Pd(0) supported onto monolithic polymers containing IL-like moieties. Continuous flow catalysis for the Heck reaction in near-critical EtOH†

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Received (in Cambridge, UK) 3rd March 2006, Accepted 30th May 2006
First published as an Advance Article on the web 14th June 2006
DOI: 10.1039/b603224a

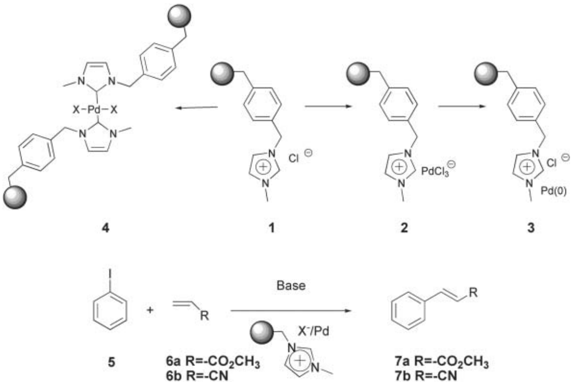
Long-term stable Pd(0) catalysts can be easily supported onto polymeric monoliths containing methyl–imidazole moieties and the corresponding reactors based on these materials can be applied for the continuous Heck reaction in near-critical EtOH.

The Heck reaction is a versatile tool for C–C bond formation by vinylation of aryl halides.[1] The current challenge for palladium catalyzed coupling reactions is the development of high performance along with sustainable and environmentally benign reaction conditions. In this regard, a specific target is to develop a phosphine-free recyclable heterogeneous catalytic system to avoid the use of expensive and air-sensitive basic phosphines.

Most of the Pd-supported catalysts used for Heck reaction are defined as "Trojan horses" because they are only the reservoirs of the "soluble" active species generated under the reaction conditions.[2] Therefore, the long term stability of the immobilised catalyst would be related to the ability of the support to release and catch the active species in order to regenerate the catalyst for a new Heck reaction cycle.

Here we report on the combined use of Pd(0) catalysts supported onto monolithic polymers containing imidazolium ionic liquid-like (ILs) fragments and supercritical fluids. The surface of our monolithic polymers contain imidazolium IL-like subunits that enable the immobilisation and improve the stability of Pd(0) particles leading to stable and active Pd(0) catalysts for the Heck reaction.

Recently ILs have been used to immobilise catalytic metal complexes[3] or to stabilise metal nanoparticles.[4] In a similar way, the surface of our monoliths modified by imidazolium IL-like moieties can be used for the immobilisation of palladium. Also, the monolithic materials have an additional advantage in their potential for development of flow-through reactor systems.[5]



Scheme 1

In preliminary studies, we and others have prepared several methylimidazolium salts supported onto polystyrene resins.[6,7] These fragments allow the immobilisation of palladium in two different ways (Scheme 1): i) *acid conditions*: polymer **1** is treated with $Pd(OAc)_2$–HCl in THF to give a red polymer **2**, which is further reduced with $NaBH_4$–EtOH, leading to polymer **3** containing supported Pd(0); ii) *basic conditions*: polymer **1** is treated with a solution of $Pd(OAc)_2$–Na_2CO_3 in DMF to afford the corresponding Pd–NHC complexes **4**.[6] Pd-supported resins **3** and **4** were used as catalysts for the Heck reaction between iodobenzene **5** and methyl acrylate **6a** using 0.02 mol% Pd and DMF as solvent.

Both catalysts showed a high efficiency for the Heck coupling reaction. Quantitative yields for the *trans*-methyl cinnamate were obtained after 3 h. Fig. 1 shows that the kinetic profiles for both resins (**3** and **4**) are quite similar. In both cases, an induction period is observed. This suggests that the reaction proceeds with a similar mechanistic pathway for both catalysts. A hot filtration test confirmed the leaching of palladium species for both resins. The reaction proceeded in the filtrate with even higher reaction rates than those observed in the presence of the Pd-supported solids. It seems reasonable to assume that resins **3** and **4** act as pre-catalysts releasing active palladium species into the solution.[2]

A significant difference was found when the resins were reused for new cycles (see Table 1). The conversion observed for **4**, prepared as a Pd–NHC complex, falls dramatically after the third use. However, polymer **3** could be reused up to 6 times without any decrease in its catalytic activity. This suggests that in the polymer **3** the IL-like units can play an important role either in inducing a slower Pd release or in

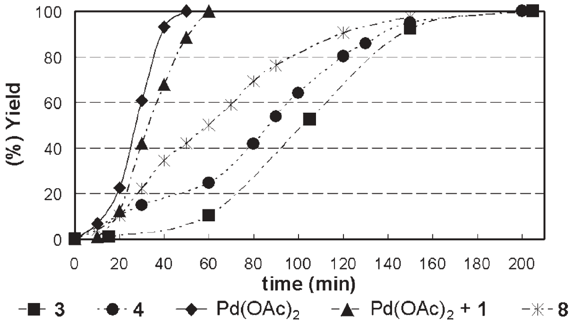


Fig. 1 Yield of *trans*-methylcinnamate **7a** using different catalytic systems at 90 °C in DMF.

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† During manuscript preparation B. Karimi and D. Enders have reported on the use of silica-supported ILs for this reaction (*Org. Lett.*, DOI: 10.1021/ol060129z). Some of their results are strongly coherent with the mechanistic considerations of the present work.

Table 1 Stability study for supported Pd catalysts **3** and **4**

		Yield (%)					
Entry	Polymer	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6
1	3[a]	99	99	99	99	99	99
2	4[b]	99	99	20	12	—	—

[a] 0.9 meq Pd g^{-1} approx. ratio NHC/Pd 1.1. [b] 0.4 meq Pd g^{-1}. approx. ratio NHC/Pd 2.2.

improving the release–catch mechanism. In order to test the ability of our functional materials to capture from the solution the catalytic Pd species, a model Heck reaction was performed using 0.02% mol of $Pd(OAc)_2$ in the presence of resin **1**. The reaction was completed after 60 min at 90 °C. The presence of resin **1** slightly decreased the reaction rate with respect to the "ligand free" catalysed reaction. Polymer **1**, which became black (resin **8**), was filtered off from the reaction medium, thoroughly washed and used as a catalyst for the model reaction. The reaction went to completion after 2.5 h. Thus, it seems that IL-like moieties in resin **1** can capture and stabilise catalytically active soluble palladium species, which are generated during the reaction. PVP-polymers and ammonium salts have shown related sequestration and stabilisation effects for Pd species.[8] Our results show the practical advantages of the heterogeneous system **3**, whose higher stability enables the achievement of high TON values by using the resin in consecutive cycles (30000 for **3** *vs.* 11000 for **4**). A continuous flow system is a simpler way to perform consecutive cycles because reaction and filtration operations are carried out simultaneously. Thus, consecutives cycles can be performed in a less time consuming mode. Simple process intensification and space–time yield are best achieved in this way.

Encouraged by the promising initial results, a continuous flow reactor system was developed (see Fig. 2). For the continuous set-up, catalysts were prepared as monolithic polymers containing imidazolium IL-like units. Monoliths are macroporous materials with a well defined structure of continuous channels and confined spaces allowing the development of flow-through reactor systems.[5,9] Functionalisation of the matrix was introduced by solventless reaction of benzyl chloride groups with methylimidazole at 90 °C. The introduction of the imidazolium IL-like moieties was monitored by the disappearance of the CH_2–Cl group using both FT-IR Raman spectrometry and a colorimetric method based on the NBP test.[10,11] A 95% conversion of the chloride groups was achieved after a 5 h reaction. Longer reaction times did not improve the conversion degree. It is possible that a small percentage C–Cl groups are located in non-accessible highly cross-linked regions.

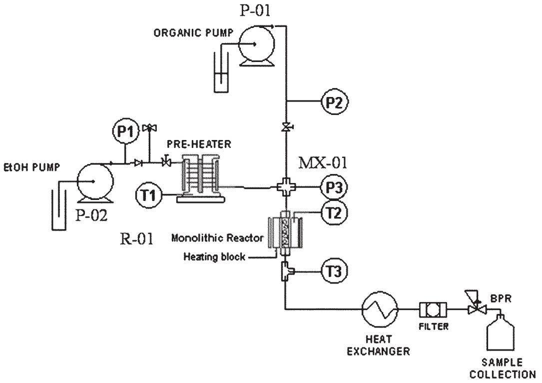

Fig. 2 Schematic diagram for the continuous flow reactor system. P-01, reagents feed pump (flow rate = 0.01–5 mL min^{-1}, maximum allowed pressure (*P*max) = 40 MPa); P-02, ethanol feed pump (flow rate = 0.25–1 mL min^{-1}, P_{max} = 40 MPa); MX-01, Mixer Gilson; R-01, monolithic microreactor (1/4 in AISI 316 tubing 15 cm, heat supplied by a band heater (Watlow, 240 V, 200 W, NTB25X6UA3, 47 02 DM)); BPR-01, back pressure regulator (Jasco BP-1580-81 P_{max} = 42 MPa, C_v < 0.01).

The reaction, under acidic conditions, of $Pd(OAc)_2$ with the IL-like units on the monolith yielded the corresponding Pd^{2+} supported complexes. The monolithic reactor was then attached to the system shown in Fig. 2 and hot pressurised ethanol (200 °C, 8 MPa) was pumped through the monolith over 4 h. Ethanol reduced Pd^{2+} to Pd(0) with the formation of Pd(0) particles on the surfaces of the monoliths. SEM and electron probe microanalysis revealed the presence of well dispersed Pd metal particles. It is of note that the final Pd(0) loading of the catalyst (0.21 meq Pd g^{-1} polymer) was kept much lower than the methyl–imidazolium content (3.07 meg g^{-1} polymer *ca.* 15 : 1 NHC : Pd ratio) to favour the "catching" effect of the IL-like moieties.

The reaction of iodobenzene **5** with methyl acrylate **6a** was examined in a continuous flow system (Fig. 2) using DMF as the solvent. A solution of **5** and **6a** (0.67 mol L^{-1} of **5** in DMF, molar ratio **5** : **6a** : Et_3N of 1 : 1.1 : 2) was pumped at flow rates of 50 μLmin^{-1} through the monolithic reactor. Aliquots were analyzed for the methylcinnamate content (**7a**) at regular time intervals. The reaction proceeds continuously with 100% yield for **7a** at 200 °C and 8 MPa. In the flow system a small amount of the substrate is actually forced into intimate contact with an "excess" of catalyst favouring higher conversions. Thus, a total conversion of **5** can be achieved with residence times as short as 3–4 min, using a monolithic mini-reactor with a free-volume of *ca.* 230 μL. Besides, the continuous flow set-up improved the stability of the system. No noticeable changes to activity were observed in both product yield and selectivity after 745 min (*ca.* 162 bed-volumes) of continuous use under the same conditions.

Some efforts have been reported to develop continuous flow systems for palladium catalysed C–C bond formation.[12] All of them, however, require conventional organic solvents to be used either for the reaction or for the extraction processes. In the search for more environmentally friendly protocols the use of supercritical fluids was considered. Initial runs were performed using $scCO_2$ as the reaction solvent. Although product formation was detected, the low product/reactants solubility in $scCO_2$ led to reactor blockage.

Hot pressurised ethanol can be a good alternative solvent. Ethanol is not only benign, easily available and relatively cheap, but is also a solvent whose properties are easily adjustable with *P* and *T*. Supercritical ethanol provides a less corrosive solvent and with more accessible critical parameters (T_c = 516 K, P_c = 6.4 MPa, ρ_c = 0.276 g·cm^{-1}) than scH_2O. Therefore, it can be seen as a non-corrosive, low pressure scH_2O. One can also expect a pronounced enhancement in the solubility compared with CO_2 due to the hydrogen-bonding ability of the former. Therefore, the use of ethanol as a reaction medium of tuneable density and polarity was evaluated. The optimisation of the conditions was systematically investigated by varying temperature, pressure and flow rate. Table 2 gathers some of the results achieved using near-critical ethanol. In general, temperatures higher than 150 °C were required to achieve significant yields of *trans*-methylcinnamate (entries 1–5, Table 2). The reaction did not take place in ethanol at atmospheric pressure and 90 °C. Conversion of **5** into **7a** reached 85% at 200 °C

Table 2 Pressure and temperature dependence for the continuous flow Heck reaction using hot pressurised ethanol

Entry	μL min^{-1}	*P*/MPa	*T*/°C^{b}	% Yield	Residence time^{c}/min	TOF^{d}
1^{a}	—	atm.	90	2	—	—
2	50	8	100	4	3.96	1.5
3	50	8	125	5	3.76	1.8
4	50	8	150	11	3.54	4.0
5	50	8	200	85	2.98	31.0
6	100	20	200	83	1.49	60.5
7	100	15	200	67	1.49	48.8
8	100	8	200	62	1.49	45.8

[a] Run under batch conditions. [b] Wall temperature. [c] Residence time = $(V_R \cdot \rho_{EtOH/Reactor})/(F_R \cdot \rho_{EtOH/STP})$ where V_R = reactor volume/cm^3, $\rho_{EtOH\ Reactor}$ = EtOH density at process *T* and *P*/g cm^{-3}. $\rho_{EtOH\ Reactor}$ = EtOH density at standard *T* and *P*/g cm^{-3}. F_R = flow rate/cm^3 min^{-1}. [d] TOF calculated as (g **7a**/g Pd)·h^{-1}.

and 8 MPa leading to a 100% selectivity for the *trans* isomer. Temperatures higher than 250 °C led to transesterification of methyl cinnamate to the corresponding ethyl cinnamate. The reaction also showed some pressure dependence. An increase in pressure is reflected in slight improvements in productivity (entries 6–8, Table 2).

The reaction was performed at 200 °C and 8 MPa and using different flow rates to evaluate the effect of the residence time (Fig. 3). As expected, an increase in the flow rate (from 50 to 500 μL min^{-1}) led to a decrease in the yield of **7a** (from 85% to 16%), which is consistent with a reduction in the residence time in the reactor.[13] On the other hand, in the continuous flow system in hot pressurised EtOH the Heck reaction did not show any significant induction period.

Again a stable performance for 420 min (*ca.* of 91 bed-volumes) was observed for the Heck reaction in near critical EtOH (200 °C and 8 MPa). After this experiment, the same mini-reactor was used for the Heck reaction between iodobezene **5** and acrylonitrile **6b**. The reaction was studied for 480 min (*ca.* 104 bed-volume) leading to 66% yield and 70 : 30 *trans–cis* selectivity.[14] These results are in agreement with the different reactivities of **6a** and **6b**. An additional test with this reactor for the reaction between **5** and **6a** gave the same results as before.

Metal analysis by ICP-MS of the solution aliquots obtained showed levels of leached total metals <1 ppm. It is known that the nature of the solvent and support, temperature and the presence of reducing agents have a dramatic effect not only in the activity of the catalysts but also on the extent of the palladium leaching.[2] The presence of IL-like moieties in the polymer seem to help to stabilise the Pd(0) reducing the leaching.

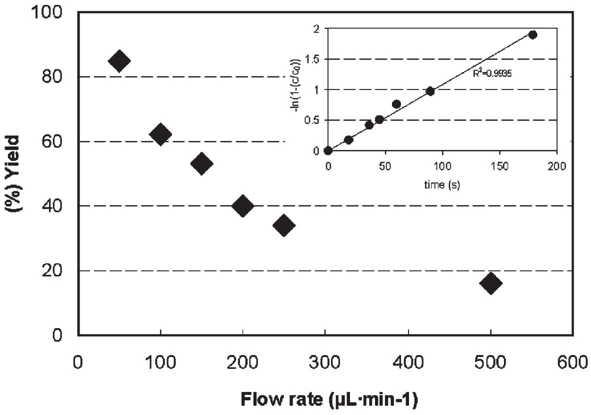

Fig. 3 % Yield **7a** *vs.* flow rate for the continuous Heck reaction between **5** and **6a** in ethanol at 200 °C and 8 MPa, 0.67 mol L^{-1} of **5**. Kinetics data showing a pseudo first order rate K_{obs} = 10.8 × 10^{-3} s^{-1} (38.9 h^{-1}).

In summary, we have developed a highly stable and efficient Pd(0) catalyst supported onto polymeric monoliths containing IL-like units. This catalyst shows a good activity and stability under continuous flow conditions. The reaction does not require the use of inert atmosphere as is typical for these processes. The presence of IL-like units seems to play an important role in the capture and stabilisation of the active Pd species. The catalytic materials presented here allow the substitution of classical solvents such as DMF by more benign solvents like near-critical ethanol.

We would like to acknowledge the Spanish Ministerio de Ciencia y Tecnología (CTQ 2005-08016) and Bancaixa-UJI (P1B2004-13) for financial support. E. G.-V. and V. S. also thank MEC for personal financial support (Ramón y Cajal and PPQ programs).

Notes and references

1 (*a*) F. Alonso, I. P. Beletskaya and M. Yus, *Tetrahedron*, 2005, **61**, 11771; (*b*) I. J. S. Fairlamb, *Tetrahedron*, 2005, **61**, 9647.
2 (*a*) A. Biffis, M. Zecca and M. Basato, *Eur. J. Inorg. Chem.*, 2001, 1131; (*b*) A. Biffis, M. Zecca and M. Basato, *J. Mol. Catal. A: Chem.*, 2001, **173**, 249.
3 (*a*) T. Welton, *Chem. Rev.*, 1999, **99**, 2071; (*b*) P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, 2000, **39**, 3773; (*c*) R. Sheldon, *Chem. Commun.*, 2001, 2399.
4 J. Dupont, G. S. Fonseca, A. P. Umpierre, P. F. P. Fichtner and S. R. Teixeira, *J. Am. Chem. Soc.*, 2002, **124**, 4228.
5 G. Jas and A. Kirschning, *Chem.–Eur. J.*, 2003, **9**, 5708.
6 (*a*) J. Schwartz, V. P. W. Böhm, M. G. Gardiner, M. Grosche, W. A. Hermann, W. Hieringer and G. Raudaschl-Sieter, *Chem.–Eur. J.*, 2000, **6**, 1773; (*b*) J. W. Byun and Y. S. Lee, *Tetrahedron Lett.*, 2004, **45**, 1837; (*c*) J. H. Kim, J. W. Kim, M. Shokouhimehr and Y. S. Lee, *J. Org. Chem.*, 2005, **70**, 6714.
7 B. Altava, M. Burguete, E. García-Verdugo, N. Karbass, S. V. Luis, A. Puzary and V. Sans, *Tetrahedron Lett.*, 2006, **47**, 2311.
8 (*a*) M. T. Reetz, R. Breinbauer and K. Wannlnger, *Tetrahedron Lett.*, 1996, **37**, 4499; (*b*) M. T. Reetz and E. Westermann, *Angew. Chem., Int. Ed.*, 2000, **39**, 165; (*c*) A. M. Caporusso, P. Innocenti, L. A. Aronica, G. Vitulli, R. Gallina, A. Biffis, M. Zecca and B. Corain, *J. Catal.*, 2005, **234**, 1.
9 These materials were prepared as mini-reactors by polymerisation of 4-chlorovinylbenzene and divinylbenzene (40 : 60 *w*/*w*$_t$ 4-ClVB:DVB) using toluene and dodecanol as porogenic agents in a stainless steel column (15 cm × ¼ inch) at 70 °C. The mean pore diameter of the monolith was *ca.* 1.0 μm with a surface area of 8.5 m^2 g^{-1}. See: (*a*) J. A. Tripp, F. Svec and J. M. J. Frechet, *J. Comb. Chem.*, 2001, **3**, 216; (*b*) B. Altava, M. I. Burguete, J. M. Fraile, J. I. García, S. V. Luis, J. A. Mayoral and M. J. Vicent, *Angew. Chem., Int. Ed.*, 2000, **39**, 1503.
10 The NBP test is a sensitive colorimetric method developed by our group for qualitative analysis of the presence of chlorine in chloromethylated polymers, either in gel type (Merrifield) or monolithic resins (Macroporous). See: F. Galindo, B. Altava, M. I. Burguete, R. Gavara and S. V. Luis, *J. Comb. Chem.*, 2004, **6**, 859.
11 B. Altava, M. I. Burguete, E. García-Verdugo, S. V. Luis and M. J. Vicent, *Tetrahedron*, 2001, **57**, 8675.
12 (*a*) T. Fukuyama, M. Shinmen, S. Nishitani, M. Sato and I. Ryu, *Org. Lett.*, 2002, **4**, 1691; (*b*) S. F. Liu, T. Fukuyama, M. Sato and I. Ryu, *Org. Process Res. Dev.*, 2004, **8**, 477; (*c*) C. K. Y. Lee, A. B. Holmes, S. V. Ley, I. F. McConvey, B. Al-Duri, G. A. Leeke, R. C. D. Santos and J. P. K. Seville, *Chem. Commun.*, 2005, 2175; (*d*) W. Solodenko, H. L. Wen, S. Leue, F. Stuhlmann, G. Sourkouni-Argirusi, G. Jas, H. Schonfeld, U. Kunz and A. Kirschning, *Eur. J. Org. Chem.*, 2004, 3601; (*e*) N. T. S. Phan, J. Khan and P. Styring, *Tetrahedron*, 2005, **61**, 12065.
13 Residence time was calculated according to standard literature: O. Levenspiel, *Chemical Reaction Engineering*, 1999, 3rd edn, Wiley, New York.
14 *Trans* : *cis* ratio was determined by GC and confirmed by NMR.