worked with phenylacetylene as *sp* counterpart.[7] On the other hand, the catalytic system $Pd_2(dba)_3$[8] promotes the copper-free Sonogashira reaction of aryl bromides at room temperature,[9] but the air-unstable tris-*tert*-butylphosphane has to be used as co-catalyst. Stoichiometric amounts of silver(I) oxide for aryl iodides, and tetrabutylammonium fluoride (TBAF) or tetrabutylammonium hydroxide (TBAOH)[10] for aryl bromides, have been used as activators in the first described copper- and amine-free procedure.[11] Very recently, phenylacetylene has been coupled with aryl chlorides under harsh conditions in the presence of $ZnCl_2$ as additive and Cs_2CO_3 as base, employing 5 mol% of the phosphinito palladium pincer complex $PdCl[C_6H_3(OPPr^i_2)_2\text{-}2,6]$.[12]



Scheme 1.

Keywords: alkynes; coupling reactions; palladium catalysis.

* Corresponding author. Fax: +34-96-5903549; e-mail: cnajera@ua.es

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Table 1. Sonogashira coupling: reaction conditions study

Entry	Solvent	Base	Additive (mol%)	T (°C)[a]	**1** (mol% Pd)	t_R (h)	Yield (%)[b]	TON[c]
1	Pyrrolidine	–	CuI (5)	90	0.5	1	84	168
2	NMP	Pyrrolidine	–	110	0.5	1	96	192
3	NMP	NaOAc	–	110	0.5	1	36[d]	72
4	NMP	NH_4OAc	–	110	0.5	3.5	29[d]	58
5	NMP	–	TBAF (150)	110	0.5	3	86[d]	172
6	NMP	–	TBAOH (150)	110	0.1	3	0	–
7	NMP	–	TBAOAc (150)	110	0.1	2	>99	990
8	NMP/H_2O: 95/5	–	TBAOAc (110)	110	0.1	1	>99	990
9	THF	–	TBAOAc (110)	–[e]	0.1	5	89	890
10	NMP	–	TBAOAc (110)	80	0.1	4	>99	990
11	NMP	–	TBAOAc (110)	110	10^{-2}	24	97	9700
12	NMP	–	TBAOAc (110)	110	10^{-3}	24	72	72000

[a] Bath temperature.

[b] Conversion determined by GC using decane as internal stardard and based on starting 1-chloro-4-iodobenzene.

[c] TON (turnover number) = mol product mol Pd^{-1}.

[d] Several non-identified enyne by-products were also obtained in variable yields as a result of the addition of the terminal alkyne to the reaction product.

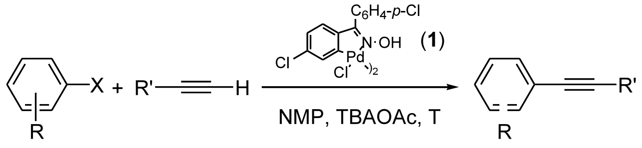
[e] Under THF reflux.

We have recently reported that oxime-based palladacycles are air and water stable precatalysts for a wide range of cross-coupling processes such as Heck, Suzuki, Stille, Sonogashira and Ullmann-type reactions in organic[13] and aqueous[14] solvents. In the preliminary studies of the Sonogashira reaction,[13a] we performed the coupling of phenylacetylene and iodobenzene in the presence of CuI and pyrrolidine as solvent at 90°C. We have found that this alkynylation process can be performed under very convenient copper- and amine-free conditions in air and using reagent-grade chemicals.

The alkynylation reaction of aryl halides was evaluated with palladium complex **1**[15] (Scheme 1). In order to determine the optimum reaction conditions, we chose the coupling between 1-chloro-4-iodobenzene and phenylacetylene in the presence of catalyst **1** (0.1–0.5 mol% of Pd) as a model reaction (Scheme 1, Table 1). As previously reported,[13a] the coupling reaction between 1-chloro-4-iodobenzene and phenylacetylene, provided a good yield when pyrrolidine was used as solvent in the presence of CuI as co-catalyst (5 mol%) at 90°C under air using 0.5 mol% of Pd (Table 1, entry 1). When using *N*-methylpyrrolidinone (NMP) as solvent and 2 equiv. of pyrrolidine as base in the absence of CuI at 110°C (Table 1, entry 2), an excellent yield was obtained. Because of this result, we carried out a base study, which showed that inorganic bases such as NaOAc and NH_4OAc only led to poor reaction yields. Other bases such as TBAF, gave an acceptable 86% yield after 3 h. Aqueous TBAOH did not promote the reaction coupling at all (Table 1, entries 5 and 6). However, tetrabutylammonium acetate (TBAOAc) showed the best activity even when the catalyst loading was reduced to 0.1 mol% of Pd (Table 1, entry 7). The presence of small amounts of water did not have a deleterious effect in the reaction yield (Table 1, entry 8). Changing the solvent from NMP to THF under reflux, resulted in a lower yield and longer reaction times (entry 9). The reaction could be carried out at lower temperature (80°C) and using 1.1 equiv. of TBAOAc as well (entry 10), and high TON accompanied with very good yields could be obtained when the catalyst loading was reduced to 10^{-3} mol% of Pd (Table 1, entry 12).

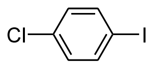
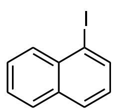
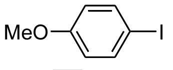
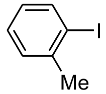
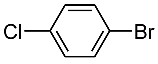
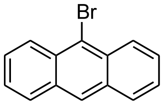
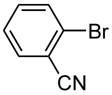
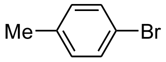
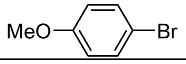
Using these conditions,[16] complex **1** catalyzed the Sonogashira coupling of a wide variety of aryl iodides and bromides and terminal acetylenes (Scheme 2, Table 2). Yields were generally high after short reaction times for all type of substrates. Activated substrates such as 1-chloro-4-iodobenzene and 1-chloro-4-bromobenzene reacted with an array of aromatic and aliphatic alkynes in good to excellent yields (Table 2, entries 1–5 and 10–11). As illustrated in entries 7, 8, 15 and 16, less reactive electron-rich 4-iodoanisole, 4-bromotoluene and 4-bromoanisole, also coupled with fairly good efficiency. Steric effects as in 2-iodotoluene and 2-bromobenzonitrile (Table 2, entries 9 and 14), did not influence the yield. 9-Bromoanthracene, reacted with phenylacetylene and (triisopropylsilyl)acetylene to afford, in high yields, the corresponding 9-alkynylanthracenes with no observable formation of aceanthrylenes.[17]

In summary, we have shown that the phosphane-free oxime-derived palladacycle **1**, is an efficient and versatile catalyst for amine- and copper-free Sonogashira reactions of aryl iodides and aryl bromides with a variety of terminal acetylenes. The catalyst system is highly active using very low loading conditions, under air and employing reagent-grade chemicals. Further studies to extent to other substrates this reaction protocol and to understand the mechanism of the process are currently under investigation in our group. This study provides further evidence of the usefulness of oxime-derived palladacycles in palladium-catalyzed reactions.



Scheme 2.

Table 2. Sonogashira coupling or aryl halides catalyzed by **1**

Entry	Aryl halide	Alkyne	**1** (mol% Pd)	T (°C)[a]	t_R (h)	Yield (%)[b]
1		H—≡—Ph	0.1	110	1	>99
2		H—≡—*n*-Hex	0.5	110	1	>99
3		H—≡—TIPS	0.5	110	1	84
4		H—≡—$C(Me)_2OH$	0.1	110	5	85
5		H—≡—CH_2OH	0.1	110	1	99[c]
6		H—≡—Ph	0.1	110	1	100 (99)
7		H—≡—Ph	0.1	110	1	100 (99)
8		H—≡—TIPS	0.1	110	1	90
9		H—≡—Ph	0.1	110	1	92
10		H—≡—Ph	0.5	110	7.5	93 (90)[d]
11		H—≡—*n*-Hex	0.1	110	2	78
12		H—≡—Ph	0.1	110	1	81
13		H—≡—TIPS	0.1	110	3.5	79
14		H—≡—Ph	1	110	1	96
15		H—≡—TIPS	0.25	130	4	81
16		H—≡—TIPS	0.25	130	1	85

[a] Bath temperature.

[b] Conversion determined by GC using decane as internal stardard and based on starting halide. In brackets, isolated crude yield after work-up. Crude products were pure (>95%, GC) and gave satisfactory spectroscopic data (^1H and ^{13}C NMR, IR and MS).

[c] A 10% of acetylated alcohol was also obatined.

[d] One additional equiv. of phenylacetylene had to be added to the reaction mixture.

Acknowledgements

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15. Other palladacycles developed in our group derived from benzophenone, acetophenone, pinacolone and 4,4′-dimethoxybenzophenone, gave very similar results.
16. *Typical experimental procedure*: A solution containing palladium catalyst **1** (0.1 mol% of Pd, 2.5×10^{-4} mmol, 0.204 mg), TBAOAc (0.53 mmol, 163 mg), 1-iodonaphthalene (0.5 mmol, 74 μL) and phenylacetylene (0.6 mmol, 67 μL) in NMP (2 mL), was stirred under air at 110°C until the aryl iodide had been consumed (1 h, reaction followed by GC, using decane as internal standard). NMP was then evaporated and the reaction crude mixture was extracted with H_2O and EtOAc (3×10 mL). The organic extracts were dried ($MgSO_4$) and evaporated to afford the crude product which was purified by column chromatography.
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