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Investigations into the Pd-catalysed cross-coupling of phenylacetylene with aryl chlorides: simple one-pot procedure and the effect of $ZnCl_2$ co-catalysis[†]

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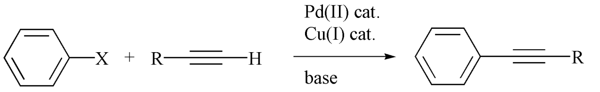
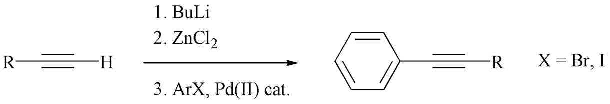
$[PdCl\{C_6H_3(OPPr^i_2)_2\text{-}2,6\}]$ 1 catalyses the coupling of electron-rich, electron-neutral and electron-deficient aryl chlorides with phenylacetylene in the presence of $ZnCl_2$ as co-catalyst to give the products in modest to excellent yields.

Acetylenes are versatile and valuable compounds in organic synthesis,[1] the preparation of liquid crystalline materials and conducting polymers.[2] Much successful research has been directed towards the coupling of terminal alkynes with aryl bromides and iodides employing either organometallic copper(I) or zinc(II) compounds; Sonogashira coupling (eqn. (1)) or Negishi coupling (eqn. (2)), respectively.



(1)



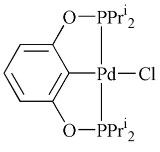
(2)

The most common methodology is the Sonogashira reaction which employs catalytic amounts of a palladium(II) complex and copper(I) iodide as co-catalyst, as well as an amine as base.[3] Copper(I) acetylides are generated *in situ* and are successfully coupled with a wide range of aryl bromides and iodides. Only isolated examples for the Sonogashira coupling of aryl chlorides are known. Ansorge and Müller activated chlorobenzene by preparing $[(chlorobenzene)Cr(CO)_2(PPh_3)]$ first which was then coupled with four different acetylenes in moderate yields.[4] Recently Erdélyi and Gogoll achieved the coupling of 2-chloropyridine with trimethylsilylacetylene at 120 °C using controlled microwave heating.[5]

The less frequently used variation of a Negishi-type coupling uses discrete zinc(II) acetylides which have to be prepared first from acetylenes, a base (*e.g*. BuLi, LDA) and $ZnCl_2$ in at least quantitative amounts and are then cross-coupled with aryl halides in the presence of a palladium–phosphine catalyst.[6] No examples for aryl chlorides are known. Recently Anastasia and Negishi showed that alkynylzinc derivatives can be generated *in situ* and be successfully coupled with aryl iodides; the organometallic compound was used in excess.[7]

Whereas catalytic amounts of copper(I) acetylides are generated *in situ* for the Sonogashira reaction this concept has rarely been applied to the Negishi method. Surprisingly, only two examples are known where $ZnCl_2$ is used as a co-catalyst. Crisp *et al*. showed that catalytic amounts of $[Pd(PPh_3)_4]$, $ZnCl_2$ and NaI or iodine efficiently coupled terminal alkynes and ArX (X = Br, I) in the presence of excess amine as base.[8] A system using $ZnCl_2$ without NaI performed poorly. Although this catalytic protocol did not offer any distinct advantage over Sonogashira-type couplings it showed convincingly that *in situ* generated zinc acetylides can be successfully used for the coupling of terminal alkynes with aryl halides.

In this communication, we report our findings that for the first time a wide array of aryl chlorides can be cross-coupled with phenylacetylene in the presence of the phosphinito palladium pincer complex **1**, catalytic amounts of $ZnCl_2$ and a base in a simple one-pot procedure. Recently there has been increased interest in PCP pincer complexes for their use in homogeneous catalysis due to their excellent moisture-, air- and temperature-stability.[9] Complex **1** was found to be an active catalyst for the Heck reaction between styrene and various aryl chlorides.[10]



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Initial studies focused on the reaction between chlorobenzene and phenylacetylene under various reaction conditions *e.g*. different ratios, solvent, temperature, base and co-catalyst. Catalytic runs with a 1 : 2 ratio of chlorobenzene to phenylacetylene gave the desired product but also led to the formation of varying amounts of symmetrical diynes *via* homocoupling of the alkyne. The amount of by-product is dependent on temperature, base and additive. Lower temperatures (100 °C) gave only small amounts of product and homocoupling was predominant. Different solvents such as amines (*e.g*. piperidine, NEt_3), THF, toluene or high boiling glycol ethers resulted in low yields and by-products. Experiments under optimised conditions were conducted with a 5 : 1 ratio of aryl chloride to alkyne at 160 °C and in dioxane as solvent. Of the bases tested, DMAP, DABCO, NaOH, $NaHCO_3$, Na_2CO_3, K_2CO_3, CsOAc and Cs_2CO_3, Cs_2CO_3 and $NaHCO_3$ were the bases of choice. Some of these bases gave either no product or only some product accompanied by various by-products. Co-catalysts such as NH_4F, KF, NaF, NaBr, NaI, $AlBr_3$, Fe, $FeCl_3$, Mg, Cu, CuI, Zn and $ZnCl_2$ were tested as well.

The results of selected cross-coupling experiments under optimised conditions are summarised in Table 1. No conversion was effected without the presence of the metal catalyst **1** (entries 1 and 2). The best result was achieved with Cs_2CO_3 that showed the cleanest conversion albeit not a high GC yield (19%; entry 3). Co-catalysis by a metal salt was found to be essential. A typical Sonogashira system using CuI and an amine or any of the other bases mentioned above did not show any notable conversion of the starting materials to diphenylacetylene (representative examples are given in entries 4 and 5). However, a combination of Cs_2CO_3 and $ZnCl_2$ (10 mol% with respect to phenylacetylene) gave the best results and cleanest conversion (up to 61% isolated yield, entry 11).

Co-catalyst $FeCl_3$ together with Cs_2CO_3 formed an active system as well (Table 1, entry 10). In contrast to the observation by Crisp *et al*. no further additive is necessary. Actually, a $Cs_2CO_3/ZnCl_2/NaI$ system gave only 9% GC yield and a system of $Cs_2CO_3/ZnCl_2/I_2$ gave only 48% GC yield.

[†] Electronic supplementary information (ESI) available: general experimental, procedure for cross-coupling experiments and characterization data for products. See http://www.rsc.org/suppdata/cc/b2/b200453b/

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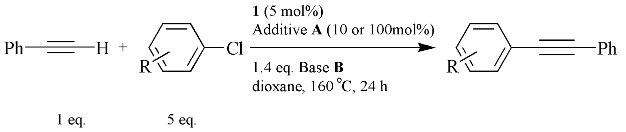
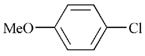
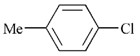
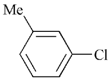
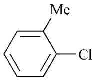
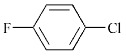
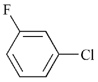
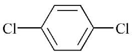
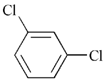
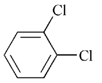
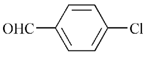
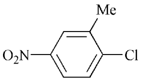
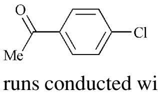
After establishing that complex **1** together with $ZnCl_2$ and Cs_2CO_3 gave good yields for diphenylacetylene this system was applied to a series of aryl chlorides (Table 1, entries 11–23). Isolated yields for these examples were determined either from a large-scale experiment or are averaged over 3 runs. Yields range from 19 to 91% and are based on phenylacetylene. The desired products were isolated and purified by column chromatography. Purity of the products was confirmed by NMR spectroscopy and gas chromatography. The excess aryl chloride can easily be recovered from the reaction mixture by distillation or column chromatography. $ZnCl_2$ acts in most cases as a co-catalyst. However, for all three chlorotoluenes as well as 2-chloro-4-nitrotoluene 100 mol% $ZnCl_2$ is necessary for the reaction to proceed successfully (Table 1, entries 13, 14, 15 and 22). For example only 26% isolated yield was obtained from the reaction of 2-chloro-4-nitrotoluene with phenylacetylene in the presence of 10 mol% $ZnCl_2$. Whereas it was established that a 5:1 ratio of alkyne to aryl chloride was preferred it is noteworthy that a ratio of 2 : 1 of phenylacetylene to 4-chloroacetophenone led to the highest isolated yield in the desired product (Table 1, entry 23).

Table 1 Scope of the Pd-catalysed cross-coupling between aryl chlorides and phenylacetylene catalysed by Pd pincer complex **1**



Entry	Aryl chloride	Additive **A**	Base **B**	Yield (%)
1[a]	R = H	$ZnCl_2$	—	—
2[a]	R = H	$ZnCl_2$	Cs_2CO_3	—
3	R = H	—	Cs_2CO_3	19[b]
4	R = H	CuI	NEt_3[d]	—
5	R = H	CuI	Cs_2CO_3	14[b,e]
6	R = H	$ZnCl_2$	K_2CO_3	42[b]
7	R = H	$ZnCl_2$	Na_2CO_3	28[b]
8	R = H	$ZnCl_2$	$NaHCO_3$	64[b]
9	R = H	$ZnCl_2$	CsOAc	—
10	R = H	$FeCl_3$	Cs_2CO_3	58[b]
11	R = H	$ZnCl_2$	Cs_2CO_3	61[c]
12		$ZnCl_2$	Cs_2CO_3	65[c]
13		$ZnCl_2$[f]	Cs_2CO_3	82[c]
14		$ZnCl_2$[f]	Cs_2CO_3	71[c]
15		$ZnCl_2$[f]	Cs_2CO_3	68[c]
16		$ZnCl_2$	Cs_2CO_3	50[c]
17		$ZnCl_2$	Cs_2CO_3	36[c]
18		$ZnCl_2$	Cs_2CO_3	80[c]
19		$ZnCl_2$	Cs_2CO_3	19[c]
20		$ZnCl_2$	Cs_2CO_3	36[c]
21		$ZnCl_2$	Cs_2CO_3	40[c]
22		$ZnCl_2$[f]	Cs_2CO_3	61[c]
23[g]		$ZnCl_2$	Cs_2CO_3	91[c]

[a] Catalytic runs conducted without complex **1**. [b] GC yield with undecane as internal standard. [c] Isolated yields; average of 3 runs or large-scale experiment. [d] Pure = 3 ml, no dioxane; alkyne : PhCl = 2 : 1. [e] 80% pure by GC. [f] 100 mol% $ZnCl_2$. [g] Phenylacetylene : 4-chloroacetophenone 2 : 1.

In summary, we have established the first catalyst system which cross-couples efficiently a wide range of electronically deactivated, non-activated and activated as well as hindered aryl chlorides with phenylacetylene. It is a very simple but effective one-pot procedure without the need of preparing or storing large quantities of potentially unstable reagents. The catalytic activity of **1** is enhanced in the presence of catalytic amounts of $ZnCl_2$. In fact, $ZnCl_2$ is essential for achieving good yields and besides $FeCl_3$ the only promoter of a series tested which was found to be active. Future research is directed towards the use of $FeCl_3$.

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