Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Palladium-catalysed ether synthesis using alkoxy silanes as nucleophiles

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Supplementary Information

General Information

An inert atmosphere of N_2 or argon and Schlenk line techniques were used throughout preparative procedures. In vacuo refers to the use of a Heidolph® Labrota 4000 rotary evaporator with a KNF® Laboport pump or a vacuum line equipped with an Edwards rotary vane high vacuum pump. Flash chromatography was performed using SiliaFlash® P60 silica gel 43-65 μ, 60 Å (Fluorochem) or Alumina (Brockmann I) 150 mesh, 58 Å (Sigma-Aldrich). Solvents were degassed by several freeze thaw cycles before use and purified via alumina columns in a Grubbs system still (Braun MSB 8000) or distilled from sodium-benzophenone (diethyl ether, THF), sodium (toluene), or CaH_2 (CH_2Cl_2). Silyl-ethers and tetra-alkoxysilanes were purchased from Aldrich or Alfa Aesar, kept under an inert atmosphere and used without further purification. All phosphine and ferrocene based ligands were purchased from Strem or Aldrich, stored under argon and used without further purification.

Reaction reflux conditions were obtained by using an oil bath equipped with a contact thermometer. All microwave syntheses were carried out in a Biotage® Initiator microwave reactor using heavy-walled reactor vials equipped with an air tight seal. The temperature was measured by an infrared temperature probe which measured the temperature on the surface of the vial. The pressure was measured by directly reading the deflection of the septa on the vial, using a load cell behind the inner part of the cavity lid. Sealed tube experiments were also carried out in Biotage® heavy-walled reactor vials equipped with an air tight seal.

^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker® Avance DPX 300/Avance II 400 Ultrashield spectrometer at 298K in the deuterated solvent stated and referenced to $Si(CH_3)_4$, residual solvent resonances (^{1}H) or external references (^{13}C). Signal positions were recorded in δ p.p.m with the abbreviations s, bs, d, dd, t, q, br and m denoting singlet, broad singlet, doublet, doublet of doublets, triplet, quartet, broad and multiplet respectively. All coupling constants, *J* are quoted in Hertz (Hz).

GC-MS spectra were acquired with an Agilent® 6890+ Series GC system equipped with an Agilent® 5973 Network Mass Selective Detector (MSD). Using a Supelco® MDN-35 column, (30 m x 250 μm, 0.25 μm) and He as the carrier gas at a constant flow rate of 1 mL/min. The temperature was ramped up to 250°C, using an injection of 1 μL of sample.

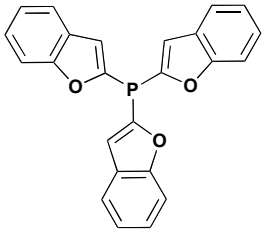
An Extended table of results is shown below:

Table 1. Effect of different pre-catalysts in the coupling of vinyl-trimethoxy silane with *para*-bromoacetophenone.[a]

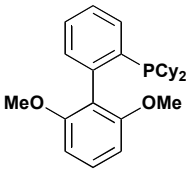
Entry	Pd source	Ligand (mol%)	NaOH (eq)	T (^{o}C)	Conversion to methyl ether (%)
1	$Pd(OAc)_2$	PPh_3 (2)	2.5	75	16
2	$Pd(OAc)_2$	PCy_3 (2)	2.5	75	10
3	$Pd(OAc)_2$	S-Phos (2)	2.5	75	8
4	$Pd(OAc)_2$	2-pyridyl-diphenyl P (2)	2.5	75	12
5	$Pd(OAc)_2$	*tris-(p*-methoxyphenyl) P (2)	2.5	75	18
6	$Pd(OAc)_2$	*tris*-(3,5-ditrifluoromethylphenyl) P (2)	2.5	75	7
7	$Pd(OAc)_2$	*tris*-(2-benzofuranyl) P (2)	2.5	75	0
8	$Pd(OAc)_2$	2-pyridyl-diphenyl P (2)	2.5	75	12
9	$Pd(OAc)_2$	Dppe (1)	2.5	75	16
10	$Pd(OAc)_2$	Dppb (1)	2.5	75	9
11	$Pd(OAc)_2$	Dcype (1)	2.5	75	21
12	$Pd(OAc)_2$	Dppf (1)	2.5	75	20
13	$Pd(OAc)_2$	Dippf (1)	2.5	75	38
14	$Pd(OAc)_2$	Dtbpf (1)	2.5	75	40
15	$Pd(OAc)_2$	Dtbdppf (1)	2.5	75	42
16	$Pd(OTfac)_2$	Dtbdppf (1)	2.5	75	9
17	$Pd(dba)_2$	Dtbdppf (1)	2.5	75	17
18	$[Pd(Dtbdppf)Cl_2]$	N/A	2.5	75	20
19	$Pd(OAc)_2$	Dtbdppf (3)	2.5	75	29
20	$Pd(OAc)_2$	Dtbdppf (2)	2.5	75	59
21[b]	$Pd(OAc)_2$	Dtbdppf (2)	2.5	105	77
22[b]	$Pd(OAc)_2$	Dtbdppf (2)	2.5	75	80
23[b,c]	$Pd(OAc)_2$	Dtbdppf (2)	2.5	130	84
24[d]	$Pd(OAc)_2$	Dtbdppf (2)	2.5	105	95
25[b,]	$Pd(OAc)_2$	Dtbdppf (2)	1.25	105	85
26[e]	$Pd(OAc)_2$	Dtbdppf (2)	2.5	80	45
27[f]	$Pd(OAc)_2$	Dtbdppf (2)	2.5	80	44
28[g]	$Pd(OAc)_2$	Dtbdppf (2)	2.5	100	60
29[h]	$Pd(OAc)_2$	Dtbdppf (2)	2.5	80	53
30[i]	$Pd(OAc)_2$	Dtbdppf (2)	2.5	120	33
31[j]	$Pd(OAc)_2$	Dtbdppf (2)	2.5	105	20
32	$Pd(OAc)_2$	Dtbdppf (2)	5	105	0
33	$Pd(OAc)_2$	Dtbdppf (2)	2.5	105	77
34	$Pd(OAc)_2$	Dtbdppf (2)	1.25	105	85
35	$Pd(OAc)_2$	Dtbdppf (2)	0.625	105	60
36	$Pd(OAc)_2$	Dtbdppf (2)	3.5	105	0
37	$Pd(OAc)_2$	Dtbdppf (2)	5	105	0
38	$Pd(OAc)_2$	Dtbdppf (2)	7.5	105	0
39	$Pd(OAc)_2$	Dtbdppf (2)	10	105	0
40[k]	$Pd(OAc)_2$	Dtbdppf (2)	1.25	105	46
41[l]	$Pd(OAc)_2$	Dtbdppf (2)	1.25	105	75
42[m]	$Pd(OAc)_2$	Dtbdppf (2)	1.25	105	85

[a] Conditions: 1 mol% Pd precursor, ligand as described in column 3, 1.5 equiv. vinyltrimethoxysilane, 2.5 equiv. NaOH unless otherwise indicated, 0.5 mmol *p*-xylene internal standard, stirred at the temperature indicated in THF for 16 hours unless otherwise indicated [b] toluene used as solvent at temperature indicated. [c] reaction carried out in a sealed tube; 74% yield after chromatography. [d] toluene used as solvent and microwave heating for 20 minutes. [e] butan-2-one [f] EtOH [g] H_2O [h] THF [i] THF + $NaOH_{(aq)}$ [j] Me-THF [k] 4h reflux in toluene [l] 6h reflux in toluene [m] 8h reflux in toluene.

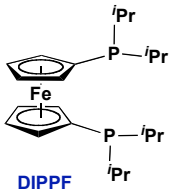
Figure 1. Examples of ligands used:



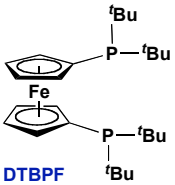
tribenzofuran-2-ylphosphine



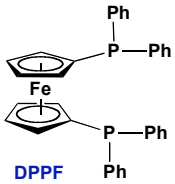
S-phos



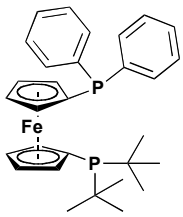
DIPPF



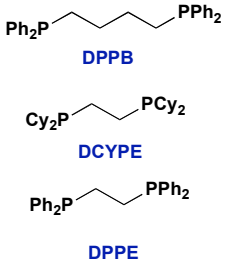
DTBPF



DPPF



DTBDPPF



Uaing the general procedures described in the paper, the following compounds were isolated in and characterised.

1-(4-Methoxyphenyl)-ethanone
The title compound was prepared according to general procedure A, using 4-bromoacetophenone (0.2 g, 1 mmol) and vinyltrimethoxysilane (1.5 eq, 0.223 g, 0.23 mL, 1.5 mmol) and purified by column chromatography (Hexane:Et_2O= 9:1) to give a colourless oil (0.111 g, 74 % yield).[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ= 2.48 (3H, s), 3.79 (3H, s), 6.86 (2H, d, *J*= 8.9 Hz), 7.86 (2H, d, *J* = 9 Hz); ^{13}C NMR (121 MHz, $CDCl_3$) δ= 25.3, 34.4, 112.6, 129.3, 129.6, 162, 197; MS (EI): m/z (%): 150.07 (100.0) [M^+], 151.07 (9.9)

1-(4-Ethoxyphenyl)-ethanone
The title compound was prepared according to general procedure B, using 4-bromoacetophenone (0.2 g, 1 mmol) and vinyltriethoxysilane (1.5 eq, 0.246 g, 0.31 mL, 1.5 mmol) and purified by column chromatography (Hexane:Et_2O= 9:1) to give a colourless crystalline solid (0.126 g, 77 % yield).[1] ^{1}H NMR (300 MHz, $CDCl_3$) δ= 1.38 (3H, t, *J* = 7 Hz), 2.50 (3H, s), 4.03 (2H, q, *J* = 7 Hz), 6.86 (2H, d, *J* = 9 Hz), 7.86 (2H, d, *J* = 9 Hz); ^{13}C NMR (121 MHz, $CDCl_3$) δ= 13.7, 25.6, 62.7, 113.1, 129.6, 161.9, 198; MS (EI) m/z (%): 164.08 (100.0) [M^+], 165.09 (11)

1-(4-*n*-Propoxyphenyl)-ethanone
The title compound was prepared according to general procedure B, using 4-bromoacetophenone (0.2 g, 1 mmol) and tetra-*n*-propoxysilane (1.5 eq, 0.267 g, 0.43 mL, 1.5 mmol.) and purified by column chromatography (Hexane:Et_2O= 9:1) to give a colourless oil (0.116 g, 65 % yield).[2]
^{1}H NMR (300 MHz, $CDCl_3$) δ= 0.98 (3H, t, *J* = 7 Hz), 1.77 (2H, septet, *J* = 7 Hz), 2.48 (3H, s), 3.92 (2H, t, *J* = 6.7 Hz), 6.86 (2H, d, *J* = 9 Hz), 7.86 (2H, d, *J* = 9 Hz); ^{13}C NMR (121 MHz, $CDCl_3$) δ= 9.4, 21.4, 25.3, 68.7, 113.1, 129.1, 129.6, 162.1, 195.8; MS (EI) m/z (%): 178.1 (100.0) [M^+], 179.1 (12)

1-(4-*n*-Butoxyphenyl)-ethanone
The title compound was prepared according to general procedure B, using 4-bromoacetophenone (0.2 g, 1 mmol), tetra-*n*-butoxysilane (1.5 eq, 0.288 g, 0.53 mL, 1.5 mmol) and TBAF (1M solution in THF) (3eq, 3 mL, 3mmol) as an activator and purified by column chromatography (Hexane:Et_2O= 9:1) to give a colourless oil (0.140 g, 73 % yield).[3] ^{1}H NMR (300 MHz, $CDCl_3$) δ= 0.85 (3H, t, *J* = 7.5 Hz), 1.30 (2H, sextet, *J* = 7.5 Hz), 1.49 (2H, quintet, *J* = 6.6 Hz), 2.50 (3H, s), 3.70 (2H, t, *J* = 6.8 Hz), 7.39 (2H, d, *J* = 8.3 Hz), 7.90 (2H, d, *J* = 8.3 Hz); ^{13}C NMR (121 MHz, $CDCl_3$) δ= 14.2, 19.6, 26.8, 31.54, 68.4, 114.5, 131, 163.5, 197.3; MS (EI) m/z (%): 192.12 (100.0) [M^+], 193.12 (13.0)

1-Methoxy-4-nitrobenzene
The title compound was prepared according to general procedure B, using 4-bromonitrobenzene (0.202 g, 1 mmol) and vinyltrimethoxysilane (1.5 eq, 0.223g, 0.23 mL 1.5 mmol) and purified by column chromatography (Hexane:Et_2O= 9:1) to give a colourless solid (0.129 g, 84 % yield).[4] ^{1}H NMR (400 MHz, $CDCl_3$) δ= 3.91 (3H, s), 6.96 (2H, d, *J* = 9 Hz), 8.20 (2H, d, *J* = 9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 59.9, 114.0, 125.9, 141.5, 164.5; MS (EI) m/z (%) = 153.04 (100.0) [M^+], 154.05 (7.8)

4-Methoxybenzonitrile
The title compound was prepared according to general procedure B, using 4-bromobenzonitrile (0.182 g, 1 mmol) and vinyltrimethoxysilane (1.5 eq, 0.223 g, 0.23 mL, 1.5 mmol) and purified by column chromatography (Hexane:Et_2O= 9:1) to give a pale yellow solid (0.097 g, 73 % yield).[5]
^{1}H NMR (300 MHz, $CDCl_3$) δ= 3.80 (3H, s), 6.88 (2H, d, *J* = 9 Hz), 7.52 (2H, d, *J* = 9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 54.5, 102.9, 113.7, 118.7, 132.9, 161.8; MS (EI) m/z (%): 133.05 (100.0) [M^+], 134.06 (8.8)

Methyl-4-methoxybenzoate

The title compound was prepared according to general procedure B, using methyl-4-bromobenzoate (0.215 g, 1 mmol) and vinyltrimethoxysilane (1.5 eq, 0.223 g, 0.23 mL, 1.5 mmol) and purified by column chromatography (Hexane:AcOEt= 6:1) to give a colourless solid (0.110 g, 66% yield).[6] ^{1}H NMR (400 MHz, $CDCl_3$) δ= 3.85 (3H, s), 3.88 (3H, s), 6.91 (2H, d, *J* = 9.0 Hz), 7.99 (2H, d, *J* = 9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 51.8, 55.4, 113.5, 122.6, 131.5, 163.3, 166.8; MS (EI) m/z (%): 166.07 (100.0) [M^+], 167.07 (10.0), 168.07 (1.0)

2-Methoxybenzonitrile
The title compound was prepared according to general procedure B, using 2-chlorobenzonitrile (0.181 g, 0.13 mL, 1 mmol) vinyltrimethoxysilane (0.223 g, 0.23 mL, 1.5 mmol) and purified by column chromatography (Hexane:Et_2O= 9:1) to give a colourless solid (0.096 g, 72 % yield).[8] ^{1}H NMR (300 MHz, $CDCl_3$) δ= 3.92 (3H, s), 6.96-7.0 (2H, m), 7.51-7.59 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 54.9, 100.7, 110.3, 115.5, 119.7, 132.7, 133.4, 160.2; MS (EI) m/z (%): 133.05 (100.0) [M^+], 134.06 (8.8)

4-ethoxynitrobenzene
The title compound was prepared according to general procedure X and purified by column chromatography (Hexane:Et_2O= 10:1) to give an white crystalline solid (81 % yield).[9]
^{1}H NMR (400 MHz, $CDCl_3$) δ= 1.39 (3H, t, *J* 7.0 Hz), 4.06 (2H, q, *J* 7.0 Hz), 6.86 (2H, d, *J* 9.2 Hz), 8.11 (2H, d, *J* 9.2 Hz); ^{13}C NMR (100 MHz, CDCl3) δ= 15.0, 64.8, 114.8, 126.3, 141.7, 164.5.

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