Reusable polystyrene-supported Pd catalyst for Mizoroki–Heck reactions with extremely low amounts of supported Pd†

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In this communication, we report that by running Mizoroki–Heck reactions of various aryl iodides in toluene–DMF, only extremely low amounts of supported Pd (0.04 mequiv.) are required to obtain almost quantitative yields. The catalyst was reused successfully up to three times.

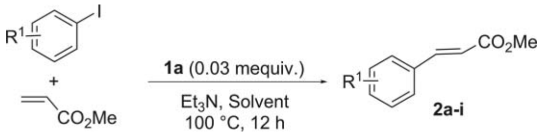
Transition metal catalyzed cross-coupling is one of the most powerful reactions for the formation of new C–C bonds.[1] Among them, the Pd catalyzed Mizoroki–Heck coupling forms efficiently alkenyl–aryl bonds.[2] It finds widespread applications for the preparation of key building blocks for the syntheses of elaborated molecules possessing interesting pharmacological,[3] biological[4] or physical properties.[5]

Although Mizoroki–Heck reactions are usually performed by coupling aryl iodides or bromides[6] with alkenes in the presence of 10–50 mequiv. of a soluble Pd catalyst,[2,7] several groups have reported Mizoroki–Heck reactions involving only 0.1 mequiv. or even less of highly active homogeneous Pd catalysts.[8,9] However in most cases, these catalysts are not commercially available, their preparation requiring several steps[8e–l] and they cannot be recovered from the reaction medium.[8] In the last decade, reusable Pd catalysts, designed to overcome the high costs of Pd salts or complexes have been reported for Mizoroki–Heck reactions. Usually, 5–50 mequiv. of Pd are required,[10] however some groups have performed couplings with 0.1 mequiv. or even less of precious metal.[11] We have recently reported a short and easy route to phosphinomethylpolystyrene-supported Pd catalysts[12] for the Suzuki coupling of the unreactive aryl chlorides,[12a] the Sonogashira reaction[12b] and, in particular, we have shown that the Mizoroki–Heck coupling from aryl iodides proceeds efficiently in MeCN in the presence of 1.5 mequiv. of supported Pd (catalyst **1b** containing 0.3% of Pd).[12b] Upon reoptimizing the conditions we found that in a 2 : 1 toluene–DMF mixture almost quantitative yields were obtained in the presence of extremely low amounts[13] of supported Pd (0.04 mequiv.) and that the catalyst could be reused. We would like to present here these results.

According to our previously published procedures[12a,b] the polystyrene-supported Pd catalysts **1a** and **1b** were prepared in two steps (Scheme 1). It is important to note that these catalysts could easily be prepared on a 20 g scale and that they are air- and moisture-stable.

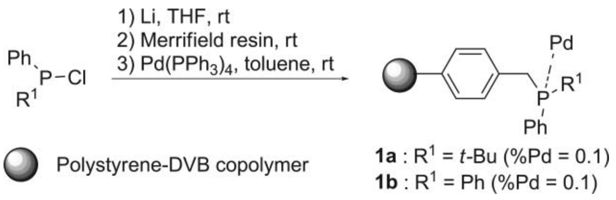
Iodobenzene ($R^1 = H$) and methyl acrylate were chosen as model substrates and a screening of solvents was performed (Table 1).

Table 1 Screening of solvents



Entry[a]	Catalyst	Solvent[b]	Yield (%)[c]
1	**1a**	Toluene/DMF (2 : 1)	91 (98)[d]
2	**1a**	Toluene/Formamide (2 : 1)	No reaction[e]
3	**1a**	Toluene	10
4	**1a**	DMF	4
5	**1a**	DMA	23
6	**1a**	MeCN	21
7	**1a**	Dioxane	6
8	**1b**	Toluene/DMF (2 : 1)	91
9	**PdEncat NP30**	Toluene/DMF (2 : 1)	77
10	**Pd(PPh$_3$)$_4$**	Toluene/DMF (2 : 1)	84

[a] Reactions performed with 1.0 equiv. (10 mmol) of iodobenzene, 2.0 equiv. of methyl acrylate, and 1.2 equiv. of Et_3N. [b] 1% of H_2O was added to the reaction medium to assure reproducibility. [c] Isolated yields by filtration of the crude reaction mixture on silica gel. [d] Reaction performed in the presence of 0.04 mequiv. of supported Pd. [e] Iodobenzene was recovered unchanged.



Scheme 1 Syntheses of catalysts **1a** and **1b**.

In a 2 : 1 mixture of toluene–DMF only 0.03 mequiv. of supported Pd were sufficient to afford **2a** in a 91% yield (entry 1). Increasing the Pd content of **1a** from 0.1% to 1% did not modify the amount of supported Pd required. The use of a toluene/formamide mixture gave no reaction and iodobenzene was recovered unchanged (entry 2). Performing the reaction either in toluene or DMF alone or in other polar solvents afforded **2a** in only poor yields (entries 3–7). The replacement of the *tert*-butylphenylphosphino group by the diphenylphosphino group gave also **2a** in an almost quantitative yield (entry 8). Good results were also obtained by using PdEncat NP30[14] or Pd(PPh$_3$)$_4$ (entries 9–10). The reason of the excellent reactivity of catalysts **1a–b**, PdEncat NP30 and Pd(PPh$_3$)$_4$ for the Mizoroki–Heck reaction seems to be the use of this particular solvent mixture.[15]

To determine the possibility to reuse catalyst **1a**, the reaction was filtered on a membrane (for further details see ESI†) and the catalyst was washed and directly reused in another Mizoroki–Heck coupling (Table 2). It turned out that after three uses, yields

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† Electronic supplementary information (ESI) available: Characterizations and ^1H NMR spectra of alkenes **2a–i**. See DOI: 10.1039/c0ob00523a

Table 2 Recycling test of catalyst **1a**

Run[a,b]	1	2	3	4
Yield (%)[c]	98	93	98	61

[a] Reactions performed with 1.0 equiv. (10 mmol) of iodobenzene, 2.0 equiv. of methyl acrylate, 1.2 equiv. of Et_3N and 0.04 mequiv. of supported Pd. [b] 1% of H_2O was added to the reaction medium to assure reproducibility. [c] Isolated yields by filtration of the crude reaction mixture on silica gel.

Table 3 Syntheses of alkenes

Entry[a,b]	R^1	Product	Yield (%)[c]
1	H	**2a**	99
2	4-Me	**2b**	91
3	3-Me	**2c**	99
4	2-Me	**2d**	99
5	4-OMe	**2e**	96
6	2-Br	**2f**	99
7	4-Ac	**2g**	98
8	3-CF_3	**2h**	99
9	2-CO_2Et	**2i**	97

[a] Reactions performed with 1.0 equiv. (10 mmol) of aryl iodide, 2.0 equiv. of methyl acrylate, 1.2 equiv. of Et_3N and 0.04 mequiv. of supported Pd. [b] 1% of H_2O was added to the reaction medium. [c] Isolated yields by filtration of the crude reaction mixture on silica gel.

were superior to 90% but after the fourth use, **2a** was obtained in a lower 61% yield. Similar results were obtained with catalyst **1b**. The amount of Pd leached in the reaction mixture was then determined after complete mineralization of the filtrate at the end of the coupling.[12a] We found that *ca.* 5 microequivalents of Pd were present in the filtrate. The presence of only negligible amounts of Pd in the reaction medium could be of notable practical importance, avoiding costly purification steps.

The scope of the Mizoroki–Heck reaction was then evaluated by reacting methyl acrylate with various aryl iodides in the presence of catalyst **1a** (Table 3).[16] Electron-rich or electron-deficient aryl iodides gave alkenes **2a–i** with excellent isolated yields. The sterically moderately hindered 2-iodotoluene and 1-bromo-2-iodobenzene afforded the corresponding alkenes in 99% yields (entries 4 and 6). In all cases, only the (*E*)-alkenes were obtained.

In conclusion, Mizoroki–Heck reactions performed in the presence of only tiny amounts of a supported Pd catalyst, which moreover is reusable, are of considerable practical and therefore industrial significance. This also fulfils the environment-related preoccupation of preservation of scarce natural resources.

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15 Only traces of **2a** were observed by replacing iodobenzene with bromobenzene (catalyst **1a**).

16 Syntheses of Alkenes **2a–i**. Catalyst **1a** (prepared according to reference 12d, 42.5 mg, 0.04 mequiv. of Pd) was added to a solution of aryl iodide (10 mmol, 1.0 equiv), methyl acrylate (1.81 mL, 20 mmol, 2.0 equiv) and Et_3N (1.67 mL, 12 mmol, 1.2 equiv) in a mixture of toluene (16 mL), DMF (8 mL) and H_2O (0.25 mL). The reaction mixture was heated at 100 °C for 20 h. After cooling to rt, **1a** was filtered off under vacuum. The mixture of solvents was concentrated under vacuum and the residue was purified by flash-chromatography on silica gel to afford pure alkenes after drying under vacuum (0.1 mbar).