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# Sonogashira cross-coupling reactions catalysed by heterogeneous copper-free Pd-zeolites

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**Abstract**—A heterogeneous $[Pd(NH_3)_4]$–NaY catalyst was applied to the copper-free Sonogashira cross-coupling of aryl halides with terminal alkynes. This copper-free heterogeneous Pd-catalyst is efficient, stable and recyclable. Aryl iodides and activated aryl bromides were converted quantitatively using 1 mol% Pd-catalyst to the corresponding diaryl-substituted alkynes within 3 h.

The Sonogashira cross-coupling of aryl halides and terminal alkynes or arylenes is a useful tool for the synthesis of alkyl–aryl and diaryl-substituted acetylenes.[1] Functionalised alkynes are important building blocks for the synthesis of biologically active molecules and, surprisingly, are common structural features of natural products that have been isolated from plants and marine organisms, or synthetic drugs.[1,2] Therefore, the Sonogashira reaction is frequently used as a key step in the synthesis of pharmaceuticals, such as the enediyne antibiotics or the contraceptive pill.[3]

Generally the Sonogashira reaction is carried out in an organic solvent such as toluene, THF or DMF, using at least a stoichiometric amount of base, and a Pd(0)/Cu(I) catalytic system.[4] To extend the Sonogashira reaction for fine chemical applications, numerous studies have been reported in the literature over the last 10 years including the use of a phase transfer agent,[5] reaction in aqueous media or without solvent,[6] reaction in ionic-liquids,[7] copper-free versions,[8] and the use of promotors such as Zn, Mg, Sn and $R_4NI$.[9] The most important improvement concerned the elimination of CuI, which is used as the co-catalyst since it can induce homocoupling reactions of terminal alkynes to diynes in the presence of oxygen (Glaser-type reactions).[10] In 1992, Genêt et al. reported the first copper-free efficient cross-coupling of alkynes with aryl or vinyl iodides using a water soluble Pd-catalyst[11] and in 1993 Alami et al. reported the reaction of aryl or vinyl halides with terminal alkynes catalysed by 5 mol% $Pd(PPh_3)_4$ in amine solvents such as pyrrolidine or piperidine (93% yield for the coupling of 1-iodoheptene with 3-butyn-1-ol).[12] More recently, Böhm and Herrmann reported a copper-free procedure using 0.5 mol% $[Pd_2(dba)_3/P(t\text{-}Bu)_3]$ as catalyst for the reaction of aryl bromides with phenylacetylene at room temperature (92% yield for the coupling of bromobenzene with trimethylsilylacetylene in $Et_3N$).[13] Pal et al. used $[PdCl_2(PPh_3)_2]$ at 80 °C for the regioselective synthesis of 4-substituted-1-aryl-1-butanones, which are useful intermediates for the preparation of agrochemicals and drugs (60% yield using 3 mol% Pd-catalyst with 8 equiv of $Et_3N$ in DMF).[14] The $Pd(OAc)_2/PPh_3$ catalytic system was described by Fu et al. for the copper-free Sonogashira coupling of vinyl tosylate and terminal alkynes[15] whilst Nájera et al. have reported the use of an oxime palladacycle, $[PdCl(2\text{-}CH{=}N(OH)(C_6H_4Cl)\text{-}5\text{-}Cl{-}C_6H_3)]_2$, for the cross-coupling of terminal acetylenes and aryl iodides and bromides (>99% for the reaction of *p*-chloroiodobenzene with phenylacetylene under reflux in $NMP/H_2O$).[16]

While these examples contributed to the improvement of the Sonogashira reaction, they remained based on homogeneous Pd-catalysts, which make the separation and the recovery of the catalysts tedious if not impossible and might result in unacceptable palladium contamination of the products. As an answer to these problems Astruc and co-workers[17] recently reported the use of a dendritic material to support the homogeneous $[Pd\{t\text{-}Bu_2PCH_2N(CH_2Ph)CH_2Pt\text{-}Bu_2\}(OAc)_2]^{8e}$ complex, which they had previously applied to the

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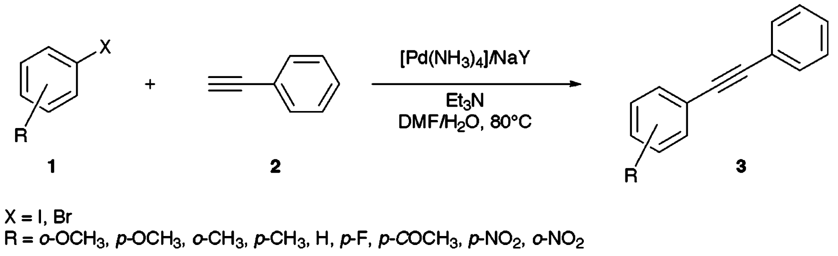

**Scheme 1.**

Sonogashira reaction (79% yield for the reaction of iodobenzene with phenylacetylene under reflux in the presence of $Et_3N$ using 1 mol% of the Pd-dendritic catalyst after 24 h). The authors claimed that the dendritic catalysts could be recovered by precipitation and reused without significant loss of activity. Although interesting, this method required the precipitation of the catalyst by a co-solvent (generally pentane), which increased the amount of effluent waste during the process.

Only few reports describe the Sonogashira reaction heterogeneously catalysed by supported palladium catalysts, examples being generally limited to highly reactive aryl iodides and 2-halopyridines. Separately, Koehler and co-workers and Kotschy and co-workers have described the Pd/C catalysed Sonogashira reaction of aryl halides with acetylenes in the presence of CuI.[18] When optimised using 5 mol% Pd/C, 10 mol% CuI as co-catalyst and diisopropylamine as the base, Kotschy and co-workers achieved the quantitative conversion of 2-bromopyridine with various acetylenes, such as 1-hexyne, after 24 h under reflux in DMAc/$H_2O$. However, the success of these examples remained linked to the use of CuI as co-catalyst. Kotschy and co-workers clearly demonstrated that the overall activity of the [Pd/C + CuI] catalytic system was related to the leaching of the active Pd-species in the solution during the reaction, thus contaminating the reaction mixture ($\leqslant 2\%$ of Pd).[18b]

The intensive application of the Sonogashira reaction in the chemical industry depends on the development of new, stable heterogeneous copper-free palladium catalysts. With this aim, the use of palladium supported on metal oxides appears to be the most appropriate heterogeneous catalyst to perform this cross-coupling reaction on a large scale.

We previously reported the first heterogeneous Pd-catalysed Heck reaction using zeolites as catalyst supports.[19] In these studies, zeolite supports were found to be particularly effective in the stabilisation of active Pd-species during the reaction, leading to highly active, easily separable and recyclable heterogeneous palladium catalysts for the Heck reaction. The present contribution describes the remarkable catalytic activity of Pd-modified zeolites for the Sonogashira cross-coupling reaction of aryl iodides and bromides with phenylacetylene.

The Pd-modified zeolite was prepared according to the literature by ion exchange of NaY zeolite using a 0.1 M aqueous solution of $[Pd(NH_3)_4]^{2+}$, $2Cl^-$. After a period of 24 h, $[Pd(NH_3)_4]$–NaY was obtained.[19,20] The absolute palladium content was determined by ICP-AES as 7% Pd.

The activity of the $[Pd(NH_3)_4]$–NaY catalyst for the cross-coupling of aryl halides with acetylene (Scheme 1) is reported in Table 1. All reactions were carried out under argon: aryl halides (10 mmol) were reacted with phenylacetylene (14 mmol) in the presence of 2 equiv of $Et_3N$ using 1 mol% [Pd]-catalyst in DMF/$H_2O$ (4:1) at 80 °C. The products were purified by column chromatography on silica gel. Isolated yields are given in Table 1.

The results demonstrate clearly the applicability of the heterogeneous $[Pd(NH_3)_4]$–NaY catalyst in the Sonogashira cross-coupling reaction for a range of substituted aryl halides with phenylacetylene.

Aryl halides activated by an electron withdrawing group lead to a quantitative conversion within 3 h (entries 5–7, 13–15). Non-activated aryl iodides gave almost quantitative conversion within 3 h, while the corresponding aryl bromides led only to moderate yields even after a

**Table 1.** Sonogashira coupling reaction of aryl halides with phenylacetylene using the $[Pd(NH_3)_4]$–NaY catalyst[a]

| Entry | X | R | Time/Yields[b] | |
|---|---|---|---|---|
| | | | 3 h | 24 h |
| 1 | I | H | 100 | — |
| 2 | | p-$OCH_3$ | 100 [54] | — |
| 3 | | p-$CH_3$ | 100 [82] | — |
| 4 | | p-F | 100 [87] | — |
| 5 | | p-$NO_2$ | 100 [85] | — |
| 6 | | p-$COCH_3$ | 100 [85] | — |
| 7 | | o-$NO_2$ | 100 [89] | — |
| 8 | | o-$CH_3$ | 82 [67] | — |
| 9 | Br | H | 45 | 63 |
| 10 | | p-$OCH_3$ | 22 | 38 |
| 11 | | p-$CH_3$ | 30 | 49 |
| 12 | | p-F | 42 | 55 |
| 13 | | p-$NO_2$ | 100 | — |
| 14 | | p-$COCH_3$ | 100 | — |
| 15 | | o-$NO_2$ | 100 | — |
| 16 | | o-$CH_3$ | 14 | 27 |

[a] Reaction conditions: 5 mmol aryl halide, 7 mmol phenylacetylene, 10 mmol $Et_3N$, 1 mol% Pd, 10 mL DMF/$H_2O$ (4:1), 80 °C.

[b] GC yields and when available [isolated yields] are given in parentheses.

longer reaction time (compare entries 1–4 and 9–12). These results are probably related to the differences in bond energy between aryl iodides (ca. 65 kcal/mol) and aryl bromides (ca. 81 kcal/mol).[21] When using *ortho*-substituted aryl halides, slightly lower yields were observed (entries 3 vs 8 and 11 vs 16), which were attributed to the limitation in the diffusion of educts and products through the zeolite micropores. However, the reactivity observed is, to our knowledge, one of the highest reported to date for copper-free, heterogeneously Pd-catalysed Sonogashira reactions.

To obtain a better insight on the effectiveness of the heterogeneous $[Pd(NH_3)_4]$–NaY catalyst, kinetic studies were performed. Using iodobenzene in the presence of 1 mol% Pd-catalyst, the reaction was quantitative after 15 min at 80 °C, while the less reactive, *p*-iodoanisole was converted to disubstituted acetylene after 90 min at 80 °C. We also examined the activity of the heterogeneous $[Pd(NH_3)_4]$–NaY catalyst at room temperature with iodobenzene: a quantitative conversion to diphenylacetylene was achieved after 24 h demonstrating the exceptional activity of this catalyst in the absence of copper.

After demonstrating the applicability of the copper-free $[Pd(NH_3)_4]$–NaY catalyst for the Sonogashira reaction, questions regarding the leaching of the active Pd-species in solution and the recyclability of the heterogeneous catalyst were addressed.

The leaching was examined for the coupling reaction of *p*-iodoanisole with phenylacetylene using the hot-filtration method: a catalytic run was started as for a standard reaction, and after 10 min of reaction, corresponding to 53% yield, the reaction mixture was filtered through a Celite pad to afford a clear filtrate. The composition of the clear filtrate was followed by GC and compared to that of a standard catalytic run. Figure 1 clearly shows that after removal of the heterogeneous $[Pd(NH_3)_4]$–NaY catalyst, the clear filtrate was weakly active suggesting that only slight leaching had occurred during the reaction. Thus, a slow progression of the conversion was observed (<10% over 300 min vs 50% for a standard catalytic run), leading after 300 min to a 61% yield to be compared to the 54% yield observed immediately after the filtration. However, the leaching observed cannot explain the overall activity of the $[Pd(NH_3)_4]$–NaY catalyst for which a quantitative conversion was obtained after 150 min of reaction under the same conditions. This result is very different from that observed by Kotschy and co-workers[18b] where 80% of the overall activity of the Pd/C catalyst was linked to dissolved (leached) Pd-species.

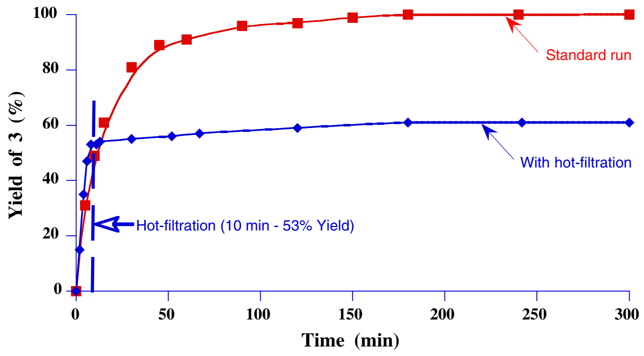

**Figure 1.** Residual activity after Hot filtration ◆ after 10 min reaction versus standard catalyst run ■. Reaction conditions: 10 mmol iodoanisole, 14 mmol phenylacetylene, 20 mmol $Et_3N$, 1 mol% Pd, 20 mL $DMF/H_2O$ (4:1), 80 °C.

The recycling of the catalyst was examined as follows: after the first run using standard reaction conditions, the reaction mixture was allowed to cool to room temperature and the catalyst was separated by filtration, washed with the $DMF/H_2O$ mixture used for the catalytic runs, then with dichloromethane and allowed to dry at room temperature for 24 h. The recycled $[Pd(NH_3)_4]$–NaY catalyst was then used without any regeneration as a fresh catalyst giving, respectively, 100%, 87% and 88% conversion of *p*-iodoanisole in 3 h at 80 °C showing only a slight deactivation of the catalyst during the first run.

In summary, we have established that the heterogeneous $[Pd(NH_3)_4]$–NaY catalyst is an efficient, stable and recyclable catalyst for the copper-free Sonogashira cross-coupling of aryl halides with terminal alkynes. Further work is in progress to develop more active and stable catalysts to improve both the activity and the recyclability of the heterogeneous copper-free supported palladium catalysts by optimisation of the preparation and/or the reaction conditions for large-scale application in the chemical industry.

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