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Reusable resin plug-bound palladium catalysts for organic synthesis

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Abstract—Resin plugs, a unique and conveniently handled form of resin, prepared by sintering high-density polyethylene (HDPE) with pre-functionalised resins, were derivatised and loaded with palladium(0). These 'plugs' were used in the preparation of a Suzuki reaction based library and the removal of allyl ester protecting groups. The 'plugs of catalyst' were easily separated from the reaction mixture and were re-used multiple times with minimal loss of activity. © 2003 Elsevier Science Ltd. All rights reserved.

Over the past decade, small molecule solid-phase synthesis has become an important part of the drug discovery process.[1] One reaction that has been highly favoured in solid-phase applications is the formation of biaryls via the palladium-catalysed Suzuki cross-coupling reactions of aryl halides or aryl triflates with arylboronic acids.[2] This is due, in part, to the observation that compounds containing the biaryl group have shown diverse spectra of biological activities. Thus compounds incorporating this structural motif[3] have been shown to possess angiotensin II antagonism, tubulin binding properties and estrogenic activity as well as being found in natural products with antitumour and antiviral activities.

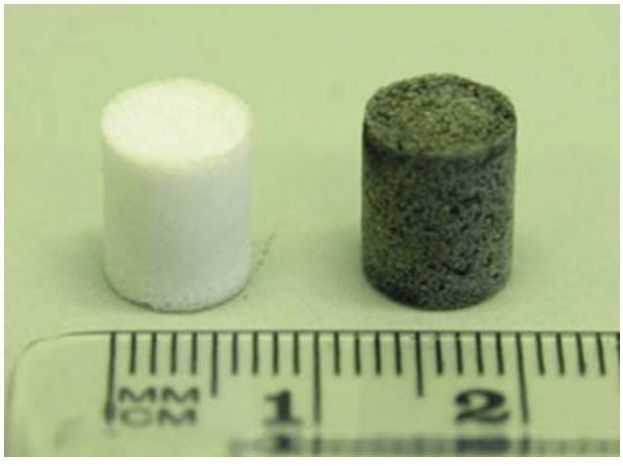

Figure 1. A palladium-loaded 'plug'.

Usually, a soluble palladium catalyst is used in the Suzuki reaction such as $Pd(PPh_3)_4$. However, recovery of the palladium catalyst is often a costly and inconvenient process. Industrially, palladium catalysts are recovered by precipitation or by the use of water-soluble phosphine ligands or at least the metal itself can be recovered by the formation of insoluble complexes,[4] hence the desirability of heterogeneous catalysts is obvious. Polystyrene (crosslinked with divinylbenzene) supported palladium catalysts have in the past been successfully used for a variety of organic reactions such as hydrogenations,[5] allylic substitutions,[6] isomerisation,[7] decarboxylations[8] and for the Heck reaction.[9] Hallberg and co-workers for example investigated various carbon–carbon bond forming reactions such as the Heck arylation,[10] using such supported catalysts. More recently, there have been reports on the preparation and utilisation of a number of highly effective polymer-supported palladium catalysts, which are easily recoverable and re-usable, the most striking of these methods being the 'micro-encapsulation' methods of Kobayashi.[11] Soluble palladium complexes are normally used to introduce the Pd metal by exchange reactions with appropriate functionality on the polystyrene backbone. Anderson,[12] for example, prepared a heterogeneous catalyst for the Heck reaction in two steps by first substituting Merrifield resin with

Keywords: resin plugs; catalysis; solid-phase synthesis; Suzuki coupling.

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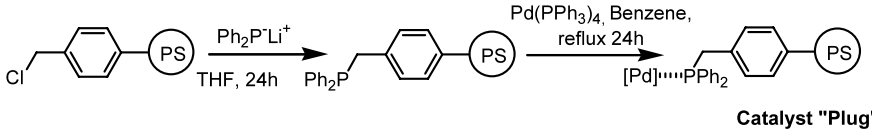


Scheme 1. Synthesis of catalyst 'plugs'.

Ph_2PLi followed by an exchange reaction with $PdCl_2(PhCN)_2$.

We have recently published[13] details of a new solid support (resin plugs) for solid-phase synthesis (see Fig. 1). Here the results on the use of this support for palladium catalysed reactions are reported. The resin 'plugs' (high-density polyethylene (HDPE) co-sintered with Merrifield resin, cross-linked with 2% divinylbenzene) were first substituted with Ph_2PLi, followed by an exchange reaction with $Pd(PPh_3)_4$ to provide the palladium supported resin plugs which were black in colour (Scheme 1).[14]

The activity of the resin plug catalysts for Suzuki reactions was first measured on a standard reaction: the coupling of phenylboronic acid with 4-bromopyridine (Scheme 2). The plug (0.05 equiv. of catalyst) was placed into the reaction vessel, which was shaken or stirred for 24 hours. The 'plug' was removed with tweezers and washed with solvent. The same resin 'plug' was recycled, carrying out the identical reaction four times. The isolated yields of purified product were: 92, 90, 86 and 85%, respectively.

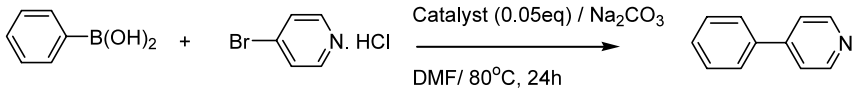
The plugs were used in the synthesis of a small library of biaryl compounds, while at the same time preparing an identical series of compounds using soluble $Pd(PPh_3)_4$ as the catalyst to compare yields. The results, as summarized in Table 1, show that the yields were almost identical.

In a further application of the 'plug' supported palladium catalysts, Boc-Phe-OAllyl was synthesized and the allyl ester was removed quantitatively by refluxing in THF for 24 h using 0.05 equiv. of catalyst and 1 equiv. of pyrrolidine.

In summary, the 'plug'-bound palladium catalysts provide a reusable and much easier to handle alternative to the homogenous analogue $Pd(PPh_3)_4$ while maintaining comparable catalytic activity. The catalyst 'plug' could also be utilized for the clean removal of the allyl ester and allyloxycarbonyl protecting groups. Importantly the 'plugs' remove the need for any purification following their use.

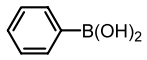
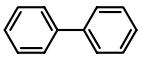
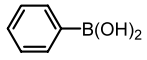
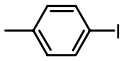
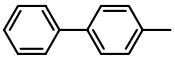
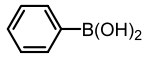
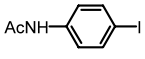
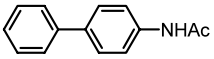
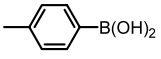
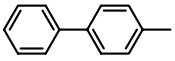
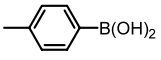
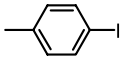
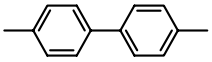
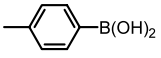
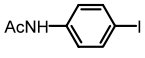
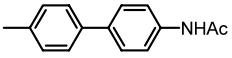
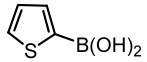
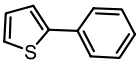
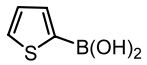
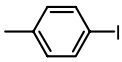
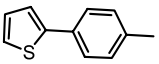
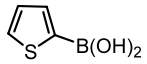
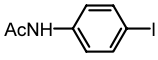
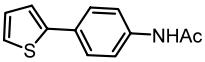
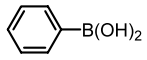
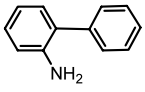
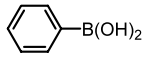
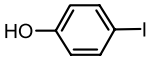
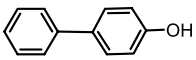
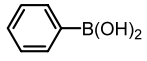
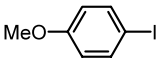
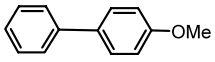
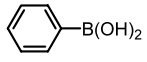
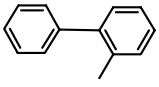
References

1. (a) Gordon, E. M.; Barrett, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1233; (b) Dolle, R. E. *J. Comb. Chem.* **2001**, *3*, 477.
2. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457; (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147; (c) *Advances in Metal-Organic Chemistry*; Miyaura, N., Ed.; JAI: London, 1998; Vol. 6, p. 187; (d) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263; (e) *Metal Catalyzed Cross Coupling Reactions*; Suzuki, A., Ed.; Wiley-VCH: New York, 1998; Chapter 2.
3. (a) Sato, T. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 1130; (b) Sato, T.; Oki, M. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 1289; (c) Sato, T.; Oki, M. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 1292; (d) Bovy, P. R.; Collins, J. T.; Olins, G. M.; McMahon, E. G.; Hutton, W. C. *J. Med. Chem.* **1991**, *34*, 2410; (e) Mantlo, N. B.; Chakravarty, P. K.; Ondeyka, D. L.; Siegl, P. K. S.; Chang, R. S.; Lotti, V. J.; Faust, K. A.; Chen, T.-B.; Schorn, T. W.; Sweet, C. S.; Emmert, S. E.; Patchett, A. A.; Greenlee, W. J. *J. Med. Chem.* **1991**, *34*, 2919; (f) Blankey, C. J.; Hodges, J. C.; Klutchko, S. R.; Himmelsbach, R. J.; Chucholowski, A.; Connolly, C. J.; Neergaard, S. J.; Van Nieuwenhze, M. S.; Sebastian, A.; Quin, J., II; Essenburg, A. D.; Cohen, D. M. *J. Med. Chem.* **1991**, *34*, 3248; (g) Okuda, T.; Yoshida, T.; Hatano, T. In *Phenolic Compounds in Food and their Effects on Health II*; Huang, M.; Ho, C.; Lee, C., Eds.; ACS Symposium Series 507; American Chemical Society: Washington, DC, 1992; Chapter 13, p. 160; (h) Thomas, A. P.; Allott, C. P.; Gibson, K. H.; Major, J. S.; Masek, B. B.; Oldham, A. A.; Ratcliffe, A. H.; Roberts, D. A.; Russell, N. T.; Thomason, D. A. *J. Med. Chem.* **1992**, *35*, 877; (i) Banwell, M. G.; Cameron, J. M.; Corbett, M.; Dupuche, J. R.; Hamel, E.; Lambert, J. N.; Lin, C. M.; Mackay, M. F. *Aust. J. Chem.* **1992**, *45*, 1967; (j) Chang, L. L.; Ashton, W. T.; Flanagan, K. L.; Strelitz, R. A.; MacCoss, M.; Greenlee, W. J.; Chang, R. S. L.; Lotti, V. J.; Faust, K. A.; Chen, T.-B.; Bunting, P.; Zingaro, G. J.; Kivlighn, S. D.; Siegl, P. K. S. *J. Med. Chem.* **1993**, *36*, 2558.
4. Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, 1995.
5. (a) Terasawa, M.; Kaneda, K.; Imanaka, T.; Teranishi, S. *J. Catal.* **1978**, *51*, 406; (b) Bar-Sela, G.; Warshawsky, A. *J. Poly. Sci., Part A: Poly. Chem.* **1990**, *28*, 1303; (c) Zhang, Y.; Liao, S.; Xu, Y. *Tetrahedron Lett.* **1994**, *35*, 4599; (d) Selvaraj, P. C.; Mahadevan, V. *J. Poly. Sci., Part A: Poly. Chem.* **1997**, *35*, 105.
6. (a) Trost, B. M.; Warner, R. W. *J. Am. Chem. Soc.* **1982**, *104*, 6112; (b) Bergbreiter, D. E.; Lynch, T. J. *J. Org. Chem.* **1983**, *48*, 4179; (c) Bergbreiter, D. E.; Weatherford, D. A. *J. Org. Chem.* **1989**, *54*, 2726.
7. (a) King, R. B.; Hanes, R. M. *J. Org. Chem.* **1979**, *44*, 1092; (b) Card, R. J.; Neckers, D. C. *J. Org. Chem.* **1978**, *43*, 2958.
8. Bergbreiter, D. E.; Chen, B.; Weatherford, D. *J. Mol. Catal.* **1992**, *74*, 409.
9. (a) Kaneda, K.; Terasawa, M.; Imanaka, T.; Teranishi, S. *Fundam. Res. Homogeneous Catal.* **1979**, *3*, 671; (b) Kaneda, K.; Terasawa, M.; Imanaka, T.; Teranishi, S. *J.*



Scheme 2. Standard Suzuki coupling reaction.

Table 1. Comparison of yields for the formation of the biaryl compounds with the 'plug' based and soluble $Pd(PPh_3)_4$ catalysts

	$Ar^1B(OH)_2$	I-Ar^2	Product	Isolated Yield[a](%)
1				84 (91)
2				82 (83)
3				78 (81)
4				86 (86)
5				82 (85)
6				71 (78)
7				78 (78)
8				75 (69)
9				74 (80)
10				82 (87)
11				83 (90)
12				80 (86)
13				77 (84)
14				87 (87)
15				92 (95)
16				88 (91)
17				86 (85)

[a]The figures in brackets are the yields obtained with $Pd(PPh_3)_4$. All based on 0.05 equiv. of catalyst. All compounds gave satisfactory analytical data.[15]

Organomet. Chem. **1978**, *162*, 403; (c) Anderson, C. M.; Karabelas, K.; Zhang, Z. Y.; Hu, H. W.; Kao, T. Y. *Synth. Commun.* **1990**, *20*, 3563; (d) Liao, Y.; Zhang, Z. Y.; Hu, H. W. *Synth. Commun.* **1995**, *25*, 595.

10. Hallberg, A.; Anderson, C. *J. Org. Chem.* **1985**, *50*, 3891.
11. (a) Jang, S. B. *Tetrahedron Lett.* **1997**, *38*, 1793; (b) Le Drian, C.; Fenger, I. *Tetrahedron Lett.* **1998**, *39*, 4287.
12. Anderson, C.; Larsson, R. *J. Catal.* **1983**, *81*, 179 and 194.
13. Atrash, B.; Bradley, M.; Kobylecki, R.; Cowell, D.; Reader, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 938.
14. In a typical procedure, 30 resin plugs (HDPE, co-sintered with Merrifield resin (crosslinked with 2% DVB, 2.4 mmol) were suspended in dry THF (60 ml). To this suspension was then added a solution of $LiPPh_2$ (12 mmol) in dry THF (10 ml). The suspension was gently stirred at 25°C under N_2 for 24 h. Acetone/H_2O (3:1, 100 ml) was added and the plugs filtered. These were then successively washed with water/acetone (2×), acetone (2×), $CHCl_3$ (2×), benzene (2×) and ether (2×). The plugs were then suspended in benzene (50 ml) and $Pd(PPh_3)_4$ (2.8 g, 2.4 mmol) was added. The mixture was heated at reflux under N_2 for 24 h. After filtration, the plugs were washed successively with ethanol (3×), ether (3×) and dried.
15. *Selected data*: **11** δ_H (300 MHz, DMSO-d_6) 7.00 (2H, d, *J* 8, Ar), 7.27 (1H, t, *J* 7, Ar), 7.40 (2H, t, *J* 7, Ar), 7.49 (2H, d, *J* 7, Ar), 7.57 (2H, d, *J* 8, Ar), 9.70 (1H, s, OH); δ_C (75 MHz, DMSO-d_6) 157.60, 140.70, 131.41, 128.96, 128.18, 126.41, 116.20, 115.85; TLC R_f 0.5 (9:1 hexane:EtOAc); ES-MS (-ve): *m*/*z* 169 (M–H); **14** δ_H (300 MHz, DMSO-d_6) 2.02 (3H, s, CH_3CO), 3.73 (3H, s, CH_3O), 6.90 (2H, d, *J* 8, Ar), 7.45 (2H, d, *J* 8.5), 7.55 (2H, d, *J* 5.5, Ar), 7.63 (2H, d, *J* 5, Ar), 9.90 (1H, s, NH); δ_C (75 MHz, DMSO-d_6) 168.67, 159.01, 138.62, 134.89, 132.67, 127.73, 126.75, 119.80, 114.76, 55.56, 24.46; TLC R_f 0.4 (9:1 hexane:EtOAc); ES-MS (+ve): *m*/*z* 242 $(M+H)^+$, 264 $(M+Na)^+$.