SHORT PAPER

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Use of a new hydrophilic phosphine: DPPPA. Rapid and convenient Heck reaction in aqueous medium under microwave irradiation[†]

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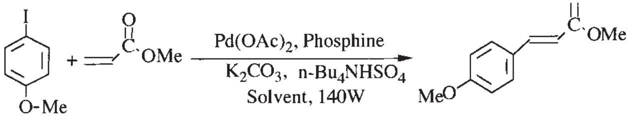
A new water soluble phosphine-ligand: diphenylphosphinyl) phenylphosphonic acid (DPPPA) was used in Heck reaction. The Heck reaction is efficiently and rapidly achieved by a palladium-catalysed reaction in water performed in a Teflon autoclave under microwave irradiation with a commercial microwave oven. The log P was used for correlating the solubility of the aryl iodide in water with the observed yield.

The Heck reaction is a powerful tool for carbon–carbon bond formation.[1] This palladium-catalysed reaction needs a stochiometric amount of base, high temperature (100°C) and long time (24 h) for complete conversion. Some alternative conditions, such a high pressure,[2] phase-transfer conditions[3] or water-soluble phosphine-ligand catalysts (*i.e.* sulfonated phosphines) have been proposed and few Heck arylations are known to proceed smoothly in water or in water/organic solvent mixtures.[4] Triarylphosphine with a meta or paraphosphonic acid moiety are more soluble than the sulphonated analogue,[5] hence we investigated the use of diphenylphosphinyl phenyl phosphonic acid (DPPPA) as water-soluble ligand in the Heck reaction in aqueous medium under phase transfer conditions according to T. Jeffery.[6] The use of water as a solvent is very attractive for safety and economic reasons.

Microwave activation is very useful because of its important rate accelerating effect (*i.e.* reduction of reaction times). Although many organometallic complexes were efficiently obtained under microwave irradiations,[7] reactions homogeneously catalysed by organometallic complexes have been rarely investigated.[8,9] The air-sensitive complexes have been prepared by Mingos[7] using commercially available Teflon autoclaves designed for mineralisation under commercial microwave-oven irradiation. The Heck reactions under microwave irradiation were recently described in organic solvents (tributylamine and DMF as solvent).[9] The scope of our work involved the use of a new water-soluble triarylphosphine with paraphosphonic acid moiety (DPPPA) and aqueous conditions.

We first studied the Heck reaction of 4-iodoanisole with methyl acrylate under Jeffery's conditions (Scheme 1) in the presence of phosphines under microwave irradiation.



Scheme 1

Various phosphines were used in order to compare their effect on the arylation of methyl acrylate in the presence of palladium acetate and water as solvent or co-solvent (Table 1). The results show that the triarylphosphine with a paraphosphonic acid moiety (DPPPA) gave the best yield (entry 8) in 8 min at 140 W in water as solvent.

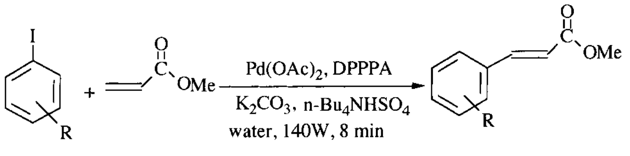
Table 1 Heck reaction of 4-iodoanisole in water-organic medium or in water 4-iodoanisole/methyl acrylate/*n*-Bu_4NHSO_4/phosphine/$Pd(OAc)_2$ = 1/1.2/1/0.1/0.05

Entry	Phosphine	Solvent	Time (min)	Yield[a] (%)
1	PPh_3	hexane / H_2O (1:1)	4	80
2	PPh_3	MeCN / H_2O (1:1)	4	5[b]
3	PPh_3	MeCN / H_2O (1:1)	4	93
4	PPh_3	H_2O	4	38
5	(o-tolyl)$_3$P	H_2O	4	40
6	TPPDS[c]	H_2O	4	50
7	DPPPA[d]	H_2O	4	63
8	DPPPA[d]	H_2O	8	93

4-Iodoanisole, 0.1g (0.5 mmol); methyl acrylate, 0.06ml 0.06 mmol, 1.3 eq.); $Pd(OAc)_2$, 5 mg (5% molar); phosphine, (10% molar); K_2CO_3, 0.17g (2.5 eq.); n-Bu_4NHSO_4, 0.17 g (1 eq.), solvent, 2 ml. Irradiation at 140 W during the time indicated. [a]Isolated yields. [b]without *n*-Bu_4NHSO_4. [c]Disodium diphenyl-3.3′-phosphinediylbis-(benzenesulphonate). [d]4-(Diphenylphosphinyl) phenyl phosphonic acid.

A yield of 80% was obtained (entry 1) with triphenylphosphine under the Jeffery conditions in a hexane-water two-phase system. With the homogeneous mixture (acetonitrile and water) as a solvent the yield increased to 93% (entry 3) but in the absence of any phase-transfer reagent the yield was very poor (entry 2). In water without solvent the situation is quite different, the yield with triphenylphosphine or tritolylphosphine was not very good (entry 4 and 5). The use of water-soluble phosphine (TPPDS or DPPPA) improved the yield and upon doubling the irradiation time to 8 min a yield similar to that observed in the presence of acetonitrile was obtained in water (entry 8).

In the second study, we performed the reaction between various iodoarenes and methyl acrylate (Scheme 2), the yield reported in Table 2 appears to depend on the solubility of the iodoarene in water.



Scheme 2

We used the hydrophobic parameter (log P) in order to quantify the solubility of the iodoarenes in water. Log P is an experimental value of a substrate partition between two phases, generally *n*-octanol and water. This parameter developed by

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[†] This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

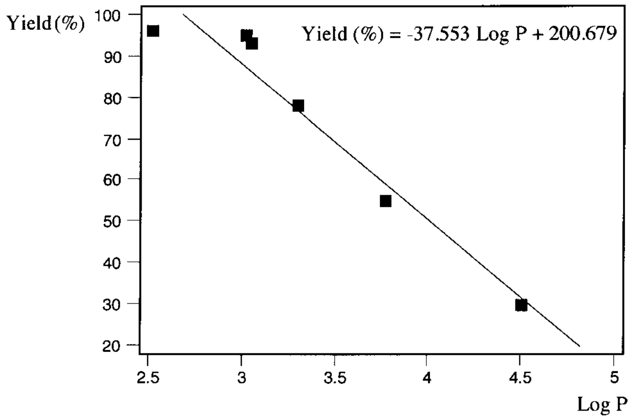
Table 2 Attempted of correlation of Heck coupling yields of aryl iodides with methyl acrylate and log P in the presence of DPPPA in water ArI/methyl acrylate/n-Bu_4NHSO_4/DPPA/$Pd(OAc)_2$ = 1/1.2/1/0.1/0.05

Entry	R	Log P[a]	Yield[b] (%)
1	4-iPr	4.50	30
2	4-Me	3.77	55
3	H	3.30	78
4	4-OMe	3.05	93
5	3-CO_2Me	3.03	79
6	2-OH	3.02	95
7	4-NH_2	2.52	96

Aryl iodide, (0.5 mmol); methyl acrylate, 0.06ml (0.6 mmol, 1.3 eq.); $Pd(OAc)_2$, 5 mg (5% molar); phosphine (DPPPA), (10% molar); K_2CO_3, 0.17g (2.5 eq.); n-Bu_4NHSO_4, 0.17 g (1 eq.); solvent, 2 ml of degassed water.

[a]Calculated with the program ChemPlus. [b]Isolated yields.

Hansch[10] is widely used in medicinal chemistry for QSAR studies, but to our knowledge scarcely in organic chemistry. Log P values can be easily calculated from molecular modelling packages. Iodoarene molecules were built in 3D by HyperChem and after minimisation with AM1 method, the Log P values were calculated using the ChemPlus extension[11] and Ghose's method.[12]



Scheme 3
Correlation between the yield and Log P of the substrate

We observed a linear correlation between the log P of the iodoarene and the yield of the reaction (Scheme 3). Thus with 4-iodoisopropylbenzene (log P = 4.50) 30% were obtained and 96% when 4-iodoaminobenzene (log P = 2.52) was used.

In the third study, we used DPPPA in acetonitrile-water solution, the results are reported in Table 3. Bromobenzene gave a poorer yield (60%) than the iodoarenes (entry 1, Table 3). In the case of 4-iodoanisole, it is possible to substitute the two β-hydrogens in the methyl acrylate (entry 2, Table 3), however, it is not the case with more hindered 4-iodoisopropylbenzene (entry 3, Table 3). When methyl acrylate was substituted by allylic alcohol (entry 4), a mixture two aldehydes was obtained.

In conclusion DPPPA [4-(Diphenylphosphinyl)phenylphosphonic acid] is a new water soluble phosphine which allows the Heck reaction to proceed in water under microwave irradiation. DPPPA is more efficient in the case studied than the disulfonic analogue. We have also obtained a linear correlation between the log P of the iodoaryle and the yield of the Heck reaction in water. Log P seems to be a convenient available parameter to quantify the solubility of a substrate for studying reaction in water.

Experimental

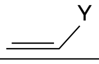
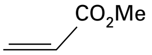
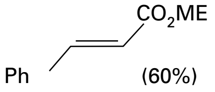
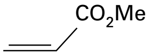
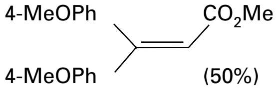
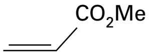
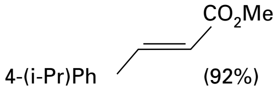
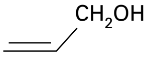
^1H and ^{13}C NMR (reference from internal Me_4Si) were recorded on a Bruker AC 250 instrument in $CDCl_3$ solution. ^{31}P NMR spectra of the phosphines (reference from external H_3PO_4) were recorded on a Brucker WP80 SY. Mass spectra were recorded on a Nermag R10 10H spectrometer. FT IR spectra were recorded on a Perkin-Elmer 16 PC spectrometer. GC yields were obtained on a Shimadzu GC-4A apparatus fitted with an OV17 column and a catharometer detector which is connected to a Spectra Physics integrator-recorder. Microwave irradiations were carried out on a Toshiba microwave oven ER 7620 operating at 2450 MHz. All reactions were performed in a Teflon Savilex autoclave under argon atmosphere. Water and all solvents were degassed before use.

Phosphines were prepared by phosphonation of the monobrominated phosphine followed by hydrolysis[13] for the DPPPA and according to Hermann's method[14] for the TPPDS by sulfonation of PPh_3 using H_2SO_4 and oleum mixture.

Typical experiment

In a typical experiment, $Pd(OAc)_2$ (5 mg), n-Bu_4NHSO_4 (0.5 mmol), K_2CO_3 (1.2 mmol) and phosphine (DPPPA) (10 mg, 6% molar) were placed in a Savilex autoclave under argon. A mixture of 4-iodoanisole (0.5 mmol) and methyl acrylate (0.6 mmol, 1.2 eq.) in 2 ml of

Table 3 Arylation with different aryl halides in acetonitrile-water with DPPPA. ArX/methyl acrylate/n-Bu_4NHSO_4/phosphine/$Pd(OAc)_2$ = 1/1.2/1/0.1/0.05 in CH_3CN/H_2O=1/1

Entry	PhX	 Y	Conditions[a]	Product (yield %)[b]
1	PhBr	 CO_2Me	DPPPA n-Bu_4NCl	 CO_2ME Ph (60%)
2	2(4-MeOPhI)	 CO_2Me	(o-tol)$_3$P, n-Bu_4NCl	 4-MeOPh CO_2Me 4-MeOPh (50%)
3	4-(i-Pr)PhI	 CO_2Me	DPPPA n-Bu_4NCl	 CO_2Me 4-(i-Pr)Ph (92%)
4	PhI	 CH_2OH	(o-tol)$_3$P, n-Bu_4NCl	Ph-$(CH_2)_2$ CHO (73%)[c] Ph-$CH(CH_3)$CHO (16%)[c]

[a]140 W for 10 minutes. [b]Isolated yields or as indicated. [c]According to ^1H NMR. [d]GC yields.

Me_3CN/water (1/1) was added under argon atmosphere and the mixture was irradiated for 2 minutes at 140 W, then 6 times for 1 minute. After cooling, the product was extracted with ether and filtered over Celite. Ether was distilled off and the residue was chromatographied on a silica gel column with CH_2Cl_2 as eluent; Rf (CH_2Cl_2) = 0.36. We obtain a white solid: m.p. 87–89 °C (Lit : 90 °C)[15]; ^1H NMR ($CDCl_3$): 3.79 (s, ^3H, CO_2CH_3); 3.84 (s, 3H, OCH_3); 6.31 (d, $^3J_{HH}$ = 16 Hz, 1H, C=CH); 6.91 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H_{arom}); 7.48 (d, 3JHH = 8.8 Hz, 2H, H_{arom}); 7.65 (d, $^3J_{HH}$ = 16 Hz, 1H, HC=C);^{13}C NMR ($CDCl_3$): 51.54 (CO_2CH_3); 55.43 (O–CH_3); 114.46 (C_{arom}); 115.49 (C=C); 127.33. 129,76 (C_{arom}); 144.55 (C=C); 161.54 (C–OCH_3, C_{arom}); 167.75 (CO_2CH_3); IR (KBr) cm^{-1}: ν(C=C) (1636); ν(C=O) (1718); ν(C-O) (1288, 1176)

G.C. analysis: column: OV17 1.5 m, oven temperature = programmation from 140 to 240°C (10°C/min), injector and detector temperature = 270°C, gas flow (H_2) = 50 ml/min. Retention time for E-methyl (4-methoxycinnamate) = 1.54 min.

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References

1 (a) C.B. Ziegler and R.F. Heck , *J. Org. Chem.*, 1978, **43,** 2941; (b) B.M. Trost and T.R. Verhoeven, *Comprehensive Organometallic Chemistry*, G. Wilkinson, Ed.; Pergamon; Oxford, 1982, Vol. 8, pp 799; (c) R.F. Heck , *Comprehensive Organic Synthesis*, B.M. Trost and I. Flemming Eds., Pergamon Press: Oxford, 1991, Vol. 4, pp 833; (d) R.F. Heck, *Palladium Reagents in Organic Synthesis*, Academic Press: London, 1985, pp 276; (e) J. Tsuji, *Palladium Reagents and Catalysts: Innovations in Organic Chemistry*, John Wiley & Sons: Chichester, 1995, pp 125; (f) S.E. Gibson, *Comp. Org. Synth.*, 1996,**43,** 447; (g) J.M. Brown and K.K. Hii, *Angew. Chem. Int. Ed Engl.*, 1997, 657; (h) J.L. Malleron, J.C. Fiaud and J.Y. Legros, *Handbook of Palladium Catalysed Organic Reactions*, Academic Press, San Diego, 1998; (i) F. Diederich and P.J. Stang, *Metal-Catalysed Cross Coupling Reactions*, Wiley-VCH, Weinheim, 1998.

2 K. Voigt, U. Schick, F.E. Meyer and de A. Meijere, *Synlett*, 1994, 189.

3 T. Jeffery and J.C. Galland, *Tetrahedron Lett.*, 1994, **35**, 4103.

4 (a) N.A. Bumagin, P.G. More and I.P. Beletskya, *J. Organomet. Chem.*, 1989, **371**, 397; (b) J.C. Calabrese and A.L. Casalnuovo, *J. Am. Chem. Soc.*, 1990, **112**, 4324; (c) M. Safi and D. Sinou, *Tetrahedron Lett.*, 1991, **32**, 2025; (d) J.P. Genet, E. Blart and M. Savignac, *Synlett.*, 1992, 715; (e) A. Hessler, O. Stelzer, H. Dibowski, K. Worm and F.P. Schmidtchen, *J. Org. Chem.*, 1997, **62**, 2362; (f) S. Sengupta and D. Bhattacharya, *J. Chem. Soc. Perkin Trans.*, 1993, 1943.

5 Knight showed that triarylphosphine with metaphosphonic acid moiety is more soluble than the sulfonated analogue (TPPMS) (0.19 and 0.08 g/ml respectively) and triarylphosphine with paraphosphonic acid moiety is the most soluble (0.41 g/ml). T.L. Schull, J.C. Fettinger and D.A. Knight, *Inorg. Chem.*, 1996, **35,** 6717; idem, *J. Chem. Soc., Chem. Commun.*, 1995, 1487.

6 (a) T. Jeffery, *Tetrahedron Lett.*, 1994, **35** , 3051; (b) T. Jeffery, *J. Chem. Soc., Chem. Commun.*, 1994, 1287.

7 D.M.R. Mingos and D.R. Baghurst , *Chem. Soc. Rev*., 1991, **20**, 1; A.G. Whittaker and D.M.P. Mingos, *J. Microw. Pow. Electr. Energ.*, 1995, **30**, 27; S. Caddick, *Tetrahedron*, 1995, **51**, 10403.

8 (a) F. Adamek and M. Hajek, *Tetrahedron Lett*., 1992, **33**, 2039; (b) E.M. Gordon, D.C. Gaba, K.A. Jebber and D.M. Zacharias, *Organometallics*, 1993, **12,** 5020; (c) M. Larhed, and A. Hallberg, *J. Org. Chem.*, 1996, **61**, 9582; (d) M. Larhed, M. Hoshino, D.P. Curran and A. Hallberg, *J. Org. Chem.*, 1997, **62**, 5583; (e) M. Hajek, *Coll. Czch. Chem. Commun.*, 1997, **62**, 347; (f) U; Bremberg, M. Larhed, C. Moberg and A. Hallberg, *J. Org. Chem.*, 1999, **64**, 1082.

9 M. Larhed and A. Hallberg, *J. Org. Chem.*, 1996, **61**, 9582; A. Diaz-Ortiz, P. Prieto and E. Vazquez, *Synlett.*, 1997, 269.

10 A. Leo, C. Hansch and D. Elkins, *Chem. Rev.*, 1971, **71** , 525.

11 ChemPlus is an extension of the software HyperChem distributed by Autodesk Inc., Scientific Modeling Division, 2320 Marinship way, Sausalito, C.A., 94965.

12 V.N. Viswanadhan, A.K. Ghose, G.N. Revankar and R.K. Robins, *J. Chem. Inf. Comput. Sci.*, 1989, **29**, 163.

13 D. Villemin, P.A. Jaffrès, B. Nechab and F. Courivaud, *Tetrahedron Lett.*, 1997, **38**, 6581.

14 W.A. Hermann, G.P. Albanese, R.B. Manetsberger, P. Lappe and H. Bahrmann, *Angew. Chem. Int. Ed. Engl.*, 1995, **34**, 811.

15 I. Heilbron, *Dictionary of Organic Compounds*, Vol. 4, Oxford University Press, New York, 1965.