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Poly(ethylene glycol) as reaction medium for mild Mizoroki–Heck reaction in a ball-mill[†]

Valérie Declerck,[‡] Evelina Colacino, Xavier Bantreil, Jean Martinez and Frédéric Lamaty*

Phosphine-free palladium-catalyzed Mizoroki–Heck reaction was performed using ball-milling in polyethylene glycol under mild conditions. Good to excellent yields of coupling products were obtained. This activation technique also allowed the concomitant formation of round shaped Pd–PEG nanoparticles that were characterized by TEM analysis.

Grinding, dry mixing or ball-milling have proved their efficiency as unconventional techniques in the field of organic chemistry in solid state.¹ These techniques have been applied to a large number of organic transformations, but with limited use in the case of C–C bond formation, to aldol and Knoevenagel condensations, Michael additions, Baylis–Hillman and Wittig reactions, and asymmetric alkylation of Schiff bases.² Transition metal-catalyzed coupling reactions, especially with palladium, are very efficient and well developed C–C bond formation reactions.³ Such reactions performed in a ball-mill have been limited to a small number of examples of transformations, mainly the Suzuki–Miyaura⁴ and Mizoroki–Heck⁵ cross couplings.

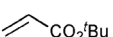
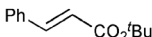
In the last few years we have developed a metal-based catalytic system using solid PEGs [poly(ethylene glycols)] as solvent and stabilizing/precipitating agents to separate the organic product from the metallic catalytic system.⁶ We questioned whether the use of solid PEG would be adapted to the development of a useful catalytic system to perform Pd-catalyzed reactions in a ball-mill.

As a model reaction, the Mizoroki–Heck arylation⁷ of *tert*-butyl acrylate to produce cinnamate was chosen. A mixture of PhI, *tert*-butyl acrylate, PEG, Pd(OAc)₂ and an inorganic base was reacted in a high energy stainless steel vibratory ball mill for 1 h at 30 Hz together with additives in some cases. Under traditional heating and microwave irradiation, PEG has already been shown to reduce Pd(OAc)₂ to Pd(0).^{6d,8} However, under ball-milling conditions, it was found necessary to add

sodium formate as a reducing agent for the activation of Pd(OAc)₂ (67% yield). This was the best from a practical point of view, as sodium formate is easy to handle, as well as from the results obtained with reducing agents such as H₂ (28%) or NaBH₄ (59%). At the end of the reaction, the mixture was dissolved in a small amount of CH₂Cl₂ and precipitated in ether, filtered, evaporated and analyzed by ¹H NMR using CH₂Br₂ as an internal standard. Integration of the signal corresponding to the H of the ester group of *tert*-butylcinnamate measured against the unique signal of the standard (CH₂Br₂) provided the yield of the product. Results are presented in Table 1.

It was shown previously that a solid additive like sodium chloride could be valuable for the Mizoroki–Heck arylation reaction.⁵ In our study, when PEG-3400-OH was used, adding NaCl was found to be detrimental to the reaction and barely any conversion was observed whilst 67% yield was obtained in the absence of NaCl (entries 1–2). Attempt to change the inorganic base by switching from K₂CO₃ to Na₂CO₃ (entry 3) resulted in a lower conversion most probably because the PEG–K⁺ interaction is stronger than the corresponding PEG–Na⁺ thus enhancing the base activity. When triethylamine

Table 1 Optimization of ball-milling Mizoroki–Heck reaction^a

	Ph–I + 	Pd(OAc) ₂ (5 mol%) K ₂ CO ₃ (3 equiv) HCO ₂ Na (0.2 equiv) PEG Ball-mill, 30 Hz, 1h		
Entry	PEG	Acrylate (equiv.)	Additive	Yield ^b (%)
1	PEG-3400-OH	1.2	NaCl	0.4
2	PEG-3400-OH	1.2	—	67
3 ^c	PEG-3400-OH	1.2	—	2
4	PEG-2000-OH	1.2	—	88
5 ^d	PEG-2000-OH	1.2	—	0
6	PEG-2000-OH	5	—	100
7	MeO-PEG-2000-OMe	5	—	46
8	MeO-PEG-2000-OH	5	—	27
9	PEG-1100-OH	5	—	74
10	—	1.2	—	0

^a Reaction conditions: phenyl iodide (0.1 mmol), *tert*-butyl acrylate, Pd(OAc)₂ (5 mol%), HCO₂Na (0.2 equiv.), K₂CO₃ (3 equiv.), PEG (110 mg). ^b Yields were determined by ¹H NMR using CH₂Br₂ as an internal standard. ^c Na₂CO₃ was used instead of K₂CO₃. ^d 1 mol% Pd(OAc)₂.

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was used, substrates also remained unchanged. We realized that during the course of the reaction, it appeared that PEG melted due to the slight heating of the ball-mill.⁹ As the viscosity of the PEG used might have an influence on the reaction, we turned our attention to shorter polymers having a lower melting point. As a result, the yield increased by 20% by using PEG-2000-OH (entry 4). While reducing catalyst loading to 1 mol% resulted in no conversion (entry 5), increasing the quantity of acrylate from 1.2 to 5 equivalents resulted in total conversion (entry 6). The exact excess amount of acrylate needed for completion of the reaction was not studied in detail. Several PEGs were then tested under these conditions. The use of mono- and di-methylated PEG-2000 was detrimental as the yields dropped down (entries 7 and 8). Finally, shorter PEG-1100-OH gave a 74% yield (entry 9). It is worth noting that due to the stabilizing effect of oxygen atoms in PEG, no phosphine ligand was necessary for the catalysis. In the absence of PEG, no reaction occurred (entry 10). In addition, Mizoroki–Heck coupling generally requires elevated temperatures, unfriendly solvent and an inert atmosphere. In our study, the use of PEG in a vibratory ball-mill allowed the reaction to proceed in air under mild conditions.

The scope of the reaction was first explored by varying the olefin part. Unfortunately, the reaction was efficient only with *tert*-butyl acrylate. Either no reaction was observed or a very poor yield was obtained with acrylonitrile (0%), acrylamide (0%), methyl methacrylate (5%) or styrene (13%). The aromatic partner was then evaluated (Table 2). Different substituents could be used on the aryl moiety.¹⁰ Electron-donating as well as withdrawing groups were well tolerated in the *para* position as *p*-MeO, *p*-CN, *p*-Br gave satisfactory yields (entries 2–4) and *p*-CHO was converted quantitatively (entry 5). Surprisingly, *p*-NO₂ substitution resulted in poor yield (entry 6). This is may be due to a physico-chemical characteristic of the starting 4-iodo nitrobenzene rather than

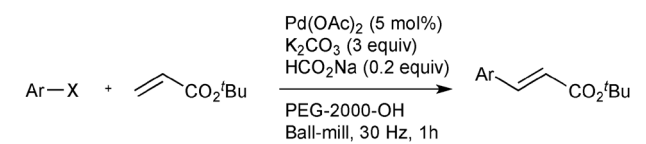
an electronic effect of the substituent. A fluorine atom in the *meta* position allowed quantitative conversion (entry 7). However, having a methyl group in the *ortho* position reduced the yield to 29% (entry 8). Finally, the influence of the halide leaving group (I vs. Br, Cl) was explored. Only the iodine atom was reactive enough to provide the expected product, even when sodium iodide was added to the reaction mixture (entries 9–12).

It has already been demonstrated that palladium salts in the presence of polyethylene glycol are transformed into nanoparticles by classical activation. Because the order of the reduction potentials of the polyol and noble metals is not favorable at rt, this method requires high temperatures to reduce the noble metals.¹¹ This was confirmed by our previous work, using convection^{6g} or microwave heating.^{6d} Furthermore, when a long chain PEG (PEG-2000-OH or PEG-4000-OH) in the presence of Pd(OAc)₂ but no substrate was stirred at a temperature of 80–120 °C, nanoparticles of 5 nm were observed.⁸ When using PEG-400-OH, phenanthroline as a reducing agent was necessary to observe the formation of 2–6 nm particles.¹² However, under vibrating ball-milling conditions, since the reaction temperature was mild,⁹ an external reducing agent such as sodium formate was required for activation of Pd(OAc)₂.

According to these results, we questioned whether formation of nanoparticles would also occur in the ball mill during the course of the reaction, knowing that physical and chemical properties would depend on the size and shape of the particles. Transition Electron Microscopy (TEM) analysis of the precipitates obtained after reactions reported in Table 1 with various PEGs was performed (Fig. 1, left column). In order to compare, experiments were run under the same reaction conditions but in the absence of phenyl iodide and *tert*-butyl acrylate (Fig. 1, right column). In all cases, light yellow Pd(OAc)₂ was transformed into a deep brown solid, indicating the formation of Pd/PEG nanoparticles. TEM analysis confirmed this experimental assumption (Fig. 1). To our knowledge, this represents the first example of generation of Pd–polymer nanoparticles using a ball-mill.¹³ In the absence of substrates, the reaction led to significant particle aggregation, regardless of the PEG used. When substrates were present, the aggregation was less important and nice round-shaped nanoparticles could be obtained. The size of nanoparticles is directly connected to the size of the polymer. Indeed, the average size of the nanoparticles observed was 6–8 nm, 8–11 nm and 7–13 nm with PEG-1100-OH, PEG-2000-OH and PEG-3400-OH, respectively (Fig. 1a, c and e). In addition, with PEG-3400-OH, particles were found to be slightly more elliptical than with other polymers. Surprisingly, when PEG-2000-OH was mono- or di-methylated, the particle size changed to 7–13 nm and 5–7 nm, respectively (Fig. 1g and i).

Formation of palladium nanoparticles in PEG after a Mizoroki–Heck reaction activated by microwave irradiation and TEM analysis has already been reported. In PEG-400-OH, which is a liquid polymer, particles of 5–8 nm were obtained.¹⁴ In PEG-3400-OH, following benzazepine synthesis, TEM analysis of the catalytic system revealed aggregated particles of 5–7 nm.^{6d} The particle aspect was quite different from those shown in Fig. 1 (left column). Thus, the activation

Table 2 Exemplification of the ball-milling Mizoroki–Heck reaction^a



Entry	ArX	Additive	Yield ^b (%)
1	PhI	—	100
2	4-MeO-C ₆ H ₄ -I	—	73
3	4-NC-C ₆ H ₄ -I	—	62
4	4-Br-C ₆ H ₄ -I	—	68
5	4-OHC-C ₆ H ₄ -I	—	100
6	4-O ₂ N-C ₆ H ₄ -I	—	35
7	3-F-C ₆ H ₄ -I	—	100
8	2-Me-C ₆ H ₄ -I	—	29
9	PhBr	—	0
10	PhBr	NaI	0
11	PhCl	—	0
12	PhCl	NaI	0

^a Reaction conditions: phenyl iodide (0.1 mmol), *tert*-butyl acrylate (0.5 mol), Pd(OAc)₂ (5 mol%), HCO₂Na (0.2 equiv.), K₂CO₃ (3 equiv.), PEG-2000-OH (110 mg). ^b Yields were determined by ¹H NMR using CH₂Br₂ as an internal standard.

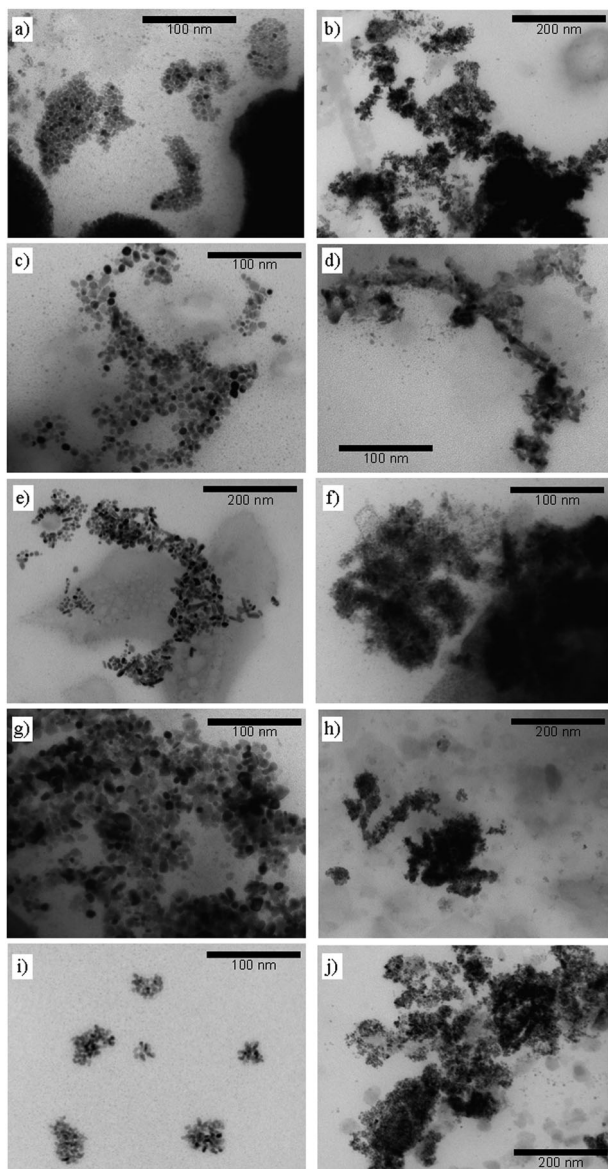


Fig. 1 TEM images of PEG-Pd nanoparticles obtained after Mizoroki-Heck reaction (left column) and without substrates (right column) in different PEGs: (a, b) PEG-1100-OH; (c, d) PEG-2000-OH; (e, f) PEG-3400-OH; (g, h) MeO-PEG-2000-OH; (i, j) MeO-PEG-2000-OMe.

method seems to have a strong influence on the size and aggregation state of the nanoparticles.

We reported herein a solvent-free/phosphine-free palladium-catalyzed Mizoroki-Heck procedure in a ball mill. Under mild conditions, quantitative yields were obtained using the appropriate polymer PEG-2000-OH, with a correct tolerance toward functional groups on the aryl moiety. Nanoparticles formed during these reactions were characterized by TEM and were found to be size-dependent on the PEG used. In addition, activation using ball-milling yielded nanoparticles different from those obtained previously using convection or microwave heating.

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- 10 Typical procedure for the ball-mill Mizoroki-Heck reaction: in a 10 mL stainless steel ball-mill reactor were added Pd(OAc)₂ (1.1 mg, 0.005 mmol), K₂CO₃ (41.4 mg, 0.3 mmol), HCO₂Na (1.4 mg, 0.02 mmol) and PEG-2000-OH (110 mg). Phenyl iodide (11.2 μL, 0.1 mmol), *tert*-butyl acrylate (73.2 μL, 0.5 mmol) and two stainless steel balls with a 7 mm diameter were then added. The mixture was then subjected to high speed vibration milling for 1 h at 30 Hz on a Retsch MM200. A minimum of CH₂Cl₂ was then added and the mixture was precipitated in Et₂O (150 mL) for 4 h at –20 °C. The solution was filtered and the filtrate concentrated *in vacuo*. After addition of 20 μL of CH₂Br₂ as an internal standard, ¹H NMR analysis allowed measurement of a quantitative yield.
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