Iron-catalysed Negishi coupling of benzyl halides and phosphates

Robin B. Bedford, Michael Huwe and Mark C. Wilkinson

Electronic Supporting Information

General information. All reagents were purchased from commercial suppliers and used without further purification. All experiments were carried out under nitrogen. Dry solvents were dried and purified using anhydrous engineering double alumina and alumina-copper catalyst dry columns then degassed prior to use. Flash chromatography was carried out with fluorochem Silica gel LC60A-40-63 micron or was performed on a Biotage SP4™ System. Analytical TLC was performed using Merck silica gel 60 F_{254} plates, products were visualised by UV detection. ^{1}H-NMR and ^{13}C-NMR (300 or 400 MHz and 100 MHz, respectively) spectra were recorded on a Varian 400MHz or a JEOL lambda 300MHz spectrometer using $CDCl_3$ as solvent. Chemical shifts are reported in ppm. Mass spectra were recorded on a VG Autospec Triple Sector Mass Spectrometer. Complexes **6** and **8** were prepared by literature methods.[1,2]

Synthesis of [FeCl$_2$(dpbz)], 6. $FeCl_2 \cdot 4H_2O$ (0.398 g, 2.00 mmol) was dissolved in THF in a Schlenk tube and after stirring for 5 min the solvent was removed *in vacuo*. This was repeated twice. 1,2-Bis(diphenylphosphino)benzene (0.893 g, 2.00 mmol) was added to the resulting $FeCl_2(THF)_{1.5}$. Anhydrous acetone (25 ml) was added and the mixture was stirred for 24 h. The suspension was filtered with a Büchner funnel and washed with cold Et_2O to yield the product as a beige powder (76%). M.p. (N_2) 241 °C (dec.) Anal. calcd. for $C_{30}H_{24}Cl_2FeP_2$: C, 62.86, H 4.22%. Found: C, 61.36; H, 4.20%. I.R. (solid, cm^{-1}): 3054w, 1588vw, 1569vw, 1481w, 1436m, 1169m, 1152m, 1118m, 1093m, 1071w, 1054w, 1027w, 998w, 951w, 746s, 721s, 689vs, 658m. Magnetic susceptibility (293 K), $\mu_{obs} = 4.31$ B.M., $\chi_{corr} = 7.913 \times 10^{-3}$.[3]

Ligand screening

Reaction employed:

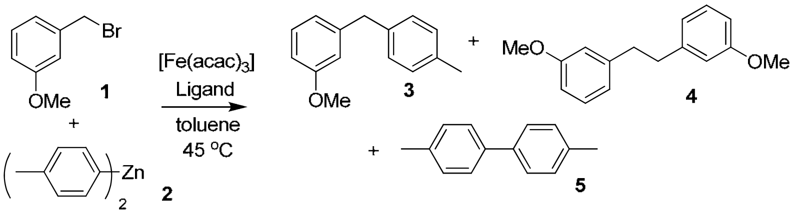
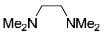
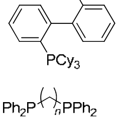
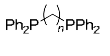
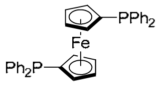
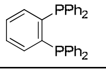
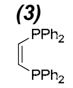
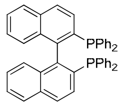
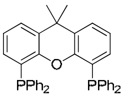


Table S1 Catalyst optimisation for the coupling of **1** with **2.**[a]

Entry	Ligand (equiv)	Conv. to (%): **3**	**4**	**5**	**1**[b]
1	- [c]	0	0	0	100
2	-	43	7	21	38
3	 (1)	28	6	12	52
4	PPh_3 (2)	28	4	16	39
5	PCy_3 (2)	26	8	16	38
6		17	3	16	48
7	 (1)				
	n = 1	50	5	10	31
8	*n* = 2	48	3	10	35
9	*n* = 3	69	2	6	18
10	*n* = 4	48	5	10	28
11		42	4	11	31
12	 (1)	79	-	12	16

13	(2)	80	-	10	10
14	***(3)***	***91***	***-***	***10***	***-***
15	 (1)	41	-	17	33
16	 (3)	38	5	10	30
17	 (3)	33	5	12	40

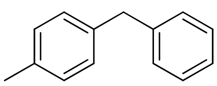
[a] Conditions: **1** (1.0 mmol), **2** (0.25 M in THF, 4 ml, 1.0 mmol), [Fe(acac)$_3$] (0.05 mmol), ligand (0.05 – 0.15 mmol), toluene (6 ml), 45 ˚C, 4h. [b] Determined by ^{1}H NMR (1,3,5-$C_6H_3(OMe)_3$ internal standard), average of two runs. [c] No catalyst.

General procedure for the iron-catalysed Negishi coupling with preformed diarylzinc reagents (GP1). Complex **6** (0.050 g, 0.05 mmol), an appropriate benzyl halide (1.00 mmol) and then toluene (6 ml) were added to a Radleys® Carousel tube under nitrogen. The reaction was warmed to 45 °C (external temperature), the appropriate diarylzinc solution (THF, 0.25M, 1.00 mmol) was added in one portion and the mixture stirred for 4 hours. The reaction was quenched with H_2O (5 ml) and the organic component extracted with CH_2Cl_2 (2 x 10 ml), dried over $MgSO_4$ and then filtered. Trimethoxybenzene (1.00 ml, 1.00 M in CH_2Cl_2) was added as an internal standard. An aliquot (2 ml) was removed from which the solvent was removed at room temperature under reduced pressure. The residue was dissolved in $CDCl_3$ (approx. 0.7 ml) and the conversion to coupled product was determined by ^{1}H NMR spectroscopy. Alternatively the crude product obtained after the filtration step was purified by flash chromatography.

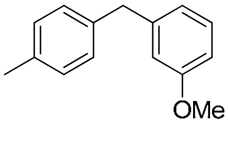
General procedure for the iron-catalysed Negishi coupling with *in situ* formed diarylzinc reagents (GP2). To a THF solution of anhydrous $ZnCl_2$ (0.5M, 2 ml) in a Radleys® Carousel tube under nitrogen was added the appropriate arylmagnesium halide (Et_2O solution, 1.5M, 2.00 mmol) and the mixture stirred for 1 hour at room temperature. Complex **6** (0.050 g, 0.05 mmol), the appropriate benzyl halide (1.00 mmol) and toluene (6 ml) were added. The reaction was warmed to 45 °C (external temperature) and stirred for 4 hours. Analysis and/or work-up as described in **GP1**.

General procedure for the iron-catalysed Negishi coupling with *in situ* formed $Zn(\kappa^2\text{-}N,C\text{-}Me_2NCH_2C_6H_4)$(4-tol), 10 (GP3). *n*-Butyllithium (hexane, 2.5 M, 2.1 ml, 5.25 mmol) was placed in a flask under nitrogen. Diethyl ether (10 ml) and *N,N*-dimethylbenzylamine (0.675 g, 5.00 mmol) were added at room temperature and the resulting mixture was stirred at room temperature for 20 hours. An anhydrous zinc chloride solution (THF, 0.7 M, 7.2 ml, 5.00 mmol) was added and after 1 hour of stirring, the resultant solution of solution of $ZnCl(\kappa^2\text{-}N,C\text{-}Me_2NCH_2C_6H_4)$ was ready for use. 2 ml of the solution (~1 mmol) was added slowly to a solution of 4-tolyl magnesium bromide (Et_2O, 1.5M, 0.67 ml) in a Radleys® Carousel tube under nitrogen and the resultant mixture was stirred for 1 hour, then complex **6** (0.050 g, 0.05 mmol), the appropriate benzyl halide and toluene (6 ml) were added, the reaction was warmed to 45 °C (external temperature) and stirred for 4 hours. Analysis and/or work-up as described in **GP1**.

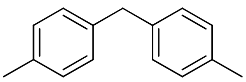
1-Benzyl-4-methylbenzene. Prepared according to **GP1** using benzyl bromide (0.171 g, 1.00 mmol) and di-*p*-tolylzinc (4.00 ml, 0.25 M in THF, 1.00 mmol). Purification by flash chromatography (silica, hexane/ethyl acetate 98:2) yielded the coupling product as a colourless oil (0.138 g, 76%). NMR: δ_H (400 MHz, $CDCl_3$) 7.29 (m, 2H) 7.18 (m, 3H) 7.10 (s, 4H), 3.96 (s, 2H), 2.33 (s, 3H); δ_C (100 MHz, $CDCl_3$) 21.0, 41.5, 125.9, 128.4, 128.8, 128.9, 129.1, 135.5, 138.0, 141.4. HRMS-EI: (m/z): $[M]^+$ calcd. for $C_{14}H_{14}$, 182.1096; found, 182.1102.



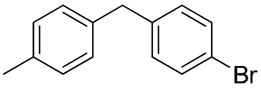
1-Methoxy-3-(4-methylbenzyl)benzene. Prepared according to **GP1** using 3-methoxybenzyl bromide (0.201 g, 1.00 mmol) and di-*p*-tolylzinc (4.00 ml, 0.25 M in THF, 1.00 mmol). Purification by flash chromatography (silica, hexane/ethyl acetate 98:2) yielded the coupling product as a colourless oil (0.195 g, 92%). NMR: δ_H 7.22 (dd, *J* = 8.8 Hz, 1H) 7.12 (s, 4H), 6.76-6.82 (m, 3H), 3.94 (s, 2H), 3.79 (s, 3H), 2.34 (s, 3H); δ_C (100 MHz, $CDCl_3$) 21.0, 41.5, 55.1, 111.2, 114.7, 121.3, 128.8, 129.1, 129.4, 135.5, 137.8, 143.0, 159.7. HRMS-EI: (m/z): $[M]^+$ calcd. for $C_{15}H_{16}O$, 212.1201; found, 212.1208.



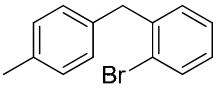
Di-*p*-tolylmethane. Prepared according to **GP1** using 4-methylbenzyl bromide (0.185 g, 1.00 mmol) and di-*p*-tolylzinc (4.00 ml, 0.25 M in THF, 1.00 mmol). Purification by flash chromatography (silica, hexane) yielded the coupling product as a colourless oil (0.169 g, 86%). NMR: δ_H 7.12 (s, 8H), 3.94 (s, 2H), 2.35 (s, 6H); δ_C (100 MHz, $CDCl_3$) 21.0, 41.1, 128.7, 129.1, 135.4, 138.3. HRMS-EI: (m/z): $[M]^+$ calcd. for $C_{15}H_{16}$,196.1252; found, 196.1250.



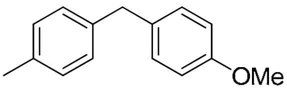
1-Bromo-4-(4-methylbenzyl)benzene. Prepared according to **GP1** using 4-bromobenzyl bromide (0.250 g, 1.00 mmol) and di-*p*-tolylzinc (4.00 ml, 0.25 M in THF, 1.00 mmol). Purification by flash chromatography (silica, hexane/ethyl acetate 99:1) yielded the coupling product as a colourless oil (0.208 g, 80%). NMR: δ_H 7.43 (d, *J* = 8.31 Hz, 2H) 7.05-7.18 (m, 6H), 3.93 (s, 2H), 2.36 (s, 3H); δ_C (100 MHz, $CDCl_3$) 21.0, 40.9, 119.8, 128.7, 129.2, 130.6, 131.5, 135.8, 137.4, 140.4. HRMS-EI: (m/z): $[M]^+$ calcd. for $C_{14}H_{13}{}^{79}Br$, 260.0201; found, 260.0192.



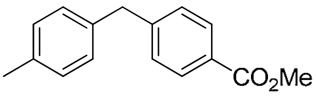
1-Bromo-2-(4-methylbenzyl)benzene. Prepared according to **GP2** using 2-bromobenzyl bromide (0.250 g, 1.00 mmol) and tolylmagnesium chloride (1.00 ml, 2.00 M in THF, 2.00 mmol) and zinc chloride (1.43 ml, 0.7 M in THF, 1.00 mmol). Purification by flash chromatography (silica, heptane/ethyl acetate 99.5:0.5) yielded the coupling product as a colourless oil (0.211 g, 81%). Further prepared according to **GP1** using 2-bromobenzyl bromide (0.250 g, 1.00 mmol) and di-*p*-tolylzinc (4 ml, 0.25 M in THF, 1.00 mmol), 94% spectroscopic yield. NMR: δ_H 7.58 (d, *J*= 7.95 Hz, 1H) 7.22-7.24 (m, 1H), 7.09-7.16 (m, 6H), 4.10 (s, 2H), 2.34 (s, 3H); δ_C (100 MHz, $CDCl_3$) 21.0, 41.3, 124.9, 127.4, 127.8, 128.9, 129.2, 131.0, 132.8, 135.7, 136.4, 140.6. HRMS-EI: (m/z): $[M]^+$ calcd. for $C_{14}H_{13}{}^{79}Br$, 260.0201; found, 260.0199.



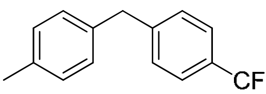
1-Methoxy-4-(4-methylbenzyl)benzene. Prepared according to **GP1** using 4-methoxybenzyl bromide (0.201 g, 1.00 mmol) and di-*p*-tolylzinc (4 ml, 0.25 M in THF, 1.00 mmol). Purification by flash chromatography (silica, hexane/ethyl acetate 99:1) yielded the coupling product as a colourless oil (0.136 g, 64%). NMR: δ_H 7.07-7.16 (m, 6H) 6.83-6.88 (m, 2H), 3.92 (s, 2H), 3.81 (3 H), 2.34 (s, 3H); δ_C (100 MHz, $CDCl_3$) 21.0, 40.6, 55.2, 113.8, 128.7, 129.1, 129.8, 133.5, 135.4, 138.5, 157.9. HRMS-EI: (m/z): $[M]^+$ calcd. for $C_{15}H_{16}O$, 212.1201; found, 212.1210.



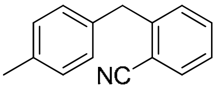
Methyl-4-(4-methylbenzyl)benzoate. Prepared according to **GP1** using methyl 4-(bromomethyl)benzoate (0.229 g, 1.00 mmol) and di-*p*-tolylzinc (4 ml, 0.25 M in THF, 1.00 mmol). Purification by flash chromatography (silica, hexane/ethyl acetate 95:5) yielded the coupling product as a colourless solid (0.166 g, 69%). NMR: δ_H 7.96 (d, *J*= 8.31 Hz, 2H), 7.25 (d, *J*= 7.83 Hz, 2H), 7.05-7.15 (m, 4H), 4.00 (s, 2H), 3.91 (3H), 2.33 (s, 3H); δ_C (100 MHz, $CDCl_3$) 21.0, 41.5, 52.0, 127.0, 128.8, 128.9, 129.3, 129.8, 135.9, 137.1, 146.8. HRMS-EI: (m/z): $[M]^+$ calcd. for $C_{16}H_{16}O_2$, 240.1150; found, 240.1154.



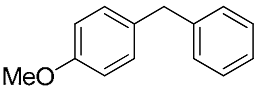
1-Methyl-4-(4-(trifluoromethyl)benzyl)benzene. Prepared according to **GP1** using 4-(trifluoromethyl)benzyl bromide (0.239 g, 1.00 mmol) and di-*p*-tolylzinc (4 ml, 0.25 M in THF, 1.00 mmol). Purification by flash chromatography (silica, hexane/ethyl acetate 99:1) yielded the coupling product as a colourless oil (0.146 g, 59%). NMR: δ_H 7.55 (d, *J*= 8.07 Hz, 2H), 7.31 (d, *J*= 7.83 Hz, 2H), 7.06-7.17 (m, 4H), 4.01 (s, 2H), 2.35 (s, 3H); δ_C (100 MHz, $CDCl_3$) 21.0, 41.3, 125.3 (q, *J*= 3.9 Hz), 126.8, 128.8, 129.3, 129.4, 136.0, 138.3, 145.5. HRMS-EI: (m/z): $[M]^+$ calcd. for $C_{15}H_{13}F_3$, 250.0969; found, 250.0961.



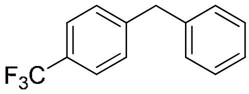
2-(4-Methylbenzyl)benzonitrile. Prepared according to **GP1** using 2-(bromomethyl)benzonitrile (0.196 g, 1.00 mmol) and di-*p*-tolylzinc (4 ml, 0.25 M in THF, 1.00 mmol). Purification by flash chromatography (silica, hexane/ethyl acetate 95:5) yielded the coupling product as a colourless solid (0.150 g, 73%). NMR: δ_H 7.63 (d, *J* = 7.34 Hz, 1H), 7.45-7.52 (m, 1H), 7.25-7.32 (m, 2H), 7.13 (s, 4H), 4.17 (s, 2H), 2.33 (s, 3H); δ_C (100 MHz, $CDCl_3$) 21.0, 39.8, 112.44, 118.2, 126.7, 128.8, 129.4, 129.9, 132.8, 135.7, 136.2, 145.3. HRMS-EI: (m/z): $[M]^+$ calcd. for $C_{14}H_{14}$, 207.1048; found, 207.1053.



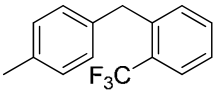
4-Benzylanisole. Prepared according to **GP1** using benzyl bromide (0.171 g, 1.00 mmol) and di-(*p*-methoxyphenyl)zinc (4 ml, 0.25 M in THF, 1.00 mmol). Purification by flash chromatography (silica, heptane/ethyl acetate 98:2) yielded the coupling product as a colourless oil (0.188 g, 95%). NMR: δ_H 7.28 (m, 2H), 7.20 (m, 3H) 7.12 (d, *J* = 8.56 Hz, 2H), 6.85 (d, *J* = 8.56 Hz, 2H), 3.95 (s, 2H), 3.79 (s, 3H); δ_C (100 MHz, $CDCl_3$) 41.0, 55.2, 113.9, 126.0, 128.4, 128.8, 129.8, 133.3, 141.6, 158.0. HRMS-EI: (m/z): $[M]^+$ calcd. for $C_{14}H_{14}O$, 198.1045; found, 198.1040.



4-Benzyl-1-(trifluoromethyl)benzene. Prepared according to **GP1** using benzyl bromide (0.171 g, 1.00 mmol) and di-(*p*-(trifluoromethyl)phenyl)zinc (4 ml, 0.25 M in THF, 1.00 mmol). Purification by flash chromatography (silica, heptane/ethyl acetate 98:2) yielded the coupling product as a colourless oil (0.124 g, 58%). NMR: δ_H 7.54 (d, *J* = 8.07 Hz, 2H), 7.16-7.35 (m, 7H), 4.05 (s, 2H); δ_C (100 MHz, $CDCl_3$) 41.7, 125.4 (q, *J*= 3.8 Hz), 126.5, 127.6, 128.3, 128.7, 128.9, 129.2, 140.0, 145.2. HRMS-EI: (m/z): $[M]^+$ calcd. for $C_{14}H_{11}F_3$, 236.0813; found, 236.0815.



1-Methyl-4-(2-(trifluoromethyl)benzyl)benzene. Prepared according to **GP2** using 2-(trifluoromethyl)benzyl bromide (0.239 g, 1.00 mmol)) and tolylmagnesium chloride (1.00 ml, 2.00 M in THF, 2.00 mmol) and zinc chloride (1.43 ml, 0.7 M in THF, 1.00 mmol). Purification by flash chromatography (silica, heptane/ethyl acetate 99.5:0.5) yielded the coupling product as a colourless oil (0.161 g, 64%). Further prepared according to **GP1** using 2-(trifluoromethyl)benzyl bromide (0.239 g, 1.00 mmol) and di-*p*-tolylzinc (4 ml, 0.25 M in THF, 1.00 mmol), spectroscopic yield, 85%. NMR: δ_H 7.67 (d, *J*= 7.8 Hz, 1H), 7.43 (t, *J*= 7.5 Hz, 1H), 7.30 (t, *J*= 7.6 Hz, 1H), 7.18 (d, *J*= 7.6 Hz, 1H), 7.04-7.13 (m, 4H), 4.15 (s, 2H), 2.34 (s, 3H); δ_C (100 MHz, $CDCl_3$) 21.0, 37.3, 123.2, 125.8 (q, *J*= 5.8 Hz), 126.0, 126.1, 129.0, 129.2, 131.6, 131.7, 135.8, 136.8, 139.8. HRMS-EI: (m/z): $[M]^+$ calcd. for $C_{15}H_{13}F_3$, 250.0969; found, 250.0970.



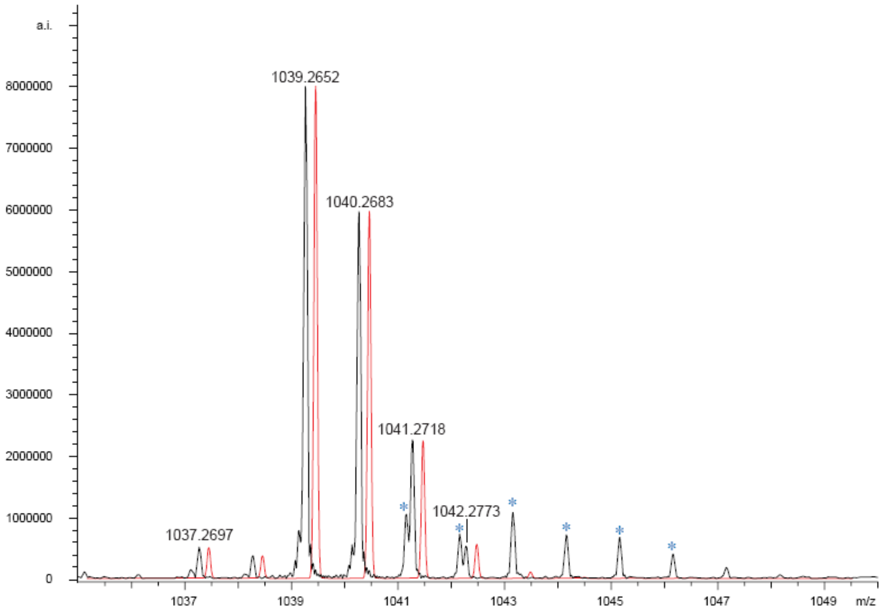


Figure S1. Part of High-resolution ESI MS of a mixture of **6** and 2 equiv. of **2**. The red trace shows calculated isotope distribution for Fe(tol)(dppz)2]+ (offset). Peaks marked '*' correspond to an undetermined species.

References

1. J. E. Barclay, G. J. Leigh, A. Houlton and J. Silver, *J. Chem. Soc., Dalton Trans.* 1988, 2865.
2. P. M. Castro, M. P. Lankinen, M. Leskelä and T. Repo, *Macromol. Chem. Phys.* 2005, **206**, 1090.
3. Value for χ_{corr} calculated using: G. A. Bain, J. F. Berry, *J. Chem. Ed.*, **2008**, *85*, 532.