Piperazine-derived palladium complexes immobilised on a Merrifield resin as a catalyst for the Heck reaction

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A palladium catalyst supported on a Merrifield resin was prepared by a simple procedure and exhibited high activity and stability for the phosphine-free Heck reaction of activated and non-activated aryl or heteroaryl substrates with olefins to afford substituted cinnamic acids, stilbenes and their hetero-aromatic relatives.

Keywords*:* Heck reaction, palladium, phosphine-free catalyst, Merrifield resin

The palladium-catalysed coupling of terminal olefins with aryl and vinyl halides (the Heck reaction) is an important reaction because of its high tolerance of functional groups and its general applicability.[1-3] The reaction is normally carried out in a homogeneous solution in the presence of a phosphine ligand and a base under an inert atmosphere. However, homogeneous catalysts create problems for recovery and reuse and they might result in palladium contamination of the product, which is a particular problem for pharmaceutical applications. Recently, several heterogeneous Pd catalysts, such as palladium supported on carbon, inorganic oxides, clays, molecular sieves and polymers have been explored.[4-9] Resins are one class of polymeric supports originating from organic precursors. Resin-supported palladium complexes having high activity and selectivity are currently attracting great interest because they can be easily separated and recovered.[10-16] In addition, resin-supported Pd catalysts are stable at the high temperature which may be necessary for Heck reactions of the less reactive and cheaper substrates. However, although resin-supported Pd catalysts possess many advantages over homogeneous systems, the typical preparations of these catalysts involve many steps. The Heck reactions which use phosphine ligands are expensive, toxic and the phosphine can contaminate the products. Herein, we report a two-step preparation of a palladium complex immobilised on Merrifield resin, designated PM–Pd(II), and its successful application as heterogeneous catalyst for Heck reaction of activated and non-activated aryl or heteroaryl substrates in the absence of phosphine ligands.

The piperazine functionalised Merrifield resin was synthesised according to the reported procedure.[17] A palladium complex was immobilised on it as described in the experimental. The palladium content in the catalyst was determined by AAS to be 3.0wt.% of Pd. TG analysis show that PM–Pd(II) is stable up to 200°C.

Initially, PM–Pd(II), bromobenzene and *n*-butyl acrylate were treated with Bu_3N in NMP under stirring at 140°C for 24 h. This only afforded a poor yield of *trans*-*n*-butylcinnamate (20%). Addition of quaternary ammonium salts is often used to enhance the reactivity and selectivity of the Heck reaction.[18-20] When Bu_4NBr was chosen as an additive (10 mol% based on aryl bromide) for the reaction, the product was obtained with 85% yield and >99% *trans*-selectivity after 12 h. To our delight, almost no difference in reactivity was observed whether the reaction was carried out in the inert atmosphere or in air (Table 1, entries 2 and 3). This might make the catalyst convenient for industrial applications. Table 1 shows the Heck vinylation of bromobenzene with *n*-butyl acrylate in various solvents and bases using Bu_4NBr as an additive. A low activity of PM–Pd(II) catalyst was obtained in the solvent other than NMP under the same reaction conditions for NMP (Table 1, entries 4–8). As for bases, potassium carbonate appeared to be a better choice (Table 1, entry 10).

Table 1 Optimisation of solvent and base for Heck reaction of bromobenzene with *n*-butyl acrylate

Entry	Solvent	Base	Yield/%[a]
1[b,c]	NMP	Bu_3N	20
2[c]	NMP	Bu_3N	85
3	NMP	Bu_3N	85
4	CH_3CN	Bu_3N	55
5	DMSO	Bu_3N	45
6	DMSO	Bu_3N	28
7	DMF	Bu_3N	40
8	DMA	Bu_3N	52
9	NMP	Et_3N	76
10	NMP	K_2CO_3	92
11	NMP	Na_2CO_3	76
12	NMP	$NaHCO_3$	65
13	NMP	NaOAc	60
14	NMP	KF	55
15	NMP	D301 resin	50
16	NMP	Triethanolamine	15

[a]Isolated yield for *trans*-isomer. [b]Without NBu_4Br as additive [c]Under a nitrogen atmosphere.

The scope of this catalytic system with other vinyl substrates, such as methyl acrylate, styrene and acrylonitrile, was also examined and medium to excellent results were obtained for bromobenzene under identical conditions (Table 2, entries 2–4). Although the reaction of acrylonitrile occurred easily and the desired *E*-isomeric product was obtained in good yield, it was accompanied by the *Z*-isomer, according to ^1H NMR analysis (Table 2, entry 4). Since PM–Pd(II) showed activity for an aryl bromide substrate, it is not surprising that catalyst was also effective for the olefination of more reactive aryl iodides. In fact, iodobenzene reacted with various alkenes and gave the corresponding products with good yields and without the presence of an additive (Table 2, entries 5–8). Furthermore there was no obvious influence of the base on the Heck reaction for iodobenzene when using different bases such as trialkylamines, carbonates, bicarbonates and acetates of alkaline metals. Similar conditions brought about the coupling of 2-nitrobromobenzene (Table 2, entries 9 and 10). Heteroaryl substrates such as 3-bromoquinoline also gave a high yield of 90%. Lower yields were obtained in the vinylation of 3-bromopyridine, 3-bromothiophene and 2-bromothiophene. We also tried the coupling reaction using aryl chlorides with *n*-butyl acrylate. The corresponding products were obtained in good yields using activated aryl chlorides such as 4-nitrochlorobenzene and 2-nitro-chlorobenzene (Table 2, entries 15 and 16). Unfortunately, there was almost no reaction of the unactivated aryl chloride (entry 17).

When the reaction of iodobenzene with *n*-butyl acrylate was complete, the supported catalyst was filtered and washed with dichloromethane, then used for the next round of the reaction. We have observed that the catalyst could be recycled, at least, four times without significant loss of activity.

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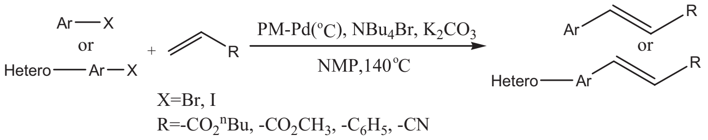
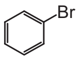
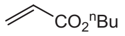
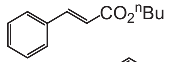
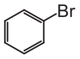
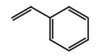
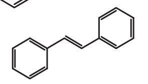
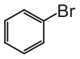
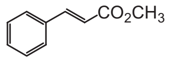
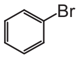
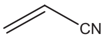
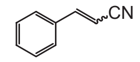
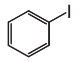
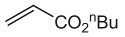
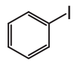
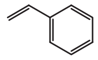
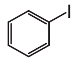
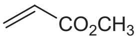
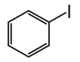
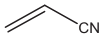
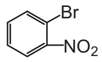
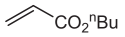
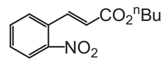
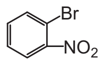
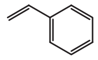
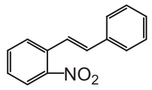
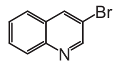
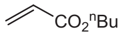
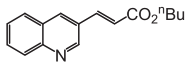
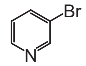
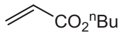
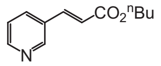
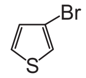
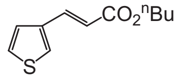
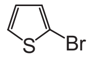
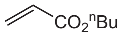
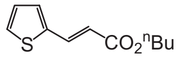
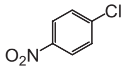
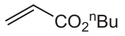
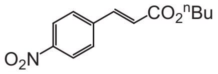
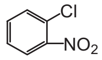
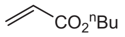
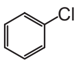
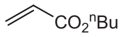


Table 2 Heck reaction of aryl or heteroaryl halides with olefins

Entry	Substrate	Olefin	Product	Time/h	Yield/%[a]
1				12	92
2				12	86
3				12	89
4[b]				12	65
5[c]			as 1	3	98
6[c]			as 2	3	95
7[c]			as 3	3	90
8[b,c]			as 4	3	75
9[c]				3	90
10[c]				3	85
11				12	90
12				12	60
13				12	61
14				12	72
15				12	88
16			as 9	12	76
17			as 1	24	<5

[a] Isolated yield for *trans*-isomer. [b] The ratio of *trans*-isomer and *cis*-isomer was characterised by ^{1}H NMR analysis (*E:Z* = 2.8:1). [c] Without NBu_4Br as additive

In summary, a Merrifield resin-immobilised palladium catalyst was prepared easily and exhibited excellent activity for the Heck vinylation of activated and non-activated aryl or heteroaryl substrates with olefins in air. Furthermore, the reaction proceeded without a phosphine ligand. Further study of the scope of the application of PM–Pd(II) is in progress in our laboratory.

Experimental

All reagents were used as received. ^{1}H NMR and ^{13}C NMR were recorded at 300 MHz and 75 MHz with Bruker Avance 300 spectrometer. Chemical shifts are reported in ppm using tetramethylsilane as an internal standard. IR spectra were obtained using a Bruker Equinox 55 FT-IR spectrophotometer in KBr pellets. Melting points were obtained with a XT4A melting point apparatus and were uncorrected. GC analyses were conducted using a Trace GC/Thermo Finnigan equipped with an SE-54 capillary column (25 m) and an FID detector. The thermal analysis was performed on STA 449 thermal analysis system at a heating rate of 10°C/min and in air. Palladium content was analysed by atomic absorption using a AA670 atomic absorption apparatus.

Preparation of palladium catalyst immobilised on the functionalised Merrifield resin

The appropriate amount of $PdCl_2$ (0.1 g) was dissolved in acetone (30 ml). Then, the functionalised Merrifield resin (1.0 g) was added to the prepared solution, and the suspension was stirred at 60°C for 72 h. Physically absorbed palladium species were removed by extraction with refluxing dichloromethane and acetonitrile for 8 h. The conditioned catalyst was dried at 90°C under vacuum for 8 h.

General procedure

Aryl or heteroaryl halide (1 mmol), *n*-butyl acrylate (1.5 mmol), base (1.5 mmol), solvent (0.5 ml), NBu_4Br (0.1 mmol) (sometimes omitted) and PM–Pd(II) (0.0005 mmol) were placed in a 25 ml two-neck flask. The mixture was heated at 140°C in air atmosphere for the required time with magnetic stirring. After cooling to room temperature, the product was diluted with H_2O, extracted with EtOAc, washed with H_2O and brine, and dried over Na_2SO_4. The solvent was filtered, and evaporated. The product was purified by chromatography on silica (eluent: EtOAc/petroleum ether = 1:5). The purity of the isolated product was determined by GC analysis or ^{1}H NMR.

Product data

(*E*)-*n-Butyl cinnamate*: Oil;[21] purity: 98.0%; ^{1}H NMR ($CDCl_3$/TMS): δ_H 7.68 (d, *J* = 16.0 Hz, 1H), 7.54–7.51 (m, 2H), 7.42–7.37 (m, 3H), 6.45 (d, *J* = 16.0 Hz, 1H), 4.21 (t, *J* = 6.7 Hz, 2H), 1.72–1.67 (m, 2H), 1.50–1.40 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 144.9, 134.9, 130.6, 129.3, 128.4, 118.7, 64.8, 31.2, 19.6, 14.2; IR: 2953, 1710, 1628, 1498, 1320, 770 cm^{-1}.

(*E*)-*Stilbene*: M.p. 123–124°C (lit.[22] m.p. 122–123°C); purity: 99.0%; ^{1}H NMR ($CDCl_3$/TMS): δ_H 7.51 (d, 4H, *J* = 7.7 Hz), 7.36 (t, 4H, *J* = 7.5 Hz), 7.27–7.23 (m, 2H), 7.11 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.5, 128.9, 128.8, 127.8, 126.7; IR: 3019, 1631, 1493, 1451, 1071, 962, 764 cm^{-1}.

(*E*)-*Methyl cinnamate*: Oil;[23] purity: 97.2%; ^{1}H NMR ($CDCl_3$/TMS): δ_H 7.69 (d, *J* = 16.1 Hz, 1H), 7.53–7.50 (m, 2H), 7.39–7.37 (m, 3H), 6.44 (d, *J* = 16.1 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 134.2, 130.2, 128.8, 128.0, 117.7, 114.7, 51.5. IR: 2951, 1719, 1638, 1450, 1434, 1276, 1203, 1172, 980, 768 cm^{-1}.

(*E*)-Cinnamonitrile and (*Z*)-cinnamonitrile were isolated as an *E:Z* mixture.[22]

(E)-Cinnamonitrile: ^{1}H NMR ($CDCl_3$/TMS): δ_H 7.50–7.38 (m, 5H), 7.39 (d, 1H, *J* = 16.6 Hz), 5.87 (d, 1H, *J* = 16.6 Hz). IR: 2952, 2206, 1643, 1614, 1600, 1181, 1110, 978, 801 cm^{-1}.

(*E*)-*n-Butyl 2-nitrocinnamate*: Oil;[24] purity: 97.0%; ^{1}H NMR ($CDCl_3$/TMS): δ_H 8.15 (d, 1H), 8.10–8.05 (m, 1H), 7.67 (m, 2H), 7.60–7.56 (m, 1H), 6.41 (d, 1H, *J* = 15.7 Hz), 4.25 (t, 2H, *J* = 6.8 Hz), 1.72–1.69 (m, 2H), 1.50–1.42 (m, 2H), 0.99 (t, 3H, *J* = 7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8, 148.2, 139.8, 133.5, 130.5, 130.2, 129.0, 124.8, 123.2, 64.5, 30.6, 19.0, 13.6. IR: 2961, 1716, 1526, 1346, 1180, 975, 757 cm^{-1}.

(*E*)-*2-Nitrostilbene*: Oil;[25] purity: 97.5%. ^{1}H NMR ($CDCl_3$/TMS): δ_H 7.95–7.92 (m, 1H), 7.73–7.70 (m, 1H), 7.59–7.49 (m, 4H), 7.38–7.28 (m, 4H), 7.04 (d, *J* = 16.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.8, 136.3, 133.7, 132.9, 132.8, 128.6, 128.5, 128.0, 127.8, 126.9, 124.6, 123.3; IR: 3022, 1604, 1508, 1339, 955, 855, 752 cm^{-1}.

(*E*)-*n-Butyl 3-(3-quinolyl)-acrylate*: M.p. 80–82°C, purity: 98.0%; ^{1}H NMR[12] ($CDCl_3$/TMS): δ_H 9.09 (d, *J* = 2.2 Hz, 1H), 8.24 (d, *J* = 2.0 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 7.84 (d, *J* = 6.3 Hz, 1H), 7.78 (d, *J* = 16.1 Hz, 1H), 7.73 (d, *J* = 6.9 Hz, 1H), 7.61–7.58 (m, 1H), 6.67 (d, *J* = 16.1 Hz, 1H), 4.25 (t, *J* = 6.7 Hz, 2H), 1.77–1.67 (m, 2 H), 1.47–1.42(m, 2 H), 0.98 (t, *J* = 7.4 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 149.2, 148.6, 141.1, 135.4, 130.6, 129.5, 128.3, 127.5, 120.3, 64.7, 30.7, 19.2, 13.7; IR: 2957, 1710, 1636, 1342, 1318, 1296, 1184 cm^{-1}.

(*E*)-*n-Butyl 3-(3-pyridyl)-acrylate*: Oil;[26] purity: 99.0%; ^{1}H NMR ($CDCl_3$/TMS): δ_H 8.75 (d, *J* = 1.9 Hz, 1H), 8.60 (dd, *J* = 1.5 Hz; 1.5 Hz, 1H), 7.86–7.83 (m, 1H), 7.67 (d, *J* = 16.1 Hz, 1H), 7.35–7.31 (m, 1H), 6.53 (d, *J* = 16.1 Hz, 1H), 4.23 (t, *J* = 6.6 Hz, 2H), 1.74–1.65 (m, 2H), 1.50–1.38 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 150.7, 149.6, 140.7, 134.1, 130.1, 123.7, 120.4, 64.5, 30.5, 19.1, 13.6. IR: 2957, 1711, 1639, 1415, 1310 cm^{-1}.

(*E*)-*n-Butyl3-(3-thiophenyl)-acrylate*: Oil;[26] purity: 97.0%; ^{1}H NMR ($CDCl_3$/TMS): δ_H 7.66 (d, *J* = 15.8 Hz, 1H), 7.48 (s, 1H), 7.32 (m, 2H), 6.26 (d, *J* = 15.8 Hz, 1H), 4.17 (t, *J* = 6.8 Hz, 2H), 1.68 (tt, *J* = 6.8, 6.8 Hz, 2H), 1.42 (qt, *J* = 7.3, 6.8 Hz, 2H), 0.95 (q, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 138.0, 137.5, 128.0, 127.1, 125.1, 117.9, 64.6, 30.6, 19.1, 13.7; IR: 2956, 2359, 1701, 1635, 1305, 1165 cm^{-1}.

(*E*)-*n*-Butyl 3-(2-thiophenyl)-acrylate: Oil;[27] purity: 98.3%; ^{1}H NMR ($CDCl_3$/TMS): δ_H 7.76 (d, *J* = 15.7 Hz, 1H), 7.35 (d, *J* = 4.9 Hz, 1H), 7.23 (d, *J* = 3.4 Hz, 1H), 7.04 (dd, *J* = 3.7 Hz; 3.7 Hz, 1H), 6.23 (d, *J* = 15.7 Hz, 1H), 4.18 (t, *J* = 6.6 Hz, 2H), 1.72–1.62 (m, 2H), 1.48–1.36 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 140.0, 137.3, 131.3, 128.7, 128.5, 117.5, 64.8, 31.2, 19.6, 14.1; IR: 2957, 1708, 1624, 1306 cm^{-1}.

(*E*)-*n-Butyl 4-nitrocinnamate*: M.p. 60–63°C (lit[21]. m.p. 59.6–64.4°C); purity: 97.4%; ^{1}H NMR ($CDCl_3$/TMS): δ_H 8.24 (d, *J* = 8.7 Hz, 2H), 7.73–7.66 (m, 3 H), 6.56 (d, *J* = 16.1 Hz, 1H), 4.24 (t, *J* = 6.7 Hz, 2H), 1.75–1.66 (m, 2H), 1.51–1.38 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 148.5, 141.5, 140.5, 128.6, 124.1, 123.2, 122.6, 64.9, 30.5, 19.1, 13.6; IR: 2959, 1709, 1641, 1599, 1518, 1343 cm^{-1}.

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References

1 R.F. Heck, *Acc. Chem. Res*., 1979, **12**, 146.
2 I.P. Beletskaya and A.V. Cheprakov, *Chem. Rev*., 2000, **100**, 3009.
3 N.J. Whitcombe, K.K.M. Hii and S.E. Gibson, *Tetrahedron*., 2001, **57**, 7449.
4 A. Hallberg and L. Westfelt, *J. Chem. Soc. Perkin Trans. 1*., 1984, 933.
5 F.Y. Zhao, B.M. Bhanage, M. Shirai and M. Arai, *Chem. Eur. J*., 2000, **6**, 843
6 L. Djakovitch and K. Koehler, *J. Mol. Catal. A.,* 1999, **142**, 275
7 L. Djakovitch and K. Koehler, *J. Am. Chem. Soc.,* 2001, **123**, 5990
8 C.P. Mehnert, D.W. Weaver and J.Y. Ying, *J. Am. Chem. Soc.,* 1998, **120**, 12289
9 R.L. Augustine and S.T.O'Leary, *J. Mol. Catal. A.,* 1995, **95**, 277.
10 C.M. Andersson, K. Karabelas, A. Hallberg and C. Andersson, *J. Org. Chem*., 1985, **50**, 3891.
11 A. Dahan and M. Portnoy, *Org. Lett*., 2003, **5**, 1197.
12 Y. Uozumi and T. Kimura, *Synlett*., 2002, **12**, 2045.
13 M. Nowotny, U. Hanefeld, H. van Koningsveld and T. Maschmeyer, *Chem. Commun*., 2000, 1877.
14 M.R. Buchmeiser and K. Wurst, *J. Am. Chem. Soc.,* 1999, **121**, 11101.
15 V. Chandrasekhar and A. Athimoolam, *Org. Lett*., 2002, **4**, 2113.
16 J. Schwarz, V.P.W. Böhm, M.G. Gardiner, M. Grosche, W.A. Herrmann, W. Hieringer and G. Raudaschl-Sieber, *Chem. Eur. J*., 2000, **6**, 1773.
17 S. Bräse and M. Schroen, *Angew. Chem. Int. Ed.,* 1999, **38**, 1071.
18 T. Jeffery. *Tetrahedron*., 1996, **52**, 10113.
19 T. Jeffery and M. David, *Tetrahedron Lett*., 1998, **39**, 5751.
20 Ö. Aksýn, H. Türkmen and L. Artok, *J. Organomet. Chem*., 2006, **691**, 3027.
21 X. Cui, Z. Li and C.Z. Tao, *Org. Lett.,* 2006, **8**, 2467.
22 A. Cwik, Z. Hell and F. Figueras, *Adv. Synth. Catal*., 2006, **348**, 523.
23 Z.H. Zhang, Z.G. Zha and C.S. Gan, *J. Org. Chem.,* 2006, **71**, 4339.
24 A.G. Myers, D. Tanaka and M.R. Mannion, *J. Am. Chem. Soc*., 2002, **124**, 11250.
25 M.J. Dai, B. Liang, C.H. Wang, J.H. Chen and Z. Yang, *Org. Lett.,* 2004, **6**, 221.
26 M. Feuerstein, H. Doucet and M. Santelli, *J. Org. Chem.,* 2001, **66**, 5923.
27 F. Berthiol, M. Feuerstein, H. Doucet and M. Santelli, *Tetrahedron Lett*., 2002, **43**, 5625.