Efficient copper-free Sonogashira coupling of aryl chlorides with palladium on charcoal†

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Palladium on charcoal serves as an efficient and reusable solid supported catalyst for the Sonogashira coupling of aryl chlorides with terminal acetylenes in the presence of a bulky, electron-rich biphenyl type ligand (XPhos), without copper co-catalyst.

The palladium-catalyzed Sonogashira reaction is one of the most frequently used synthetic tools for the construction of new C(sp)–C(sp^2) bonds in organic synthesis.[1] While both aryl iodides[2] and bromides[3] are excellent coupling partners of terminal acetylenes, the achievement of cross couplings on the more practical and accessible aryl chlorides[4] is still challenging. Generally, the Sonogashira reaction required Cu(I) co-catalyst for the achievement of efficient coupling, but the presence of the copper salt can also facilitate the homocoupling of the terminal acetylene as a side reaction. Therefore, considerable effort has been directed to the development of effective copper-free processes.[5] Additionally, the reduction of the catalyst loading and the recycling of the palladium metal are also quite important in this field of synthesis. For these reasons, utilization of the most readily available palladium on charcoal[6] catalysts under copper-free conditions would provide a good opportunity for recycling of the relatively expensive transition metal and would also reduce the metal and butadiyne contamination of the products.

Herein we report a straightforward procedure for the Sonogashira coupling of aryl chlorides with acetylenes under copper-free conditions in the presence of a palladium on charcoal catalyst using a non-toxic carbonate base.

At the begining of our examination we screened a variety of ligands in the palladium on charcoal catalyzed Sonogashira coupling (see ESI†). As a model reaction, coupling of chlorobenzene and phenylacetylene was chosen to optimize reaction conditions. The application of both electron-rich and electron-deficient triarylphoshanes were not effective in the coupling. Surprisingly, in the presence of bulky trialkyl phosphanes, such as $^t\mathrm{Bu}_3\mathrm{P}$, we did not observe detectable product formation. In contrast, application of Cy_3P gave 20% conversion after 12 h. Among bidentate ligands dppf showed the highest activity (37%), while biphenyl type ligands proved to be more effective than the former. Almost complete conversions were obtained with the application of triisopropyl substituted *ortho*-biphenylphosphane ligand (XPhos).

After the ligand screening we chose XPhos as an excellent candidate for further optimization. First, we studied the applicability of different bases for the coupling, and we found that organic bases such as amines (DIPA, $MeNCy_2$) are not effective at all. Although in the presence of strong inorganic (KOH, NaOH) and organic bases (^{t}BuOK, ^{t}BuONa and MeONa) the conversion of chlorobenzene was almost complete,[7] we detected only a small amount of the desired product. Among the carbonates, Li_2CO_3 was not effective, but in the presence of Na_2CO_3 the conversion was 96% and K_2CO_3 resulted in full conversion in 12 h.

After finding a suitable non-toxic base, we used K_2CO_3 for further optimization studies concerning the effect of the solvent, the amount of catalyst and the reaction temperature. While in light of our earlier results,[11b] the choice of DMA as solvent was obvious, we tested different solvents and we optimized the reaction time. In DMA the reaction was complete in 2 h at 110 °C with 5% Pd/C and 5% XPhos. DMF and DMSO showed similar results to DMA, but slower reaction was found in dioxane (90% conversion) and toluene (62% conversion), and MeCN was not applicable at all.

Our attempt to decrease both the reaction temperature and the catalyst loading simultaneously caused significantly lower conversions and the necessity of longer reaction times even in the case of all three applicable polar solvents. In addition, keeping the temperature at 110 °C we were able to reduce the catalyst loading to 0.5 mol% without significant change in reaction time (2 h) necessary for full conversion in DMA.

The palladium : ligand ratio is also important in solid-supported coupling reactions. We have found that a 1 : 1 Pd : ligand ratio is optimal from the point of view of efficiency and ligand saving. Our final optimizations addressed the effect of copper. We have found that the presence of CuI in the reaction mixture, even in a minimal amount, caused significant disruption to the catalytic activity.

Finally, the comparison of the activity of the Pd/C[8] to several homogeneous palladium sources showed that the solid supported catalyst has very high activity under the applied conditions compared to the tested catalysts (Table 1).

After the optimization studies, we applied our conditions in the coupling of aryl chlorides and terminal acetylenes to assess the scope of the reaction.‡ First, a wide range of aryl chlorides bearing either electron-withdrawing or electron-donating

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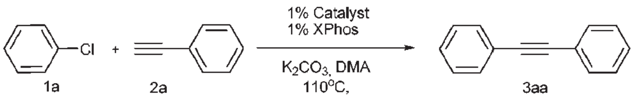
† Electronic supplementary information (ESI) available: Results of the optimization studies, experimental procedures and characterization data for the products (the identity and purity of the known products was confirmed by ^1H and ^{13}C NMR spectroscopic analysis, and the new products were fully characterized). See DOI: 10.1039/b810928a

Table 1 Comparison of palladium catalysts



Entry	Catalyst	Time (h)	Conv. (%)
1	Pd/C	1	65 (88)[a]
2	$PdCl_2$	1	34
3	$Pd(OAc)_2$	1	6
4	$Pd(NO_3)_2$	1	29
5	$Pd(dba)_2$	1	24
6	$Pd_2(dba)_3$	1	70 (85)[a]
7	$(Allyl)_2Pd_2Cl_2$	1	21
8	$PdCl_2(PhCN)_2$	1	12

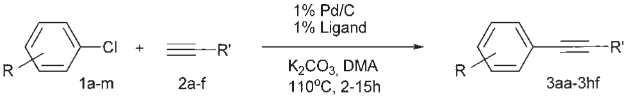
[a] Conversion after 1.5 h, determined by GC, in parentheses.

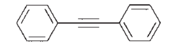
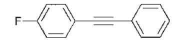
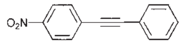
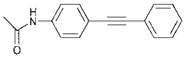
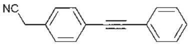
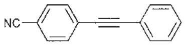
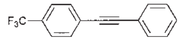
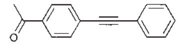
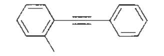
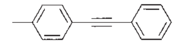
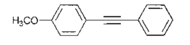
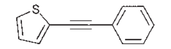
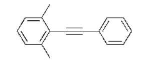
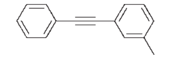
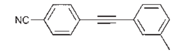
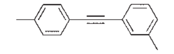
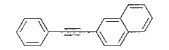
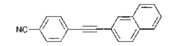
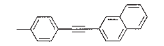
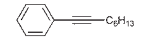
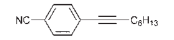
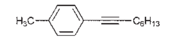
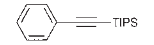
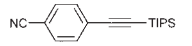
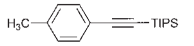
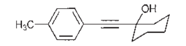
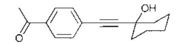
functional groups were coupled to phenylacetylene **2a** (Table 2, entries 1–11) with excellent yields in 2 h. Among the substrates, sterically hindered *ortho*-chlorobenzene **1i** and 2-chloro-1,3-dimethylbenzene were also successfully coupled with phenylacetylene (entries 9 and 14). These results demonstrate the high functional group tolerance of the catalyst system and the applied conditions.

Besides aromatic systems we have also examined the behavior of heterocyclic chlorides in the Sonogashira reaction. Coupling of phenylacetylene with 2-chloropyridine **1l** and 2-chlorothiophene **1m** afforded the appropriate internal acetylene with very good yields (entries 12, 13) in the same reaction time. The coupling reactions of other aromatic acetylenes such as 3-tolylacetylene **2b** or 2-naphthylacetylene **2c** and aryl chlorides having different electronic properties also gave excellent isolated yields (entries 15–20). In contrast to the straightforward coupling of arylacetylenes we have found that the aliphatic alkynes showed lower reactivity toward the aryl chlorides and gave slightly lower yields under our conditions. Reaction of chlorobenzene with 1-octyne **2d** required prolonged reaction time to complete the reaction even in the case of electron-deficient 4-cyanochlorobenzene (entry 22), but after the appropriate reaction time we obtained all the internal acetylenes in good isolated yields (entries 21–23). While our attempts to couple trimethylsilylacetylene have been to date unsuccessful due to its sensitivity, the TIPS protected acetylene **2e** proved to be an excellent coupling partner (entries 24–26). Besides the silyl-protected acetylenes, carbinol type acetylene sources also play an important role for the introduction of triple bonds into organic molecules.[9] Therefore we examined the possibility of coupling of 1-ethynyl-1-cyclohexanol[10] **2f** with different aryl chlorides for the construction of carbinol protected internal acetylenes. These reactions also take place in 8 h with full conversion obtaining the appropriate products in good yields (entries 27–29).

Considering the mechanism of the reaction, it is important to note that these kinds of solid supported systems are not truly heterogeneous catalysts. It is well known, that palladium on charcoal serves only as a heterogeneous source of catalytically active palladium species for homogeneous coupling involving leaching and redeposition steps.[11] To prove this presumption, we performed phase separation by hot filtration

Table 2 Sonogashira coupling of aryl chlorides with acetylenes[a]



Entry	Product		Time (h)	Yield (%)[b]
1		**3aa**	2	92
2		**3ba**	2	82
3		**3ca**	2	99
4		**3da**	4	80
5		**3ea**	2	93
6		**3fa**	2	95
7		**3ga**	2	95
8		**3ha**	2	92
9		**3ia**	2	82
10		**3ja**	2	81
11		**3ka**	2	93
12		**3la**	2	99
13		**3ma**	2	78
14		**3na**	8	80
15		**3ab**	2	96
16		**3fb**	2	94
17		**3jb**	2	96
18		**3ac**	2	80
19		**3fc**	2	95
20		**3jc**	2	93
21		**3ad**	15	72
22		**3fd**	8	74
23		**3jd**	15[c]	72
24		**3ae**	8	93
25		**3fe**	8	86
26		**3je**	8	84
27		**3af**	6	89
28		**3ff**	8	77
29		**3hf**	6	82

[a] *Reaction conditions*: 0.5 mmol aryl chloride, 0.75 mmol acetylene, 0.75 mmol K_2CO_3, 0.25 mL DMA, 1 mol% palladium using 10% w/w Pd/C, and 1 mol% XPhos. [b] Yields of isolated product after chromatographic purification. [c] 3 mol% Pd and ligand was used.

after 30 min. Examination of the filtered homogeneous reaction mixture showed that the reaction took place after the separation of the support, which is the sign of the presence of leached palladium species.

After the demonstration of applicability of palladium on charcoal in Sonogashira coupling of aryl chlorides we addressed our next examination to the possibility of recycling the palladium catalyst. Using the developed condition for the coupling described above, we studied the activity of the recycled catalyst in the coupling of chlorobenzene and phenylacetylene. We found that the Pd/C catalyst can be reused after filtration and subsequent treatments such as washing with water, acetone and DCM, and drying. However, the activity of the recycled catalyst decreased after each use, though prolonged reaction time did result in full conversion in every repeated run (12, 16, 18, 20 and 24 h, respectively). It is of note that the addition of ligand to the reused catalysts was necessary in every repeated run.

In conclusion, we have successfully achieved the Sonogashira reaction of aryl chlorides and terminal acetylenes without copper co-catalyst in the presence of only 1 mol% palladium on charcoal and 1 mol% of a bulky biaryl type phosphane ligand. We established that the optimal choice of the solvent, base and temperature are crucial for the completion of the reactions. In addition, the conditions developed not only provide one of the most efficient methodologies to date for the coupling of aryl acetylenes with a wide variety of structurally and electronically diverse aryl chlorides, but also offers an alternative tool for the coupling of aliphatic acetylenes, silyl or carbinol protected acetylenes. Besides the synthetic value of the reaction conditions, the application of Pd/C as the most readily available solid supported Pd catalyst provides convenient and easy catalyst separation and the possibility of reuse the catalyst after the reaction.

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Notes and references

‡ *General procedure* for the Pd/C-catalyzed Sonogashira coupling of aryl chlorides: A dry 4 ml screw capped vial with septa was charged with 5 mg of 10% Pd/C Selcat Q6 (0.005 mmol), 2.4 mg of XPhos (0.005 mmol) and 97 mg K_2CO_3 (0.75 mmol). The vial was purged with argon, then 0.25 mL DMA was added followed by 0.5 mmol of the aryl chloride and 0.75 mmol of the acetylene. The reaction mixture was placed into a 110 °C oil-bath and was stirred for the appropriate reaction time. After the mixture was cooled to ambient temperature, the charcoal was filtered off and water was added to the reaction mixture. The aqueous phase was extracted with diethyl ether, and the combined organic phases were dried over magnesium sulfate. After the removal of the solvent in vacuum, the crude products were purified by column chromatography using pure hexane or hexane–ethyl acetate mixtures as eluent.

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7 We have not been able to identify the side products of these reactions yet, but significant decomposition of the aryl chloride was observed under the applied reaction conditions.

8 All the coupling reactions were performed with Pd/C catalyst containing 10% w/w palladium. The type of the applied catalyst is very important for the successful coupling, therefore we also tested several commercially available Pd/C catalysts. For the results of such comparative studies see ESI†.

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