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A copper-free Sonogashira reaction using a Pd/MgLa mixed oxide

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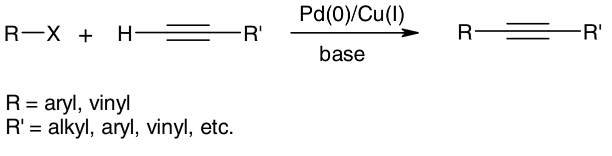
Abstract—A new Pd/MgLa mixed oxide is found to be an efficient catalyst for the Sonogashira reaction of aryl iodides, bromides and even activated chlorides in the absence of a copper salt.

The Sonogashira cross-coupling reaction,[1] discovered in the mid seventies is a powerful method for C(sp)–C(sp^2) bond formation. It can be used in the synthesis of a variety of compounds,[2] including heterocycles,[3] several natural products and pharmaceuticals.[4] Besides natural products, oligomers and polymers have also been prepared via the Sonogashira reaction.[5]

The reaction is generally carried out in an organic solvent such as an amine, benzene, THF or DMF with a complex palladium catalyst in conjunction with copper(I) iodide as a co-catalyst, and in the presence of a stoichiometric amount of base.[6] These palladium catalysts, such as $Pd_2(dba)_3$, $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$ are expensive and sometimes difficult to handle and recover. These reactions usually require high catalyst loadings (up to 5 mol %), the diminution of which is important from both economical and environmental points of view.



In recent years numerous modifications have been reported for the Sonogashira coupling procedure, such as reaction in ionic liquids,[7] reaction in aqueous media,[8] phase-transfer catalytic reaction conditions,[9] use of a variety of promotors, such as Zn, Mg, Sn,[10] and the use of microwave irradiation.[11] Various copper-free conditions have also been developed for homogeneous catalysis,[12] which provides the opportunity to develop the Sonogashira reaction under an ambient atmosphere, as the copper-mediated (Glaser-type reaction)[13] oxidative homocoupling of acetylenes is prevented. These by-products (diaryldiacetylenes) are generally difficult to separate from the desired products and copper acetylide is a potentially explosive reagent.[14] Furthermore, extensive research has been carried out to discover and develop more facile procedures, to improve metal acetylide coupling partners and to prepare more active palladium catalysts.[2a]

Recently we have developed a new, air- and moisture-stable Pd/MgLa mixed oxide, which proved to be an efficient heterogeneous catalyst in the Heck and the Suzuki–Miyaura reactions.[15] The reactions can be performed with only 1.5 mol % of the Pd catalyst. The catalyst can be stored and handled under ambient atmosphere, and it can be recovered from the reaction mixture by simple filtration and reused without significant loss of activity.

In this letter, we have explored the activity of this new catalyst towards the Sonogashira cross-coupling reaction. The alkynylation process can be performed under copper-free conditions in an air atmosphere.

The Pd^{II}/MgLa mixed oxide was prepared by ion exchange of the MgLa mixed oxide with Na_2PdCl_4 using the method reported by Choudary et al.[16] We obtained the Pd^0/MgLa mixed oxide by reduction of Pd^{II}/MgLa with hydrazine hydrate. The palladium content was

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Keywords: Heterogeneous catalysis; MgLa mixed oxide; Sonogashira reaction.

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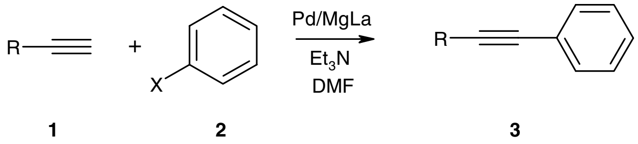
determined by ICP-OES and shown to be 0.84 and 0.73 mmol/g in Pd^{II}/MgLa and Pd^{0}/MgLa, respectively.

Based on our previous results for the Heck cross-coupling reaction,[15a] DMF was chosen as solvent and triethylamine as base. In accordance with the results described in the literature Pd^0 also showed higher catalytic activity than Pd^{II} in our heterogeneous system.[17] In a typical experiment (Scheme 1), a slight excess of the acetylene (1.2 equiv) was added to a solution of the aryl halide in freshly distilled DMF and Et_3N. Then, the catalyst was added and the reaction mixture was stirred at 80 °C. The course of the reaction was followed by TLC. Thus, in the reaction of iodobenzene with phenylacetylene in the presence of Pd^0/MgLa oxide, the coupling product was obtained in 90% yield after 10 h (Table 1, entry 1). When the less reactive acetylene, 1-heptyne was used under these conditions, the coupling product **3d** was produced efficiently (entry 4). The coupling of propargyl alcohol with phenyl iodide also led to the corresponding product, although extraction of the product was laborious, because of the formation of an emulsion (entry 2). An improved result was obtained when the hydroxyl group was protected with a THP group (entry 3).

Under homogeneous copper-free coupling reaction conditions, aryl bromides give rather low conversions (10–60%).[6] In our case, the reaction of bromobenzene with phenylacetylene afforded a 64% yield after 24 h. However, chlorobenzene, under the above reaction conditions showed less activity and gave only 22% of diphenylacetylene even after 24 h. Increased catalyst loading (0.05 g, 3.7 mol %) did not improve the yield significantly. The effect of substituents was also examined in this reaction. The results are summarized in Table 1. Aryl bromides and electron deficient aryl chlorides with aryl alkynes gave the corresponding aryl-substituted acetylenes in high yield. The less active electron-rich *p*-bromotoluene produced a lower yield (entry 6). Steric effects did not influence the yield significantly, for example, in the reaction of *o*-bromoacetophenone with phenylacetylene the corresponding coupled product was obtained in 84% yield (entry 8). The reaction also showed excellent functional group tolerance as was evident from the successful coupling of *o*-bromo-, or *o*- and *p*-chlorobenzaldehyde with phenylacetylene (entries 9, 13 and 14).



Scheme 1.

Comparing these results with those obtained using current Pd-catalysts, we have found that the yields are almost the same as the described ones, for example, with the homogeneous catalyst $Pd(PPh_3)_2Cl_2$.[6] The reactivity of the different aryl halides followed the established order, iodide > bromide ≫ chloride. A somewhat longer reaction time was required in order to obtain good yields; this is a result of the heterogeneous reaction system. Excellent results were obtained with only 1.5 mol % Pd. No by-products were observed, diaryldiacetylenes, which are the most common by-products observed in the reaction using a homogeneous catalyst together with a copper salt co-catalyst were not isolated. Another advantage of our catalyst is that the reactions can be carried out under an ambient atmosphere. The handling of the catalyst is also simple. The heterogeneous reaction system allows easy work-up; the catalyst was filtered off and could be recovered quantitatively. The pure product was also obtained easily.

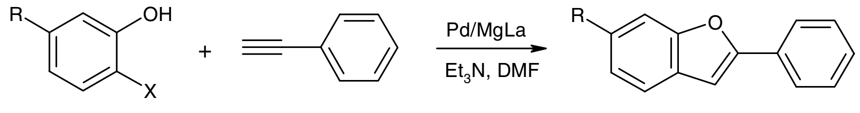
We also examined the reusability of the Pd/MgLa catalyst in the reaction between iodobenzene and phenylacetylene. After the first run the catalyst was separated by filtration, and was then reused in the presence of Et_3N in DMF without any regeneration at 80 °C. It was observed, that the catalyst could be used without any significant loss of activity (the use of 1.5 mol % of

Table 1. Sonogashira reaction of aryl halides catalyzed by the Pd^0/MgLa mixed oxide[19]

Entry	Aryl halide	Acetylene	Product	Catalyst (Pd mol %)	Time (h)	Yield (%)[a]
1	C_6H_5I	Phenylacetylene	**3a**[20]	1.5	10	90 (85)[b]
2	C_6H_5I	Propargyl alcohol	**3b**	1.5	20	70
3	C_6H_5I	3-Tetrahydropyranyloxy-prop-1-yne	**3c**	1.5	20	74
4	C_6H_5I	1-Heptyne	**3d**	1.5	10	81
5	C_6H_5Br	Phenylacetylene	**3a**	1.5	24	64
6	$4\text{-}CH_3C_6H_4Br$	Phenylacetylene	**3e**	1.5	20	60
7	$4\text{-}CH_3COC_6H_4Br$	Phenylacetylene	**3f**	1.5	20	86
8	$2\text{-}CH_3COC_6H_4Br$	Phenylacetylene	**3g**	1.5	20	84
9	$2\text{-}CHOC_6H_4Br$	Phenylacetylene	**3h**	1.5	20	82
10	C_6H_5Cl	Phenylacetylene	**3a**	1.5	24	22
				3.7	24	28
11	$4\text{-}CH_3COC_6H_4Cl$	Phenylacetylene	**3i**	1.5	24	55
12	$2\text{-}CH_3COC_6H_4Cl$	Phenylacetylene	**3j**	1.5	24	63
13	$4\text{-}CHOC_6H_4Cl$	Phenylacetylene	**3k**	1.5	24	68
14	$2\text{-}CHOC_6H_4Cl$	Phenylacetylene	**3l**	1.5	24	67

[a] Isolated yield.

[b] Yield with recycled catalyst.



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Scheme 2.

Table 2. Sonogashira reaction between phenylacetylene and halophenols

Entry	R	X	Yield (%)[a]
1	H	I	61
2	CH_3	Br	<10
3	H	Cl	<10

[a] Based on ^1H NMR spectra.

Pd catalyst in the third cycle gave diphenylacetylene with 85% isolated yield). The recovered catalyst was examined by ICP and no significant decrease in the palladium content was found. The leaching of palladium was examined using the hot filtration test. When the catalyst was removed from the hot reaction mixture by filtration the reaction stopped as was evident from the spectroscopic examination of the reaction mixture. This indicates that using our heterogeneous Pd catalyst, palladium-contamination of the product, which is one of the biggest problems of the homogeneous catalyst systems, can be eliminated.

Larock et al.[18] have reported that benzofurans and indoles can be obtained during the palladium-catalyzed Sonogashira coupling in the reaction of terminal alkynes with *o*-iodophenols and *o*-iodoaniline. We investigated the reactivity of various phenols in the Sonogashira reaction with phenylacetylene (Scheme 2). In the reaction of *o*-chlorophenol and 2-bromo-5-methyl-phenol with phenylacetylene (Table 2, entries 2 and 3), based on ^1H NMR spectra, only ca. 10% yield of the desired benzofurans was observed, which can be explained due to the low activity of the bromo- and chloro-compounds. However, in the reaction with *o*-iodophenol (entry 1) benzofuran **5** was obtained in 61% yield.

In summary, the Pd/MgLa mixed oxide is an efficient catalyst in the Sonogashira cross-coupling reaction. The advantages of this method are as follows: a heterogeneous system, which allows the full recovery and reuse of the catalyst, the palladium remains on the surface of the solid material, no leaching was observed and no copper salt is required.

Acknowledgements

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19. General procedure for the Sonogashira cross-coupling reaction: In a typical reaction, Pd/MgLa (0.02 g,

1.5 mol % of Pd) was added to a mixture of aryl halide (1 mmol), acetylene (1.2 mmol) and Et_3N (1.2 mmol) in DMF (5 mL). The mixture was stirred at 80 °C for 10–25 h. Then the catalyst was filtered out and washed with hexane. The reaction mixture was diluted with water and extracted with hexane (2 × 10 mL). The combined organic extracts were washed with water and brine, dried over $MgSO_4$ and evaporated to give the product. The residue, if necessary, was purified by column chromatography or recrystallized, yielding the corresponding acetylene. Known products were characterized by comparing their ^1H NMR, ^{13}C NMR and melting points with those reported in the literature.

20. Selected data of diphenylacetylene (**3a**): mp: 58–60 °C (lit. 59–61 °C). ^{13}C NMR (75.48 MHz, $CDCl_3$) δ (ppm): 89.5, 123.4, 128.2, 128.4, 131.5.