Sonogashira Cross-Coupling Reactions Catalysed by Copper-Free Palladium Zeolites

Laurent Djakovitch,* Patrick Rollet

Institut de Recherches sur la Catalyse, UPR CNRS 5401, 2 Avenue Albert Einstein, 69626 Villeurbanne, France
Phone: (+33)-4-72-44-53-81, Fax: (+33)-4-72-44-53-99, e-mail: laurent.djakovitch@catalyse.cnrs.fr

Received: May 19, 2004; Accepted: September 5, 2004

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de or from the author.

Abstract: A heterogeneous copper-free $[Pd(NH_3)_4]^{2+}$/$(NH_4)Y$ catalyst was employed to achieve the heterogeneous Sonogashira reaction of aryl halides with terminal alkynes. Several reaction parameters like solvent, base and temperature were evaluated. When optimised, the coupling reaction of bromobenzene with phenylacetylene gave a 45% yield of diphenylacetylene within 3 h using only 1 mol % Pd. This catalyst was successfully applied to the coupling reaction of a range of aryl iodides and bromides: aryl iodides and activated aryl bromides gave almost quantitative yields and non-activated aryl bromides led to reasonable yields (20% to 45%). This heterogeneous $[Pd(NH_3)_4]^{2+}$/$(NH_4)Y$ catalyst was shown to be efficient, stable towards leaching and recyclable for the copper-free Sonogashira reaction.

Keywords: Copper-free Sonogashira reaction; heterogeneous catalysis; palladium modified zeolite

Introduction

The Sonogashira cross-coupling of aryl halides and terminal alkynes or arylenes is a useful tool for the synthesis of alkyl-aryl- and diaryl-susbtituted acetylenes.[1] Functionalised alkynes are important building blocks for the synthesis of biologically active molecules and, surprisingly, have common structural features with natural products that have been isolated from plants and the marine organisms, or with 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 ten 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 promoters such as Zn, Mg, Sn and R_4NI.[9] Alternatively, nickel-catalysed Sonogashira reactions have been described by Beletskaya et al. using homogeneous Ni(II) species[10] and by Wang et al. using Ni(0) particles.[11] However, these catalysts require the use of CuI as a co-catalyst and PPh_3 in order to achieve high activities. Alternatively, Leadbeater et al. reported a transition metal-free procedure for the Sonogashira coupling reactions of aryl iodides and bromides with phenylacetylene under phase-transfer conditions using microwave irradiation to activate efficiently the aryl halides.[12] Nevertheless, although interesting, these Pd-free methodologies remain limited by the narrow choice of the reactants and the right reaction conditions to achieve high conversions.

The most important improvement concerned the elimination of CuI used as co-catalyst since it can induce homocoupling reactions of terminal alkynes to diynes in the presence of oxygen (Glaser-type reactions).[13] This improvement is also of importance for industrial applications of the Sonogashira cross-coupling reactions, since this metal is very tedious to recycle.

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).[15] 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).[16] Pal et al. used $[PdCl_2(PPh_3)_2]$ at 80 °C for the regioselective synthesis

DOI: 10.1002/adsc.200404141

of 4-substituted 1-aryl-1-butanones that are useful intermediates for the preparation of agrochemicals and drugs (60% yield using 3 mol % Pd catalyst with 8 equivalents of Et_3N in DMF).[17] 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[18] whilst Nájera et al. have reported the use of an oxime palladacycle, $[PdCl(2\text{-}CH{=}N(OH)(C_6H_4Cl)\text{-}5\text{-}Cl\text{-}C_6H_3)]_2$, 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).[19] Lately, Sakai et al. reported the use of a catalytic amount of $InBr_3$ in the presence of a base to activate acetylenes prior to their coupling with aryl iodides catalysed by $[PdCl_2(PPh_3)_2]$ at room temperature.[20]

While these examples contributed to the improvement of the Sonogashira reaction, they remained based on homogeneous Pd catalysts, which makes 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 et al.[21] recently reported the use of a dendritic material to support the homogeneous $[Pd\{t\text{-}Bu_2PCH_2N(CH_2Ph)CH_2Pt\text{-}Bu_2\}(OAc)_2]$ complex[8e] which they had previously applied to the 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 any 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.

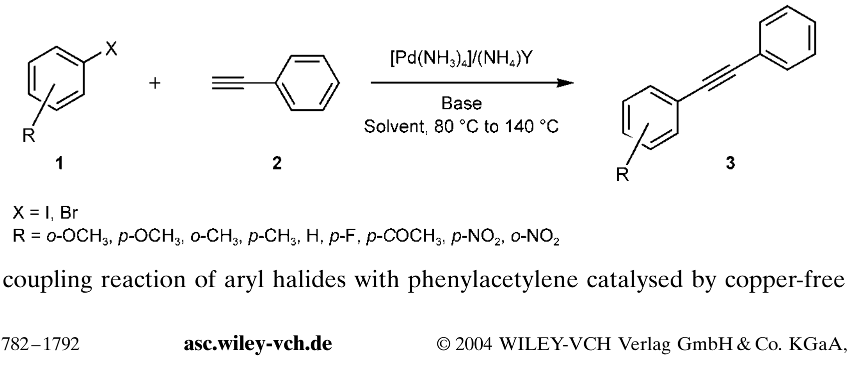
Only few reports describe the Sonogashira reaction heterogeneously catalysed by supported palladium catalysts, examples being generally limited to highly reactive aryl iodides and 2-halopyridines. Separately, Koehler et al.[22] and Kotschy et al.[23] have described the Pd/C-catalysed Sonogashira reaction of aryl halides with acetylenes in presence of CuI. When optimised using 5 mol % Pd/C, 10 mol % CuI as co-catalyst and diisopropylamine as the base, Kotschy et al. 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 et al. 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 (>2% of Pd).[23]

The intensive application of the Sonogashira reaction in the chemical industry depends on the development of new, stable and recyclable, 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.

Some of us have previously reported the first heterogeneous Pd-catalysed Heck reaction using zeolites as catalyst supports.[24] 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.

Results and Discussion

Initially, we examined the catalytic activity of Pd-exchanged zeolites for the Sonogashira coupling reaction of bromobenzene with phenylacetylene (Scheme 1, X = Br and R = H). Using homogeneous, copper-free palladium catalysts, aryl bromides are known to give low conversion (10–60%) under standard reaction conditions (polar solvent like NMP, 1 mol % Pd, 100–120 °C, 20 h).[4] With heterogeneous supported palladium species (particles, organometallic complexes), the use of CuI as co-catalyst is required in order to attain reasonable activities.[23] Therefore, the coupling reaction of bromobenzene with phenylacetylene appears to be of interest for developing new, heterogeneous, copper-free palladium catalysts. In order to optimise the reaction several parameters like the solvent, temperature and base, were evaluated as well as the catalyst's composition and stability.



Scheme 1. Sonogashira coupling reaction of aryl halides with phenylacetylene catalysed by copper-free Pd-zeolites.

Table 1. Sonogashira coupling reaction of bromobenzene with phenylacetylene catalysed by $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ catalyst. Reaction conditions: 5 mmol bromobenzene, 8 mmol phenylacetylene, 10 mmol Et_3N, 1 mol % $[Pd(NH_3)_4]^{2+}/(NH_4)Y$, 80 °C, 3 h, solvent.

Entry	Solvent	Conversion[a] [%]	Yield of **3** [%][a]
1	DMF	20	19
2	DMSO	12	12
3	NMP	11	10
4	DMAc	7	7
5	DMF/H_2O (4:1)	46	45
6	DMSO/H_2O (4:1)	41	41
7	NMP/H_2O (4:1)	39	39
8	DMAc/H_2O (4:1)	40	39
9	Dioxane/H_2O (4:1)	11	11
10	DME/H_2O (4:1)	18	17
11	Et_3N/H_2O (4:1)	7	7
12	CH_3CN/H_2O (4:1)	6	5
13	DMF/H_2O (1:1)	26	24
14	DMF/H_2O (2:1)	34	33
15	DMF/H_2O (3:1)	43	42
16	DMF/H_2O (6:1)	31	29
17	H_2O	<1	<1

[a] Conversions based on unreacted bromobenzene and yields were determined by GC with an internal standard (diethylene glycol di-*n*-butyl ether) ($\Delta_{rel} = \pm 5\%$).

The heterogeneous $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ zeolite was prepared, according to procedures reported in the literature, by ion exchange of $(NH_4)Y$ zeolite using a 0.1 M aqueous solution of $[Pd(NH_3)_4]^{2+}2Cl^-$.[24,25] After a period of 24 h, the exchanged $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ catalyst was obtained. The absolute palladium content of the catalyst was determined by ICP-AES as 5.2% wt Pd. Analogously, the heterogeneous $\{[Pd(NH_3)_4]$-$[Cu(NH_3)_4]\}/(NH_4)Y$ zeolite was prepared by ion co-exchange of $(NH_4)Y$ zeolite using a 0.1 M aqueous solution of $[Pd(NH_3)_4]^{2+}2Cl^-$ and $[Cu(NH_3)_4]^{2+}2Cl^-$ stirred for 24 h. The absolute metal content of the catalyst was determined by ICP-AES as 4.7% wt Pd, and 2.3% wt Cu.

Table 1 describes the results obtained from the Sonogashira reaction of bromobenzene with phenylacetylene to diphenylacetylene **3** (Scheme 1, X = Br and R = H) using standard reaction conditions (5 mmol bromobenzene, 8 mmol phenylacetylene, 10 mmol base, 1 mol % $[Pd(NH_3)_4]^{2+}/(NH_4)Y$, 80 °C, 3 h, polar solvent).

It was found that the Sonogashira reaction was very dependent on the nature of the solvent and the composition of the solvent mixture. Generally, after 3 h of reaction pure organic polar solvents like DMF, DMSO, NMP and DMAc lead to a low conversion of bromobenzene resulting in poor yields of diphenylacetylene **3** (7% to 19%) (Table 1, entries 1–4). However, used in mixture with water (solvent/water = 4:1), these solvents gave clearly higher yields in **3**, as high as 39% and 45% under otherwise the same reaction conditions (Table 1, entries 5–8). Other solvents commonly used for this reaction like dioxane, DME, Et_3N and CH_3CN, while unreactive when used pure, gave appreciable yields of **3** when used in a mixture with water (Table 1, entries 9–12). The highest conversion was obtained with the mixture DMF/H_2O = 4:1, giving a 45% yield in diphenylacetylene **3** within 3 h (Table 1, entry 5). When water was used as solvent, insignificant product amount was detected for the Sonogashira reaction of bromobenzene with phenylacetylene (Table 1, entry 17).

The influence of the amount of water added to DMF was also evaluated. As reported in Table 1 (entries 5 and 13–16), the optimum was attained with a ratio DMF/H_2O = 4:1 for which the yield in **3** rises to 45% within 3 h. Using these optimised reaction conditions (5 mmol bromobenzene, 8 mmol phenylacetylene, 10 mmol Et_3N, 1 mol % $[Pd(NH_3)_4]^{2+}/(NH_4)Y$, 80 °C, DMF/$H_2O$ = 4:1), a higher yield of **3** was achieved by a longer reaction time: 63% yield within 24 h.

Next the influence of the base was studied. As reported in Table 2, inorganic bases such as K_2CO_3 and Cs_2CO_3 gave poor conversion (0% and 6%, respectively) probably due to their lack of basicity under the reaction conditions (Table 2, entries 1 and 2). Other inorganic bases like $Ca(OH)_2$, *t*-BuOK, KOH and KOAc gave reasonable conversions leading to 15% to 24% yields in **3** (Table 2, entries 3–6). However, these catalytic performances appeared limited when compared to those obtained using basic organic amines for which 25% to 45% product yields were achieved. The best catalytic result (45% yield in **3** within 3 h) was obtained using Et_3N (Table 2, entries 7–10).

In order to optimise further the performance of the catalytic system (1 mol % $[Pd(NH_3)_4]^{2+}/(NH_4)Y$, DMF/$H_2O$ = 4:1, 2 equivalents Et_3N) for the Sonoga-

Table 2. Influence of the base on the Sonogashira coupling reaction of bromobenzene with phenylacetylene catalysed by $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ catalyst. Reaction conditions: 5 mmol bromobenzene, 8 mmol phenylacetylene, 10 mmol base, 1 mol % $[Pd(NH_3)_4]^{2+}/(NH_4)Y$, 80 °C, 3 h, DMF/$H_2O$ (4:1).

Entry	Base	Conversion[a] [%]	Yield of **3** [%][a]
1	K_2CO_3	0	0
2	Cs_2CO_3	6	6
3	$Ca(OH)_2$	19	18
4	*t*-BuOK	13	13
5	KOH	22	21
6	KOAc	26	24
7	Et_3N	46	45
8	Piperidine	35	35
9	Pyrrolidine	27	25
10	*i*-Pr_2NH	33	31

[a] Conversions based on unreacted bromobenzene and yields were determined by GC with an internal standard (diethylene glycol di-*n*-butyl ether) ($\Delta_{rel} = \pm 5\%$).

Table 3. Influence of the temperature on the Sonogashira coupling reaction of bromobenzene with phenylacetylene catalysed by $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ catalyst. Reaction conditions: 5 mmol bromobenzene, 8 mmol phenylacetylene, 10 mmol Et_3N, 1 mol % $[Pd(NH_3)_4]^{2+}/(NH_4)Y$, 60–140 °C, 3 h, DMF/$H_2O$ (4:1).[a]

Entry	T [°C]	Conversion[b] [%]	Yield of **3** [%][b]
1	60	0	0
2	80	27	25
3	100	56	45
4	120	68	54
5[c]	140	100	0

[a] All reactions were carried out in pressure sealed tubes.

[b] Conversions based on unreacted bromobenzene and yields were determined by GC with an internal standard (diethylene glycol di-*n*-butyl ether) ($\Delta_{rel} = \pm 5\%$).

[c] The mass balance between conversion and yields in **3** and the side product **4** is related to the relatively high formation of benzene (*ca.* 20%) due a rapid dehydrohalogenation of bromobenzene at this relatively high reaction temperature.

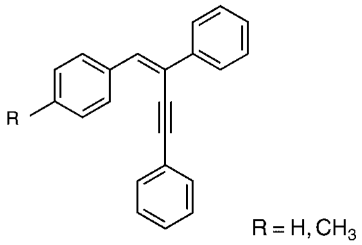


Figure 1. Proposed structure of the poly-aromatic compound **4** formed during the Sonogashira coupling reactions of bromobenzene or *p*-iodotoluene with phenylacetylene above 80 °C.

shira coupling reaction of bromobenzene with phenylacetylene, we examined the influence of the reaction temperature. For this purpose, the reactions were performed in sealed tubes rather than in flasks to ensure that no edducts evolved during the catalytic tests. The results obtained, while following the same trends as those observed when performing the reaction in flasks, could not be directly compared in terms of catalytic activity since generally lower conversion and yields are obtained under strictly similar reaction conditions. This was attributed to inefficient stirring when sealed tubes are used: in a flask 0–5% yield *versus* 45% yield for the model reaction is obtained when the stirring is turned off.

The results reported in Table 3 show that no reaction occurs at 60 °C, and, as expected, increasing the reaction temperature resulted in higher product yields: 25%, 45% and 54% at, respectively, 80 °C, 100 °C and 120 °C (Table 3, entries 2–4). However, above 80 °C the selectivity decreased. At 140 °C no product corresponding to the coupling reaction of bromobenzene with phenylacetylene was detected. Instead another poly-aromatic compound was the unique product whose mass spectrum could correspond to several possible structures.

In order to elucidate the structure for this poly-aromatic compound, mass spectroscopy and NMR experiments were performed on the methyl-substituted derivative **4** obtained in 28% yield by the coupling of *p*-iodotoluene with phenylacetylene at 100 °C for 24 h using 1 mol % $[Pd(NH_3)_4]/(NH_4)Y$ catalyst in DMF/H_2O (4:1). All analytical methods (mass spectroscopy, ^1H, ^{13}C and COSY NMR) point to the structure proposed in Figure 1. The most probable hypothesis for its formation during the catalytic experiments is the thermal coupling of the intermediate 1-methyl-4-phenylethynylbenzene with the excess of phenylacetylene. However, we cannot exclude at relatively high reaction temperature and longer reaction time a leaching of palladium species in solution that could catalyse its formation.

As it is generally reported that the reactivity of aryl bromides in the Sonogashira reactions is clearly higher in presence of the CuI as co-catalyst,[1c] we decided to use a [Pd-Cu]/$(NH_4)Y$ catalyst in the coupling reaction of bromobenzene with phenylacetylene under the most efficient reaction conditions. With 1 mol % $\{[Pd(NH_3)_4][Cu(NH_3)_4]\}/(NH_4)Y$ in DMF/H_2O (4:1) at 80 °C for 3 h in presence of 2 equivalents of Et_3N, the Sonogashira reaction of bromobenzene (5 mmol) with phenylacetylene (8 mmol) gave only a 6% yield (21% after 24 h) of diphenylacetylene **3**. This result clearly indicates that, under our reaction conditions, copper salts did not enhance the reactivity of aryl bromides toward the Sonogashira coupling reactions but rather deactivated the catalyst.

Table 4. Sonogashira coupling reaction of bromobenzene with phenylacetylene catalysed by $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ catalyst. Reaction conditions: 5 mmol aryl halide, 8 mmol phenylacetylene, 10 mmol Et_3N, 1 mol % $[Pd(NH_3)_4]^{2+}/(NH_4)Y$, 80 °C, DMF/$H_20$ (4:1).

Entry	X	R	Time/Yields of **3** [%][a]	
			3 [h]	24 [h]
1	I	H	100	–
2	–	p-OCH_3	100 [67]	–
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] Yields were determined by GC with an internal standard (diethylene glycol di-*n*-butyl ether) ($\Delta_{rel} = \pm 5\%$). When available [isolated yields] are given in parentheses.

The optimised reaction conditions {5 mmol aryl halide, 8 mmol phenylacetylene, 10 mmol Et_3N, 1 mol % $[Pd(NH_3)_4]^{2+}/(NH_4)Y$, 80 °C, DMF/$H_2O = 4:1$} were applied to a range of aryl bromides and iodides. As reported in Table 4, $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ showed an exceptional catalytic activity. Aryl halides activated by an electron-withdrawing group react quantitatively within 3 h (Table 4, entries 5–7 and 13–15). Non-activated aryl iodides gave almost quantitative yields within 3 h, while the aryl bromides gave only moderate yields even after a longer reaction period (Table 4, compare entries 1–4 to 9–12). The differences in bond energy between aryl iodides (*ca.* 65 kcal/mol) and aryl bromides (*ca.* 81 kcal/mol) probably account for these observations.[26]

When using *ortho*-substituted aryl halides, lower yields were observed (Table 4, compare entries 3 *versus* 8 and 11 *versus* 16), which could be attributed to the diffusion limitation of edducts and products through the zeolite micropores. However, the catalytic activity observed is, to our knowledge, one of the highest reported to date for a copper-free heterogeneous Pd-catalysed Sonogashira coupling reaction.

Regarding the high activity of the $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ catalyst for the Sonogashira reaction of aryl iodides and bromides with phenylacetylene, we were interested in evaluating its catalytic performances for the synthesis of important substructures of natural or synthetic biologically active organic molecules such as propargylic alcohols, indoles or furans. As reported in Table 5, high isolated yields were achieved using only 1 mol % $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ catalyst under the optimised reaction conditions within short reaction times (3 h to 6 h).

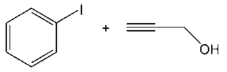
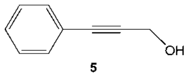
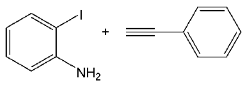
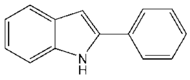
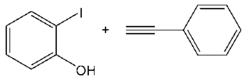
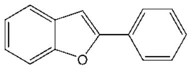
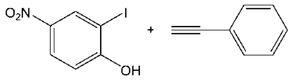
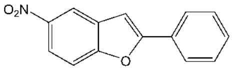
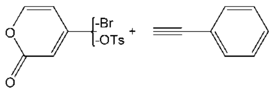
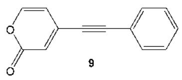
After demonstrating the applicability of the copper-free $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ catalyst for the Sonogashira reaction through the synthesis of various compounds, the questions regarding the leaching of the active Pd species in solution and the recyclability of the heterogeneous catalyst were addressed.

The leaching was examined for the coupling reaction of *p*-iodoanisole with phenylacetylene under optimised reaction conditions (10 mmol *p*-iodoanisole, 15 mmol phenylacetylene, 20 mmol Et_3N, 1 mol % $[Pd(NH_3)_4]^{2+}/(NH_4)Y$, 80 °C, 20 mL DMF/$H_2O = 4:1$) using the hot-filtration method: a catalytic run was started as for a standard reaction, and after 10 min of reaction, corresponding to 55% yield, the reaction mixture was filtered through a celite pad to afford a clear filtrate. The clear filtrate was then treated as a standard catalytic run and its evolution was followed by GC. The results were compared to that of a standard catalytic run. Figure 2 clearly shows that, after removal of the heterogeneous $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ 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 *versus* 50% for a standard catalytic run), leading after 300 min to a 65% yield to be compared to the 57% yield observed immediately after the filtration. However, the leaching observed cannot explain the overall activity of the $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ catalyst for which a quantitative conversion was obtained after 150 min of reaction under the same conditions. When repeating this procedure with bromobenzene instead of *p*-iodoanisole, no evolution of the composition of the reaction mixture (clear filtrate) was observed. These results are very different from that observed by Kotschy et al. where 80% of the overall activity of the Pd/C catalyst was linked to dissolved (leached) Pd species.[23]

In addition, the AAS palladium determination performed on clear solutions at completion of the reactions gave in most cases a palladium concentration <10 ppm, accounting for a negligible leaching.

The recycling of the catalyst was first examined for the coupling reaction of *p*-iodoanisole with phenylacetylene under optimised reaction conditions (10 mmol *p*-iodoanisole, 15 mmol phenylacetylene, 20 mmol Et_3N, 1 mol % $[Pd(NH_3)_4]^{2+}/(NH_4)Y$, 80 °C, 20 mL DMF/$H_2O = 4:1$). The method used corresponds to the following procedure: after the first run of the catalyst, the reaction mixture was allowed to cool to room temperature and the catalyst was separated by centrifugation, washed with DMF/H_2O (4:1) and allowed to "dry" at room temperature for 24 h. The recycled $[Pd(NH_3)_4]^{2+}$ $/(NH_4)Y$ catalyst was then used without any regenera-

Table 5. Sonogashira coupling reaction catalysed by $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ catalyst applied to the synthesis of target organic molecules. Reaction conditions: 5 mmol aryl or vinyl halide, 8 mmol alkyne, 10 mmol Et_3N, 1 mol % $[Pd(NH_3)_4]^{2+}/(NH_4)Y$, 80 °C, DMF/$H_2O$ (4:1).

Substrates	Product	Time [h]	Conversion [%][a]	Isolated yield [%]
	 **5**	6	100	73
	 **6**	6	93	72
	 **7**	6	99	78
	 **8**	6	100	69
	 **9**	3	100	95

[a] Conversion were determined by GC with an internal standard (diethylene glycol di-*n*-butyl ether) ($\Delta_{rel} = \pm 5\%$).

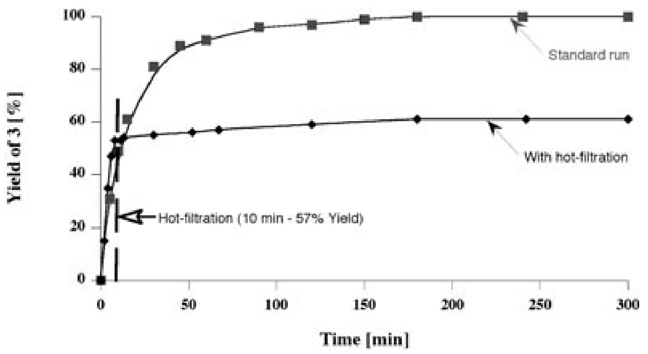


Figure 2. Residual catalytic activity after hot filtration (◆) after 10 min reaction *versus* standard catalytic (■) run. Reaction conditions: 10 mmol *p*-iodoanisole, 15 mmol phenylacetylene, 20 mmol Et_3N, 1 mol % $[Pd(NH_3)_4]^{2+}/(NH_4)Y$, 80 °C, 20 mL DMF/$H_2O$ (4:1).

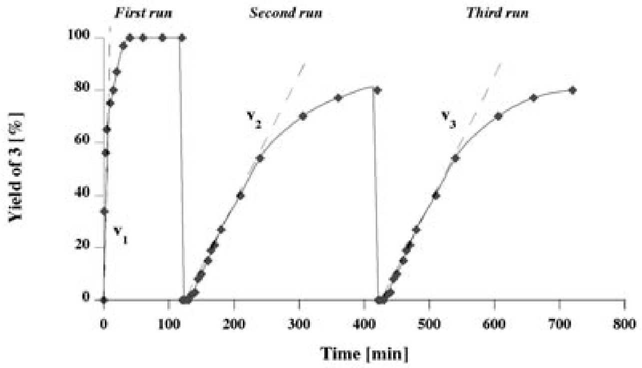


Figure 3. Recyclability of the $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ catalyst for the Sonogashira coupling reaction of *p*-iodotoluene with phenylacetylene. Reaction conditions: 10 mmol *p*-iodotoluene, 15 mmol phenylacetylene, 20 mmol Et_3N, 1 mol % $[Pd(NH_3)_4]^{2+}/(NH_4)Y$, 80 °C, 20 mL DMF/$H_2O$ (4:1).

tion as the fresh catalyst under the same reaction conditions giving 100%, 87%, 88%, 86% and 87% conversion of *p*-iodoanisole for the 1st, the 2nd, 3rd, 4th and 5th runs, respectively. The same procedure was repeated using bromobenzene as aryl halide: under the same conditions 44%, 43%, 40%, 42% and 41% conversion were achieved for the 1st, 2nd, 3rd, 4th and 5th runs, respectively. These results showed that only a slight deactivation of the catalyst occurs during the first run.

To get a better insight on that deactivation, another procedure, based on the coupling reaction of *p*-iodotoluene with phenylacetylene, was used to evaluate the activity of the $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ catalyst over several cycles: at the completion of the 1st run of the fresh catalyst (i.e., after 2 h), new edducts (*p*-iodotoluene, phenyl acetylene and Et_3N) were added under argon to the reaction mixture. Immediately after the additions, the reaction mixture was analysed by GC and the amount corresponding to the 1-methyl-4-phenylethynylbenzene **3** was set to "0" at the corresponding "initial time" for the 2nd run of the catalyst. This procedure was repeated once. Figure 3 shows clearly that a deactivation occurs during the first run of the catalyst as indicated by the determination of the initial rate $v_1 = 126$ mmol/min · g_{cat} for the 1st run (fresh catalyst) and $v_2 = v_3 = 5$ mmol/min · g_{cat} for 2nd and the 3rd runs (recycled catalyst). These results are in agreement with those obtained previously, while small differences in terms of conversions are observed between the two methods (i.e., for the second method:100% for the 1st run and *ca.* 80% for the 2nd and 3rd runs).

Conclusion

The Sonogashira coupling reaction of bromobenzene with phenylacetylene (i.e., model reaction) was found to be particularly suitable for developing and optimising the new heterogeneous catalytic system. It was found that the Sonogashira coupling reaction is very dependent on solvent, base additives and temperature. The most polar solvents like DMF, DMSO or NMP, used in the ratio 4:1 with water, led to the highest reactivity of the $[Pd(NH_3)_4]$-$(NH_4)Y$ catalyst in the model reaction. It was shown that the base also plays a determining role, organic amines like Et_3N giving the highest conversions. When optimised, the Sonogashira coupling reaction of bromobenzene with phenylacetylene gave a 45% yield in diphenylacetylene using only 1 mol % $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ catalyst at 80 °C in DMF/H_2O (4:1) within 3 h.

The optimised reaction conditions developed for the coupling reaction of bromobenzene with phenylacetylene using the heterogeneous $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ catalyst were successfully applied to a wide range of aryl iodides and bromides. Aryl iodides and activated aryl bromides gave almost quantitative yields and non-activated aryl bromides led to reasonable yields for the Sonogashira coupling reaction with phenylacetylene. These reaction conditions were also successfully applied to the synthesis of important substructures of natural and synthetic biologically active organic compounds.

The stability towards leaching and the recyclability of the heterogeneous $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ catalyst were also evaluated. While the catalyst showed an excellent stability towards leaching, since the clear filtrate obtained by hot filtration was little active, it was found that the catalyst is strongly deactivated during the first run. Whereas the initial activity of the fresh catalyst amounted to *ca* 125 mmol/min · g_{cat}, the used catalyst showed an initial activity of only 5 mmol/min · g_{cat}. However, the activity remained then stable over the 5th run and high product yields (*ca.* 87% for the coupling of *p*-iodoanisole with phenylacetylene) could be achieved.

In summary, it was established that the heterogeneous $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ catalyst is an efficient, relatively stable to leaching, and recyclable agent 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 further 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 fine chemical industry.

Experimental Section

All preparations, manipulations and reactions were carried out under argon, including the transfer of the catalysts to the reaction vessel. All glassware was base- and acid-washed and oven dried.

The zeolite $(NH_4)Y$ was purchased from Sigma-Aldrich Chemicals. The catalyst support was dried before use at 120 °C for 48 h under $5 \cdot 10^{-2}$ mmHg. The other chemicals (organic reagents and solvents) were deaerated by an argon flow before they were used. The catalysts were stored after drying under an Ar atmosphere.

The 2-iodo-4-nitrophenol used for the synthesis of the furan **8** was prepared following the procedure described by Dai et al.[27] The 4-bromo-6-methyl-2*H*-pyran-2-one used for the synthesis of **9** was prepared following the procedure described by Cervera et al.[28]

Solution NMR spectra of the organic products were recorded with a Bruker AM 250 spectrometer (^1H NMR were referenced to the residual protio-solvent: $CDCl_3$, $\delta = 7.25$ ppm; ^{13}C NMR were referenced to the C signal of the deutero solvent: $CDCl_3$, $\delta = 77$ ppm). The palladium and copper content determinations of the $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ and $\{[Pd(NH_3)_4][Cu(NH_3)_4]\}/(NH_4)Y$ zeolites were performed by ICP-AES spectroscopy from a solution obtained by treatment of the catalysts with a mixture of HBF_4, HNO_3 and HCl in a Teflon reactor at 180 °C. GC were performed on an HP 4890 chromatograph equipped with an FID detector, an HP 6890 autosampler and an HP-5 column (cross-linked 5% phenyl-methylsiloxane, 30 m × 0.25 mm i. d. × 0.25 μm film thickness). Nitrogen was used as carrier gas. GC-MS were performed on an HP 6890 chromatograph equipped with a Mass detector HP 5973 and an HP-5 MS column (cross-linked 5% phenyl-methylsiloxane, 30 m × 0.25 mm i. d. × 0.25 μm film thickness). Helium was used as carrier gas. The experimental error $\Delta_{rel} = \pm 5\%$.

Flash chromatography was performed at a pressure slightly greater than atmospheric pressure using silica (Merck Silica Gel 60, 230–400 mesh). Thin layer chromatography was performed on Fluka Silica Gel 60 F_{254}.

Catalyst Preparations

All catalysts were prepared according procedures previously described in the literature.[24,25]

Preparation of the $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ Catalyst

A 0.1 M ammonia solution of $[Pd(NH_3)_4]Cl_2$ – prepared from $PdCl_2$ and a commercial ammonia solution – was added dropwise (4 mL/g zeolite, corresponding to *ca.* 5% wt Pd in the final catalyst) to a suspension of the zeolite $(NH_4)Y$ in bidistilled water (100 mL/g zeolite). The mixture was stirred for 24 h at room temperature and the exchanged zeolite was filtered off and washed until no trace of chloride was detected in the filtrate ($AgNO_3$ test).

Then the zeolite was allowed to dry at room temperature to give the entrapped $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ catalyst as slightly yellow materials. ICP-AES analysis: 5.19% wt Pd.

Preparation of the $\{[Pd(NH_3)_4][Cu(NH_3)_4]\}/(NH_4)Y$ Catalyst

A 0.1 M ammonia solution of $[Pd(NH_3)_4]Cl_2$ and $[Cu(NH_3)_4]Cl_2$ – prepared from $PdCl_2$ and $CuCl_2$ by dissolution in a commercial ammonia solution – was added dropwise (4 mL/g zeolite, corresponding respectively to *ca.* 5% wt Pd or *ca.* 2.5% wt Cu in the final catalyst) to a suspension of the zeolite $(NH_4)Y$ in bidistilled water (100 mL/g zeolite). The mixture was stirred for 24 h at room temperature and the exchanged zeolite was filtered off and washed until no trace of chloride was detected in the filtrate ($AgNO_3$ test). Then the zeolite was allowed to dry at room temperature to give the entrapped $\{[Pd(NH_3)_4][Cu(NH_3)_4]\}/(NH_4)Y$ catalysts as a blue material. ICP-AES analysis: 4.72% wt Pd and 2.27% wt Cu

Catalytic Test Reactions

The catalytic reactions were carried out in a three-necked flask, or alternatively in pressure sealed tubes, under argon. The qualitative and quantitative analysis of the reactants and the products was made by gas chromatography. Conversion and yields were determined by GC based on the relative area of GC signals referred to an internal standard (diethylene glycol di-*n*-butyl ether) calibrated to the corresponding pure compound ($\Delta_{rel} = \pm 5\%$). All catalysts were handled and transferred under Ar.

General Procedure for the First Runs of the Catalysts

A total of 5 mmol of aryl halide, 8 mmol of phenylacetylene, 10 mmol of base and 1 mol % Pd catalyst was introduced in a three-necked flask under argon. Then 10 mL of solvent (previously deaerated) were added and the mixture was further deaerated by an argon flow for 5 min. The reactor was placed in a preheated oil bath at 80 °C. The reaction was conducted under vigorous stirring for 3 h and then the reaction mixture was cooled to room temperature before GC analysis.

General Procedure for the Recycling of Separated Catalysts

For recycling experiments the catalyst used in a first run was separated by centrifugation, washed with the 2 × 10 mL DMF/H_2O (4:1) and reused after drying at room temperature as described for the fresh catalyst.

General Procedure for the Evaluation of the Catalytic Activity of Non-Separated Catalysts

A total of 10 mmol of *p*-iodotoluene, 15 mmol of phenylacetylene, 20 mmol of Et_3N and 1 mol% $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ was introduced in a three-necked flask under argon. Then 20 mL of DMF/H_2O (4:1), previously deaerated, were added and the mixture was further deaerated by an argon flow for 5 min. The reactor was placed in a preheated oil bath at 80 °C. The reaction was conducted under vigorous stirring and followed by GC analysis until completion of the reaction. At completion of the first run (i.e., 2 h) new amounts of reagents (10 mmol of *p*-iodotoluene, 15 mmol of phenylacetylene, 20 mmol of Et_3N) were added, and the volume of solvent adjusted in order to set-up the same concentrations of reagents as those of the initial run. Immediately after addition, based on GC analysis, the concentration of the *p*-iodotoluene was set to 100% and the concentration in 1-methyl-4-phenylethynylbenzene to 0%. The reaction was followed by GC until 80% conversion and the procedure was repeated once more.

General Procedure for Leaching Studies by Hot Filtration

A total of 10 mmol of *p*-iodotoluene, 15 mmol of phenylacetylene, 20 mmol of Et_3N and 1 mol % $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ was introduced in a three-necked flask under argon. Then 20 mL of DMF/H_2O (4:1), previously deaerated, were added and the mixture was further deaerated by an argon flow for 5 min. The reactor was placed in a preheated oil bath at 80 °C. The reaction was conducted under vigorous stirring for 10 minutes. The supernatant solution was filtered through a cannula with a microglass Whatman filter (in order to remove all fine particles) and then treated for further 5 h under the standard reaction conditions.

The reaction was monitored over the total period by GC and the results compared to a standard catalytic reaction.

GLC Analysis

A 3 mL sample of the reaction mixture was quenched with 3 mL of water in a test tube. The mixture was extracted with 2 mL of CH_2Cl_2 and the organic layer was filtered through an $MgSO_4$ pad. The resulting dry organic layer was then analyzed by GLC. GLC rate program: 2 min at 100 °C, heating 15 K/min up to 170 °C, 2 min at 170 °C, heating 35 K/min up to 240 °C, 10 min at 240 °C, heating 50 K/min up to 270 °C and 2 min at 270 °C.

Purification of the Products 3, 5–9

The reaction mixture was diluted with 250 mL of water and the resulting mixture extracted with 4 × 20 mL CH_2Cl_2. The combined organic layers were washed three times with 15 mL H_2O, once with 15 mL brine, dried over $MgSO_4$ and evaporated. The residue was then purified by flash chromatography on silica gel.

Data for the Compounds 3, 5 – 9

1-Methoxy-4-phenylethynylbenzene (**3**; R = *p*-OCH_3): Eluent: petroleum ether (40–60 °C)/CH_2Cl_2 = 70/30; $R_f = 0.34$; yield: 67% as a yellow solid; mp 62.8–63.1 °C; $C_{15}H_{12}O$: mol. wt.: 208.26 g·mol^{-1}; MS: *m/z* (%) = [M$^+$] 208 (100), [M$^+$ – CH_3] 193 (45), [M$^+$ – CH_3 – OH] 176 (7). ^{1}H and ^{13}C NMR data are consistent with those reported.[29]

1-Methyl-4-phenylethynylbenzene (**3**; R = CH_3): Eluent: petroleum ether (40–60 °C)/CH_2Cl_2 = 80/20; $R_f = 0.52$; yield: 82% as a white solid; mp 69.8–70.1 °C; $C_{13}H_{12}$: mol. wt.: 192.26 g·mol^{-1}; MS: *m/z* (%) = [M$^+$] 192 (100), [M$^+$ – CH_3 – H] 176 (2), [M$^+$ – CH_2=CH] 165 (12), [M$^+$ – C_6H_5] 115 (4). ^{1}H NMR data are consistent with those reported.[30] ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 138.42$ (C_q-CH_3, C_6H_4), 131.58 (*m*-CH_3, C_6H_4 and *o*-C≡C, C_6H_5), 129.17 (*o*-CH_3, C_6H_4), 128.37 (*m*-C≡C, C_6H_5), 128.13 (*p*-C≡C, C_6H_5), 123.53

(C_q-C≡C, C_6H_5), 120.24 (C_q-C≡C, C_6H_4), 89.55 (C≡*C*-C_6H_4), 88.72 (C≡*C*-C_6H_5), 21.53 (*C*H_3).

1-Fluoro-4-phenylethynylbenzene (**3**; R = F): Eluent: petroleum ether (40–60 °C)/CH_2Cl_2 = 80/20; R_f = 0.55; yield: 87% as a white solid; mp 110.8–111.3 °C; $C_{14}H_9F$: mol. wt.: 196.22 g·mol^{-1}; MS: *m/z* (%) = [M$^+$] 196 (100), [M$^+$ – F] 177 (10); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.44 (m, 4H, *m*-F-C_6H_4 and *o*-C≡C-C_6H_5), 7.26 (m, 3H, *p*-C≡C-C_6H_5 and *m*-C≡C-C_6H_5), 6.96 (*pseudo*-t, ^3J(H,H) = 8.7 Hz, *o*-F-C_6H_4); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 164.46 (C_q-F, C_6H_4), 133.40 (*m*-F, C_6H_4), 131.54 (*o*-C≡C, C_6H_5), 128.36 (*p*-C≡C, C_6H_5), 128.33 (*m*-C≡C, C_6H_5), 123.06 (C_q-C≡C, C_6H_5), 119.32 (C_q-C≡C, C_6H_4), 115.45 (*o*-F, C_6H_4), 89.00 (C≡*C*-C_6H_4), 88.26 (C≡*C*-C_6H_5).

1-Nitro-4-phenylethynylbenzene (**3**; R = NO_2): Eluent: petroleum ether (40–60 °C)/CH_2Cl_2 = 80/20; R_f = 0.26; yield: 85% as a white crystalline solid; mp 119.8–120.3 °C; $C_{14}H_9NO_2$: mol. wt.: 223.23 g·mol^{-1}; MS: *m/z* (%) = [M$^+$] 223 (100), [M$^+$ – OH] 207 (7), [M$^+$ – NO] 193 (60), [M$^+$ – NO_2] 176 (90). ^{1}H and ^{13}C NMR data are consistent with those reported.[29]

1-(4-Phenylethynylphenyl)-ethanone (**3**; R = CH_3CO): Eluent: petroleum ether (40–60 °C)/CH_2Cl_2 = 60/40; R_f = 0.26; yield: 85% as an orange crystalline solid; mp 99.8–100.2 °C; $C_{16}H_{12}O$: mol. wt.: 220.27 g·mol^{-1}; MS: *m/z* (%) = [M$^+$] 220 (60), [M$^+$ – CH_3] 205 (100), [M$^+$ – CH_3CO] 176 (50). ^{1}H and ^{13}C NMR data are consistent with those reported.[29]

1-Nitro-2-phenylethynylbenzene (**3**; R = NO_2): Eluent: petroleum ether (40–60 °)/CH_2Cl_2 = 60/40; R_f = 0.76; yield: 89% as an orange oil; $C_{14}H_9NO_2$: mol. wt.: 223.23 g.mol^{-1}; MS: *m/z* (%) = [M$^+$] 223 (10), [M$^+$ – OH] 206 (30), [M$^+$ – NO] 193 (20), [M$^+$ – NO_2] 176 (30), [M$^+$ – C_6H_5C≡C – OH] 105 (100), [M$^+$ – $C_6H_4NO_2$ – C≡C] 77 (80). ^{1}H NMR data are consistent with those reported.[30] ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 146.51 (C_q-NO_2, C_6H_4), 134.57 (*p*-NO_2, C_6H_4), 132.89 (*o*-C≡C, C_6H_4), 132.01 (*o*-C≡C, C_6H_5), 129.27 (*p*-C≡C, C_6H_4), 128.60 (*p*-C≡C, C_6H_5), 128.49 (*m*-C≡C, C_6H_5), 124.69 (*o*-NO_2, C_6H_4), 122.38 (C_q-C≡C, C_6H_5), 118.66 (C_q-C≡C, C_6H_4), 97.12 (C≡*C*-C_6H_5), 84.88 (C≡*C*-C_6H_4).

1-Methyl-2-phenylethynylbenzene (**3**; R = CH_3): Eluent: petroleum ether (40–60 °C)/CH_2Cl_2 = 80/20; R_f = 0.47; yield: 67% as a colourless oil; $C_{13}H_{12}$: mol. wt.: 192.26 g·mol^{-1}; MS: *m/z* (%) = [M$^+$] 192 (100), [M$^+$ – CH_3 – H] 176 (10), [M$^+$ – C_6H_5] 115 (25). ^{1}H and ^{13}C NMR data are consistent with those reported.[29]

3-Phenyl-2-propyn-1-ol (**5**): Eluent CH_2Cl_2/ethanol = 90/10; R_f = 0.73; yield: 73% as a colourless oil; C_9H_8O: mol. wt.: 132.16 g·mol^{-1}; MS: *m/z* (%) = [M$^+$ – H] 131 (100), [M$^+$ – OH] 115 (22), [M$^+$ – CHO] 103 (46) [$C_6H_5^+$] 77 (32). ^{1}H and ^{13}C NMR data are consistent with those reported.[31]

2-Phenylindole (**6**): Eluent: petroleum ether (40–60 °C)/CH_2Cl_2 = 2/1; R_f = 0.72; yield: 72% as a light brown compound; mp 188.3–189.6 °C; $C_{14}H_{11}N$, mol. wt.: 193.25 g·mol^{-1}; MS: *m/z* (%) = [M$^+$] 193 (100), [M$^+$ – CHNH] 165 (43), [M$^+$ – NH-C-C_6H_5] 89 (22). ^{1}H and ^{13}C NMR data are consistent with those reported.[32]

2-Phenylbenzofuran (**7**): Eluent: petroleum ether (40–60 °C)/CH_2Cl_2 = 30/70; R_f = 0.72; yield: 78% as a slightly brown solid; mp 118.3–120.1 °C; $C_{14}H_{10}O$, mol. wt.: 194.23 g·mol^{-1}; MS: *m/z* (%) = [M$^+$] 194 (100), [M$^+$ – CHO] 165 (60). ^{1}H and ^{13}C NMR data are consistent with those reported.[33]

2-Phenyl-5-nitrobenzofuran (**8**): Eluent: petroleum ether (40–60 °C)/CH_2Cl_2 = 20/80; R_f = 0.73; yield: 63% as a slightly brown solid; mp 131.8–132.5 °C; $C_{14}H_9NO_3$; mol. wt.: 239.23 g·mol^{-1}; MS: *m/z* (%) = [M$^+$] 239 (100), [M$^+$ – CHO – H] 203 (70), [M$^+$ – NO_2] 193 (43), [M$^+$ – NO_2 – CHO] 165 (49). ^{1}H and ^{13}C NMR data are consistent with those reported.[34]

4-(Phenylethynyl)-6-methyl-2-pyrone (**9**): Eluent: petroleum ether (40–60 °C)/CH_2Cl_2 = 35/65; R_f = 0.71; yield: 95% as a slightly brown solid; mp 65.3–66.7 °C; $C_{14}H_{10}O_2$, mol. wt.: 210.23 g·mol^{-1}; MS: *m/z* (%) = [M$^+$] 210 (100), [M$^+$ – CO] 182 (85), [M$^+$ – CO – CH_2O] 153 (40), [M$^+$ – CO – C_2H_4O] 139 (52). ^{1}H and ^{13}C NMR data are consistent with those reported.[35]

Preparation of (*Z*)-1-(1,4-Diphenylbut-1-en-3-yn-2-yl)-4-methylbenzene (4)

A total of 10 mmol of *p*-iodotoluene, 15 mmol of phenylacetylene, 20 mmol of Et_3N and 1 mol % Pd catalyst was introduced in a three-necked flask under argon. Then 20 mL of solvent (previously deaerated) were added and the mixture was further deaerated by an argon flow for 5 min. The reactor was placed in a preheated oil bath at 100 °C under vigorous stirring for 24 h. The reaction mixture was then diluted with 250 mL of water and the resulting mixture extracted with 4 × 20 mL CH_2Cl_2. The combined organic layers were washed three times with 15 mL H_2O, once with 15 mL brine, dried over $MgSO_4$ and evaporated. The residue was then purified by flash chromatography on silica gel eluting with petroleum ether (40–60 °C)/ether (80:20) to give the product **4** as a microcrystalline slightly yellow compound; yield: 28%; R_f = 0.33; mp 88.6–90.8 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.86 [d, ^3J(H,H) = 8.2 Hz, 2H, *o*-C=C-C_6H_4), 7.71 (m, 2H, *o*-C≡C-C_6H_4), 7.48 (m, 2H, *o*-C=C-C_6H_5), 7.30 (m, 6H, *m*-C=C-C_6H_5, *p*-C=C-C_6H_5, *m*-C≡C-C_6H_5, *p*-C≡C-C_6H_5), 7.15 (m, 3H, C=C*H*; *o*-CH_3-C_6H_4), 2.31 (s, 1H, *C*H_3); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 139.80 (C_q-CH_3, C_6H_4), 138.58 (C_q-C=C, C_6H_5), 134.98 (C=*C*-C_6H_5), 134.10 (C_q-C=C, C_6H_4), 131.65 (*o*-C≡C, C_6H_5), 129.29 (*m*-C=C, C_6H_5), 129.20 (*m*-C=C, C_6H_4), 128.61 (*o*-C=C, C_6H_5), 128.58 (*m*-C≡C, C_6H_5, *p*-C≡C, C_6H_5), 127.89 (*p*-C=C, C_6H_5), 126.55 (*o*-C=C, C_6H_4), 123.61 (C≡C-*C*=C), 120.72 (C_q-C≡C, C_6H_5), 97.00 (C≡*C*-C_6H_5), 89.08 (C≡*C*-C=C), 21.58 (*C*H_3); $C_{23}H_{18}$: mol. wt.: 294.39 g·mol^{-1}; MS: *m/z* (%) = [M$^+$] 294 (100), [M$^+$ – CH_3] 279 (75), [M$^+$ – CH_3 – C_6H_4] 215 (25), [M$^+$ – C≡C – C_6H_5] 202 (30).

Preparation of 4-Tosyl-6-methyl-2*H*-pyran-2-one

A total of 8 mmol (1 g) of 4-hydroxy-6-methyl-2H-pyran-2-one and 71 mmol of triethylamine in 15 mL of CH_2Cl_2 were introduced in a three-necked flask under argon. The mixture was deaerated by an argon flow for 5 min and 10 mmol of tosyl chloride were added under argon flow. The mixture was stirred for 24 h at room temperature. After evaporation, the product was precipitated by treatment with 25 mL of water, filtered off, washed with 3 × 15 mL of ethanol and dried under high vacuum. The 4-tosyl-6-methyl-2*H*-pyran-2-one was obtained as a white solid; yield: 74%; mp 101.2–102.0 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.75 [d, ^3J(H,H) = 8.3 Hz, 2H, *m*-CH_3-

C_6H_4[], 7.32 [d, ^3J(H,H) = 8.0 Hz, 2H, *o*-CH_3-C_6H_4], 5.93 [*pseudo*-q, ^4J(H,H) = 1.5 Hz, 1H, CH_3-C(O)=*C*H-C(OSO_2)], 5.74 [d, ^4J(H,H) = 1.8 Hz, 1H, O-C(O)-C*H*=C(OSO_2)], 2.41 (s, 3H, C_6H_4-CH_3), 2.17 [s, 3H, CH=C(O)-CH_3]; ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 162.27 (SO_2-O-*C*=CH), 160.82 (*C*=O), 159.94 (CH_3*C*=CH), 144.72 (C_q-SO_2, C_6H_4), 129.58 (C_q-CH_3, C_6H_4), 128.28 (*o*-CH_3, C_6H_4), 126.35 (*o*-SO_2, C_6H_4), 98.71 [CH_3-C=*C*H-C(OSO_2)], 98.60 [O-C(O)-*C*H-C(OSO_2)], 19.79 (C_6H_4-*C*H_3), 18.16 [CH=C(O)-*C*H_3]; $C_{13}H_{12}O_5S$: mol. wt.: 280.29 g·mol^{-1}; MS: *m/z* (%) = [M^+] 280 (4), [$C_7H_7O_2S^+$] 155 (47), [$C_5H_4O_2S^+$] 132 (32), [$C_7H_7^+$] 91 (100).

References

[1] a) J. S. Moore, *Acc. Chem. Res.* **1997**, *30*, 402 and references cited therein; b) T. Hiyama, in: *Metal-Catalyzed Cross-Coupling Reactions*, (Eds.: F. Diederich, P. J. Stang), Wiley-VCH Weinheim, **1998**, Chapter 10 and references cited therein; c) K. Sonogashira, *J. Organomet. Chem.* **2002**, *653*, 46; d) K. Sonogashira, in: *Handbook of Organopalladium Chemistry for Organic Synthesis*, (Ed.: E. Negishi), Wiley-VCH, New York, **2002**; e) R. R. Tykwinski, *Angew Chem. Int. Ed. Engl.* **2003**, *42*, 1566; f) E.-I. Negishi, L. Anastasia, *Chem. Rev.* **2003**, *103*, 1979.

[2] a) *Modern Acetylene Chemistry*, (Eds.: P. J. Stang, F. Diederich), VCH, Weinheim, **1995**; b) *Modern Arene Chemistry,* (Ed.: D. Astruc), Wiley-VCH, Weinheim, **2002**.

[3] a) L. Brandsma, S. F. Vasilevsky, H. D. Verkruijsse, *Applications of Transition Metal Catalysts in Organic Synthesis*, Springer, Berlin, **1988**, Chap. 10, pp. 179–225; b) K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis,* Wiley-VCH, Weinheim, **1996**, p. 582; c) A. E. Graham, D. McKerrecher, D. H. Davies, R. J. K. Taylor, *Tetrahedron Lett.* **1996**, *37*, 7445; d) M. W. Miller, C. R. Johnson, *J. Org. Chem.* **1997**, *62*, 1582; e) A. Sakai, T. Aoyama, T. Shioiri, *Tetrahedron Lett.* **1999**, *40*, 4211; f) F. Yoshimura, S. Kawata, M. Hirama, *Tetrahedron Lett.* **1999**, *40*, 8281; g) M. Toyota, C. Komori, M. Ihara, *J. Org. Chem.* **2000**, *65*, 7110; h) I. Paterson, R. D. M. Davies, R. Marquez, *Angew. Chem. Int. Ed.* **2001**, *40*, 603; i) J.-i. Uenishi, K. Matsui, H. Ohmiya, *J. Organomet. Chem.* **2002**, *653*, 141.

[4] K. Sonogashira, in: *Comprehensive Organic Synthesis*, Vol. 3 (Eds.: B. M. Trost, I. Fleming), Pergamon Press, New York, **1991**, pp. 521–549.

[5] H.-F. Chow, C.-W. Wan, K.-H. Low, Y.-Y Yeung,. *J. Org. Chem.* **2001**, *66*, 1910.

[6] a) A. L. Casalnuovo, J. C. Calabrese, *J. Am. Chem. Soc.* **1990**, *112*, 4324; b) H. Dibowski, F. P. Schmidtchen, *Tetrahedron Lett.* **1998**, *39*, 525; c) G. W. Kabalka, L. Wang, V. Namboodiri, R. M. Pagni, *Tetrahedron Lett.* **2000**, *41*, 5151; d) D. T. Bong, M. R. Ghadiri, *Org. Lett.* **2001**, *3*, 2509; e) M. J. Mio, L. C. Kopel, J. B. Braun, T. L. Gadzikwa, K. L. Hull, R. G. Brisbois, C. J. Markworth, P. A. Grieco, *Org. Lett.* **2002**, *4*, 3199; f) H. Remmele, A. Köllhofer, H. Plenio, *Organometallics* **2003**, *22*, 4098.

[7] T. Fukuyama, M. Shinmen, S. Nishitani, M. Sato, I. Ryu, *Org. Lett.* **2002**, *4*, 1691.

[8] a) T. Okita, M. Isobe, *Synlett* **1994**, 589; b) J.-F. Nguefack, V. Bolitt, D. Sinou, *Tetrahedron Lett.* **1996**, *37*, 5527; c) T. Hundertmark, A. F. Littke, S. L. Buchwald, G. C. Fu, *Org. Lett.* **2000**, *2*, 1729; d) M. R. Netherton, G. C. Fu, G. C. *Org. Lett.* **2001**, *3*, 4295; e) D. Méry, K. Heuzé, D. Astruc, *Chem. Commun.* **2003**, 1934; f) N. E. Leadbeater, B. J. Bonnie, *Tetrahedron Lett.* **2003**, *44*, 8653; g) A. Soheili, J. Albaneze-Walker, J. A. Murry, P. G. Dormer, D. L. Hughes, *Organic Lett.* **2003**, *5*, 4191; h) Y. Uozumi, Y. Kobayashi, *Heterocycles* **2003**, *59*, 71; i) L. Djakovitch, P. Rollet, *Tetrahedron Lett.* **2004**, *45*, 1367; j) A. Arquès, D. Auñon, P. Molina, *Tetrahedron Lett.* **2004**, *45*, 4337.

[9] a) N. A. Powell, S. D. Rychnosky, *Tetrahedron Lett.* **1996**, *37*, 7901; b) G. T. Crisp, P. D. Turner, K. A. Stephens, *J. Organomet. Chem.* **1998**, *570*, 219; c) K. Nakamura, H. Ohubo, M. Yamaguchi, *Synlett* **1999**, 549; d) W.-M. Dai, D.-S. Guo, L.-P. Sun, *Tetrahedron Lett.* **2001**, *42*, 5275.

[10] I. P. Beletskaya, G. V. Latyshev, A. V. Tsvetkov, N. V. Lukashev, *Tetrahedron Lett.* **2003**, *44*, 5011.

[11] L. Wang, L. Pinhua, Y. Zhang, *Chem. Commun.* **2004**, 514.

[12] N. E. Leadbeater, M. Marco, B. J. Tominack, *Organic Lett.* **2003**, *5*, 3919.

[13] P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem. Int. Ed.* **2000**, *39*, 2632.

[14] J.-P. Genêt, E. Blart, M. Savignac, *Synlett* **1992**, 715.

[15] M. Alami, F. Ferri, G. Linstrumelle, *Tetrahedron Lett.* **1993**, *34*, 6403.

[16] V. P. Böhm, W. A. Herrmann, *Eur. J. Org. Chem.* **2000**, 3679.

[17] M. Pal, K. Parasuraman, S. Gupta, K. R. Yeleswarapu, *Synlett* **2002**, 1976.

[18] X. Fu, S. Zhang, Y. Yin, D. Schumacher, *Tetrahedron Lett.* **2002**, *43*, 6673.

[19] a) D. A. Alonso, C. Nájera, M. C. Pacheco, *Tetrahedron Lett.* **2002**, *43*, 9365; b) D. A. Alonso, C. Nájera, M. C. Pacheco, *Adv. Synth. Catal.* **2003**, *345*, 1146.

[20] N. Sakai, K. Annaka, T. Konakahara, *Organic Lett.* **2004**, *6*, 1527.

[21] K. Heuzé, D. Méry, D. Gauss, D. Astruc, *Chem. Commun.* **2003**, 2274.

[22] R. G. Heidenreich, K. Köhler, J. G. E. Krauter, J. Pietsch, *Synlett* **2002**, 1118.

[23] Z. Novák, A. Szabó, J. Répási, A. Kotschy, *J. Org. Chem.* **2003**, *68*, 3327.

[24] a) L. Djakovitch, K. Köhler, *J. Mol. Catal. A: Chem.* **1999**, *142*, 275; b) L. Djakovitch, H. Heise, K. Köhler, *J. Organomet. Chem.* **1999**, *584*, 16; c) L. Djakovitch, K. Köhler, *J. Am. Chem. Soc.* **2001**, *123*, 5990.

[25] a) J. Michalik, M. Narayana, L. Kevan, *J. Phys. Chem.* **1985**, *89*, 4553; b) W. M. H. Sachtler, F. A. P. Cacalcanti, *Catal. Lett.* **1991**, *9*, 261.

[26] A. Streitwieser, C. K. Heathcock, E. M. Kosower, *Introduction to Organic Chemistry*, 4th edn., MacMillan Press, London, **1992**.

[27] W.-M. Dai, K. W. Lai, *Tetrahedron Lett.* **2002**, *43*, 9377.

[28] M. Cervera, M. Moreno-Mañas, R. Pleixats, *Tetrahedron Lett.* **1990**, *31*, 7885.

[29] S. Urgaonkar, J. G. Verkade, *J. Org. Chem.* **2004**, *69*, 5752.

[30] K. Okuro, M. Furuune, M. Enna, M. Miura, M. Nomura, *J. Org. Chem.* **1993**, *58*, 4716.

[31] S. B. Park, H. Alper, *Chem. Commun.* **2004**, 1306.

[32] S. Chouzier, M. Gruber, L. Djakovitch, *J. Mol. Catal. A: Chem.* **2004**, *21*, 43.

[33] G. W. Kabalka, L. Wang, R. M. Pagni, *Tetrahedron* **2001**, *57*, 8017.

[34] A. Chilin, P. Rodighiero, A. Guitto, *Synthesis* **1998**, 309.

[35] I. J. S. Fairlamb, F. J. Lu, J. P. Schmidt, *Synthesis* **2003**, 2564.