Alkynylation of aryl halides with perfluoro-tagged palladium nanoparticles immobilized on silica gel under aerobic, copper- and phosphine-free conditions in water†‡

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The utilization of perfluoro-tagged palladium nanoparticles immobilized on fluorous silica gel through fluorous–fluorous interactions (Pd_{np}-A/FSG) or linked to silica gel by covalent bonds (Pd_{np}-B) in the alkynylation of terminal alkynes with aryl halides under aerobic, copper- and phosphine-free conditions in water, and their recovery and re-utilization, is described.

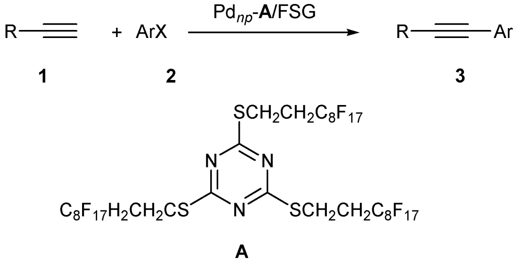
The palladium-catalyzed cross-coupling of terminal alkynes with aryl and vinyl halides or triflates is one of the most powerful tools for the formation of C–C bonds. The reaction, developed independently by Sonogashira,[1] Heck,[2] and Cassar[3] in 1975, has found a large number of applications ranging from the preparation of fine chemicals to the synthesis of biologically active substances. Under Sonogashira conditions (copper salts are used as co-catalysts) the reaction can be carried out using milder conditions than those typical of Heck and Cassar protocols and this can explain the enormous success of the Pd/Cu co-catalyzed cross-coupling chemistry.[4]

Nevertheless, since its discovery a great deal of work has been done to modify the original protocol so as to include an even wider range of reactants as well as to limit some of the major drawbacks of the process: the presence of copper salts and phosphines. Indeed, copper salts can induce Glaser-type homocoupling[5] of terminal alkynes when copper acetylide intermediates are exposed to oxidative agents or air. In addition, the utilization of two metals hinders the recovery and re-utilization of the expensive palladium catalysts (its recovery would be the best way to overcome cost related problems). Phosphines, which are frequently used in this reaction, are often air-sensitive. As to this point, interesting results have been achieved by enhancing the catalyst efficacy employing more efficient phosphines.[6] However, these phosphines are not readily available and some limits to their use in large scale applications still remain.

To avoid these drawbacks, and consequently to provide access to alkynylation reactions under aerobic conditions, copper- and phosphine-free procedures have been developed. This approach is exceedingly convenient in industrial applications as well as in cases when the reactions are carried out in multiple vessels for library generation. Particularly attractive would be a combination of copper- and phosphine-free conditions with the use of a solid-supported palladium catalyst.[7] This approach could provide two additional advantages: it could facilitate the recovery and reuse of palladium and could also reduce the palladium contamination of the isolated product, a significant problem for the pharmaceutical industry.[8] As to the solvent, the use of water as the reaction medium is very attractive in organic synthesis due to safety, economical, and environmental reasons.[9] In addition, water has a high dielectric constant and density so that when reactions involving water insoluble substrates are carried out in water they often benefit from the hydrophobic effect.[10]

There are only a few reports of alkynylation reactions of aryl halides in the presence of immobilized palladium catalysts under copper- and phosphine-free conditions in water[11] or using water as co-solvent.[12] None of them, however, involve palladium nanoparticles.

In this context, on the basis of the positive results we obtained with air-stable perfluoro-tagged palladium nanoparticles supported on fluorous silica gel (Pd_{np}-A/FSG) in the Heck reaction in terms both of yields and recovery and re-utilization of the catalyst system,[13] we became interested in investigating their use in the reaction of terminal alkynes with aryl halides under aerobic, copper- and phosphine-free conditions in water (Scheme 1).



Scheme 1 Alkynylation of aryl halides under aerobic, copper- and phosphine-free conditions in water.

The air-stable immobilized pre-catalyst was prepared by adsorbing palladium nanoparticles stabilized by the perfluoro-tagged

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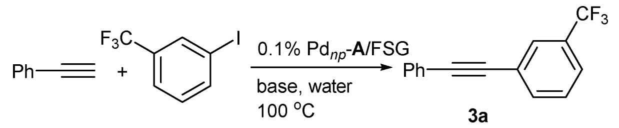
Table 1 The influence of bases on the reaction of phenylacetylene with 3-(trifluoromethyl)iodobenzene catalyzed by Pd$_{np}$-**A**/FSG[a] in water



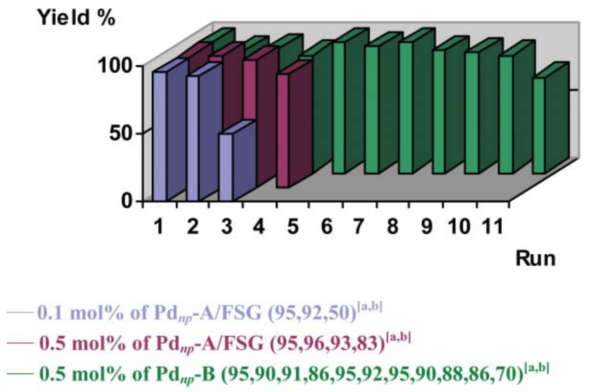
Entry	Base	Yield % of **3a**[b]
1	K_2CO_3	50
2	KOAc	50
3	Et_2NH	89
4	Et_3N	91
5	piperidine	95
6	pyrrolidine	99

[a] Reactions were carried out using 1 mmol of 3-(trifluoromethyl)iodobenzene, 1 mmol of phenylacetylene, 2 mmol of base at 100 °C for 5 h in the presence of 0.1 mol % of Pd$_{np}$-**A**/FSG in 2 mL of water. [b] Yields are given for isolated products.

heterocyclic derivative **A** (Pd$_{np}$-**A**) onto commercially available fluorous silica gel (FSG).[13,14]

Using the reaction of 3-(trifluoromethyl)iodobenzene with phenylacetylene as a probe for evaluating the reaction conditions, we observed that the corresponding coupled product could be isolated in moderate yields after 5 h at 100 °C in H_2O using 0.1 mol% Pd$_{np}$-**A**/FSG with K_2CO_3 or KOAc as the base under aerobic conditions (Table 1, entries 1 and 2). No homocoupling derivative was observed. We then explored the effect of nitrogen bases and found that an almost quantitative yield could be obtained with pyrrolidine (Table 1, entry 6).

Although the coupled product was isolated in excellent yield under the best conditions found (0.1 mol% Pd$_{np}$-**A**/FSG, pyrrolidine, H_2O, 100 °C, 5 h), recycling studies revealed a limited capacity for Pd$_{np}$-**A**/FSG to be reused. Indeed, a significant loss of activity was observed in the third run (Fig. 1). Increasing the catalyst loading to 0.5 mol% resulted only in a slight increase of the number of runs that could be performed without a significant loss of activity (Fig. 1).

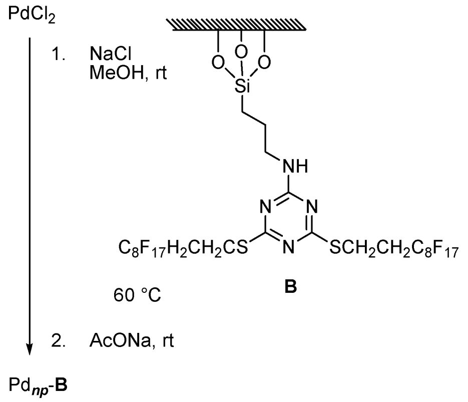


[a] Reactions were carried out using 1 mmol of 3-(trifluoromethyl)iodobenzene, 1 mmol of phenylacetylene, 2 mmol of pyrrolidine at 100 °C for 1 h in the presence of Pd$_{np}$-**A**/FSG or Pd$_{np}$-**B** in 2 mL of H_2O. [b] Figures in parentheses refer to yields for isolated products.

Fig. 1 Recycling studies for the reaction of 3-(trifluoromethyl)iodobenzene with phenylacetylene catalyzed by Pd$_{np}$-**A**/FSG or Pd$_{np}$-**B**.

Sector field inductively coupled plasma mass spectrometry (SF-ICP-MS) analysis indicated the level of palladium to be in the range of only 0.05–0.08 ppm in water. However, a high level of palladium (39–240 ppm) was found in the crude product. Most probably, the main cause of this result is the relative weakness of fluorous–fluorous interactions, responsible for binding Pd$_{np}$-**A** to the FSG, in the alkynylation reaction (no such effect was observed in the Heck reaction[13]). Accordingly, ^{19}F NMR analysis of the crude mixture derived from the reaction of phenylacetylene with *m*-(trifluoromethyl)iodobenzene after filtration revealed the presence of significant amounts of **A**, corresponding to an original nanoparticle support loss of about 50% per run.

Consequently, we decided to investigate the use of palladium nanoparticles stabilized by a perfluorinated compound covalently bound to silica gel. This precatalyst system (Pd$_{np}$-**B**), containing 3.47% of palladium in the form of nanoparticles with an average particle size of 3.9 ± 0.9 nm, was prepared by the sol-gel process described previously[15] (Scheme 2).

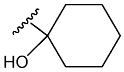


Scheme 2 Synthesis of Pd$_{np}$-**B**.

The catalytic activity and stability of Pd$_{np}$-**B** was tested using our model system in water with a variety of bases (K_2CO_3, KOAc, pyrrolidine, piperidine, Et_2NH, and Et_3N). After some experimentation, we found that **3a** could be isolated in 95% yield using 0.5 mol% of Pd$_{np}$-**B** and 2 equiv. of pyrrolidine at 100 °C for 1 h. Recycling studies were then performed which showed that this supported catalyst system allowed for a number of cycles largely higher than with Pd$_{np}$-**A**/FSG (Fig. 1). The recovery of the supported palladium involves centrifugation and decanting the solution in the presence of air, without any particular precautions. The Ostwald ripening process[16] was not observed upon recycling. The recovered material after 11 runs was examined by TEM and showed nanoparticles of about 3.2 nm of diameter (Fig. 2).

A variety of terminal alkynes and aryl halides were then subjected to the optimized conditions using both Pd$_{np}$-**A**/FSG (procedure A) and Pd$_{np}$-**B** (procedure B). Our preparative results are summarized in Table 2. Acetylenes bearing electron-rich and electron-poor aryl groups, as well as alkyl substituents, give coupling products in excellent yields when reacted with aryl iodides which in turn can accommodate electron-withdrawing and electron-donating substituents. Ortho substituents in the aryl halide are also tolerated (Table 2, entries 9 and 10). With aryl bromides, longer reaction times are required and similar or lower

Table 2 The reaction of terminal alkynes **1** with aryl iodides and bromides **2** in the presence of Pd$_{np}$-**A**/FSG or Pd$_{np}$-**B**[a]

Entry	Terminal Alkyne **1** R	ArX **2**	Proc.	Time (h)	Yield% of $\mathbf{3}^b$	
1	Ph	3-$CF_3C_6H_4$-I	A	3	**3a**	95
2		3-CF_3-C_6H_4-I	A	3	**3a**	95[c]
3		3-CF_3-C_6H_4-I	B	1	**3a**	95
4		4-EtO_2C-C_6H_4-I	A	5	**3b**	95
5		4-NO_2-C_6H_4-I	A	5	**3c**	93
6		4-MeO-C_6H_4-I	B	12	**3d**	90
7	4-MeO-C_6H_4	4-CN-C_6H_4-I	A	5	**3e**	85
8		4-CN-C_6H_4-I	B	7	**3e**	95
9		2-Me-C_6H_4-I	A	29	**3f**	80
10		2-Me-C_6H_4-I	B	9	**3f**	90
11	4-CN-C_6H_4	3-CF_3-C_6H_4-I	A	2	**3g**	89
12		3-CF_3-C_6H_4-I	B	2	**3g**	99
13	4-MeCO-C_6H_4	4-CN-C_6H_4-I	A	4	**3h**	90
14		4-CN-C_6H_4-I	B	2	**3h**	99
15	4-CN-C_6H_4	4-MeO-C_6H_4-I	A	3	**3e**	85
16		4-MeO-C_6H_4-I	B	24	**3e**	87
17	$HOCH_2$	4-CN-C_6H_4-I	B	24	**3i**	89
18	$HO(Me)_2C$	4-MeO-C_6H_4-I	A	48	**3j**	83
19	HOMe(Ph)C	4-MeO-C_6H_4-I	B	24	**3k**	90
20		4-MeCO-C_6H_4-I	B	14	**3l**	92
21	Ph	4-MeCO-C_6H_4-Br	A	44	**3m**	50
22		3-CF_3-C_6H_4-Br	B	9	**3a**	91
23		4-MeO-C_6H_4-Br	B	48	**3d**	65

[a] Reactions were carried out under aerobic conditions using 1 mmol of aryl halide, 1 mmol of terminal alkyne, 2 mmol of pyrrolidine at 100 °C in 2 mL of H_2O with 0.1 mol % of Pd$_{np}$-**A**/FSG (procedure A) or 0.5 mol% of Pd$_{np}$-**B** (procedure B). [b] Yields are given for isolated products. [c] In the presence of 0.5 mol% of Pd$_{np}$-**A**/FSG.

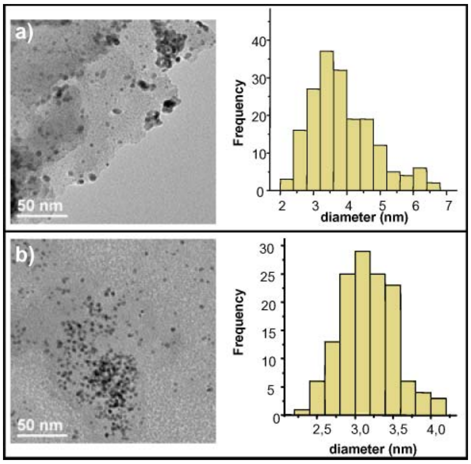


Fig. 2 (a) TEM image and particle size distribution histogram of Pd$_{np}$-**B** (particle size 3.9 ± 0.9 nm) (b) TEM image and particle size distribution histogram of Pd$_{np}$-**B** after 11 runs (particle size 3.2 ± 0.4 nm).

yields are obtained (Table 2, compare entry 3 with entry 22, and entry 6 with entry 23).

In conclusion, we have demonstrated that perfluoro-tagged palladium nanoparticles immobilized on fluorous silica gel by fluorous-fluorous interactions (Pd$_{np}$-**A**/FSG) or linked to silica gel by covalent bonds (Pd$_{np}$-**B**) can be successfully used in the alkynylation of aryl halides under aerobic, copper- and phosphine-free conditions in water. Both catalyst systems allow for the isolation of coupled products in high to excellent yields. However, the use of Pd$_{np}$-**B** gives the best results in term of recovery (which can be carried out in the presence of air without any particular precautions) and re-utilization.

Notes and references

1 K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **16**, 4467.
2 H. A. Diek and F. R. Heck, *J. Organomet. Chem.*, 1975, **93**, 259.
3 L. Cassar, *J. Organomet. Chem.*, 1975, **93**, 253.
4 (*a*) K. Sonogashira, in *Metal-Catalyzed Cross-Coupling Reactions*, F. Diederich, P. J. Stang, Eds.; Wiley-WCH, Weinheim, 1998, p. 203; (*b*) K. Sonogashira, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, E. Negishi, Ed.; John Wiley & Sons, New York, 2002, Vol. 1, p. 493; (*c*) For recent reviews on the Sonogashira cross-coupling, see: R. Chinchilla and C. Najera, *Chem. Rev.*, 2007, **107**, 874; (*d*) H. Doucet and J.-C. Hierso, *Angew. Chem., Int. Ed.*, 2007, **46**, 834.
5 For some selected references, see: (*a*) C. Glaser, *Ber. Dtsch. Chem. Ges.*, 1869, **2**, 42; (*b*) A. S. Hay, *J. Org. Chem.*, 1962, **27**, 3320; (*c*) R. Rossi, A. Carpita and C. Bigelli, *Tetrahedron Lett.*, 1985, **26**, 523; (*d*) N. G. Kundu, M. Pal and C. Chowdhury, *J. Chem. Res.*, 1993, 432; (*e*) A. Lei, M. Srivastava and X. Zhang, *J. Org. Chem.*, 2002, **67**, 1969 and references therein; (*f*) I. J. S. Fairlamb, P. S. Bauerlein, L. R. Marrison and J. M. Dickinson, *Chem. Commun.*, 2003, 632; (*g*) A. S. Batsanov, J. C. Collings, I. J. S. Fairlamb, J. P. Holland, J. A. K. Howard, Z. Lin, T. B. Marder, A. C. Parsons, R. M. Ward and J. Zhu, *J. Org. Chem.*, 2005, **70**, 703; (*h*) for a review of alkyne coupling, see: P. Siemsen, R. C. Livingston and F. Diederich, *Angew. Chem., Int. Ed.*, 2000, **39**, 2632.
6 (*a*) V. P. W. Böhm and W. A. Herrmann, *Eur. J. Org. Chem*, 2000, **22**, 3679; (*b*) T. Hundertmark, A. F. Littke, S. L. Buchwald and G. C. Fu, *Org. Lett.*, 2000, **2**, 1729; (*c*) M. Eckhardt and G. C. Fu, *J. Am. Chem. Soc.*, 2003, **125**, 13642; (*d*) K. W. Anderson and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2005, **44**, 6173.
7 For a recent review on C–C bond forming reactions catalyzed by heterogeneous palladium catalysts, see: L. Yin and J. Liebscher, *Chem. Rev.*, 2007, **107**, 133.

8 C. E. Garret and K. Prasad, *Adv. Synth. Catal.*, 2004, **346**, 889.

9 For a recent review on C–C bond forming reactions in aqueous media, see: C.-J. Li, *Chem. Rev.*, 2005, **105**, 3095.

10 M. Cai, Q. Xu and J. Sha, *J. Molec. Cat. A: Chemical*, 2007, **272**, 293.

11 (*a*) J. Gil-Moltó, S. Karlström and C. Nájera, *Tetrahedron*, 2005, **61**, 12168; (*b*) Z.-W. Ye and W.-B. Yi, *J. Fluorine Chem.*, 2008, **129**, 1124.

12 L. Djakovitch and P. Rollet, *Tetrahedron Lett.*, 2004, **45**, 1367.

13 R. Bernini, S. Cacchi, G. Fabrizi, G. Forte, S. Niembro, F. Petrucci, R. Pleixats, A. Prastaro, R. M. Sebastiàn, R. Soler, M. Tristany and A. Vallribera, *Org. Lett.*, 2008, **10**, 561.

14 S. Niembro, A. Vallribera and M. Moreno-Mañas, *New J. Chem.*, 2008, **32**, 94.

15 S. Niembro, A. Shafir, A. Vallribera and R. Alibes, *Org. Lett.*, 2008, **10**, 3215.

16 (*a*) A. Howard, C. E. J. Mitchell and R. G. Egdell, *Surf. Sci.*, 2002, **515**, L504; (*b*) A. Imre, D. L. Beke, E. Gontier-Moya, I. A. Szabo and E. Gillet, *Appl. Phys. A*, 2000, **71**, 19.