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Investigations into Ambient Temperature Biaryl Coupling Reactions

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Abstract: An ambient temperature, unsymmetrical, biaryl coupling reaction for hindered systems based on Suzuki methodology has been developed. A description of the optimisation of this process leading to the recommendation of aqueous thallium hydroxide as base, in dimethylacetamide, with hindered boronic acids and aryl halides to achieve good to moderate yields of hindered biaryls is presented, along with an interpretation of the reaction conditons. The yields of hindered Stille biaryl coupling reactions seemed to be little enhanced by the use of less coordinating ligands such as tri-2-furylphosphine and triphenylarsine.

INTRODUCTION

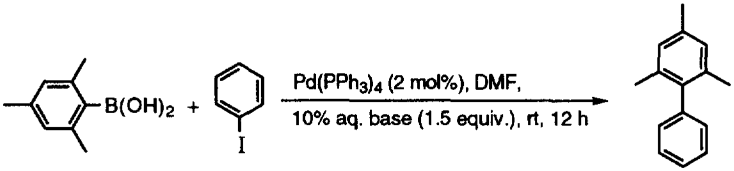
Axially chiral biaryl compounds are an important constituent of many biologically active natural products[1] and chiral ligands for asymmetric synthesis.[2] There is currently a geat deal of interest in the development of efficient methods for the synthesis of biaryls in atropisomerically pure form. Methods reported include the use of; asymmetric nucleophilic aromatic substitutions,[3] stereocontrolled torsion of lactones by optically active ring opening nucleophiles,[4] enantiomerically pure planar chiral arene chromium complexes,[5] cyanocuprate mediated intramolecular coupling[6] and enantioselective oxidative coupling.[2e] Probably the most powerful method of constructing an unsymmetrical biaryl axis is through the transition metal catalysed cross coupling between an aryl electrophile and aryl nucleophile.[7] This methodology coupled with the use of chiral ligands has produced some atropisoselective biaryl couplings through the direct formation of the biaryl bond[8] and through the symmetry breaking of meso substrates.[9] In palladium catalysed biaryl cross coupling reactions the nucleophilic partner is commonly an aryl boronic acid (Suzuki reaction[10]) or an arylstannane (Stille reaction[11]). However these particular biaryl bond forming reactions require high temperatures[12,13] which would not be compatible with any atropisoselective biaryl coupling induced by chiral ligands on palladium, as the biaryl axis is sensitive to heat.[14] Consequently we investigated methods of conducting the Suzuki biaryl coupling reaction at ambient temperature and reported a preliminary procedure.[15] In this paper we detail in full our studies of this particular reaction and report our findings concerning the Stille biaryl coupling.

MODIFICATIONS OF SUZUKI TYPE BIARYL COUPLINGS

Investigations started with the Suzuki reaction as the Stille reaction demands the stoichiometric use of tin which makes it less applicable to the pharmaceutical industry.

Base effect. From Suzuki's first report[16] it was suggested that base and water are essential for the coupling reaction to proceed at 80 °C. We investigated the use of various bases at room temperature using Suzuki's protocol.[12] We were also interested in sterically hindered biaryl couplings so all our investigations were conducted between sterically hindered mesitylboronic acid and phenyl iodide (Table 1).

Table 1. Effect of Base



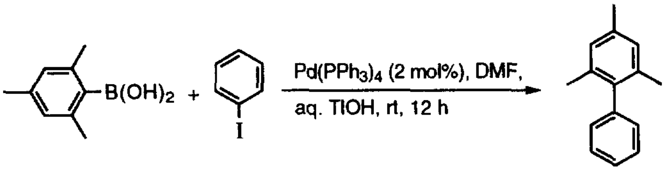
Entry	10% aq. Base	Yield/%[a]
1	Cs_2CO_3	0
2	K_3PO_4	24
3	$Ba(OH)_2$	10
4	NaOH	5
5	TlOH	68
6	Tl_2CO_3	11

[a]Isolated yields of pure products as judged by 1H nmr, based on iodobenzene

A considerable increase in yield was noted with the use of thallium (I) hydroxide[17] (CAUTION: Thallium is known to be toxic[18]) as base (entry 5) with respect to the more commonly used bases,[10,12,16] at room temperature. Thallium hydroxide was investigated as it is responsible for a dramatic rate enhancement in Suzuki vinyl-vinyl couplings.[19] Thallium (I) carbonate has also been used to good effect in Suzuki aryl-vinyl couplings[20] but at ambient temperature, under our chosen conditions, it gave poor yields of coupled products.

Stoichiometry of TlOH. The quantity of TlOH in the standard experiments above was 1.5 mole equivalents. We investigated the effect of changing this stoichiometry (Table 2).

Table 2. Effect of Stoichiometry of TlOH



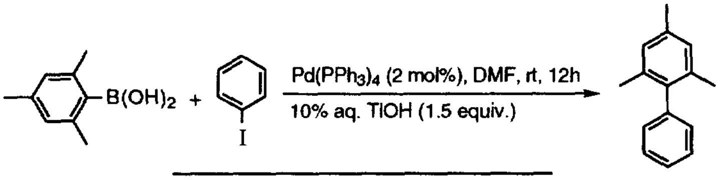
Entry	mmol TlOH	% aq. TlOH	Yield/%[a]
1	1.5	10	54
2	0.3	2	39
3	0.8	5	30
4	3.2	20	27

[a]Isolated yields of pure products as judged by 1H nmr, based on iodobenzene

In these experiments the amount of water remained constant and only the amount of TlOH was altered. Although this did not determine the exact amount of TlOH needed to give good yields, it is clear that more than 1 molar equivalent of base is needed and that too much of an excess retards the reaction. The use of 1.5 molar equivalents gave excellent yields when the solvent was changed (*vide supra*) and superseded any further stoichiometry studies. Reactions run without water, but in the prescence of 1.5 mole equivalents of TlOH or Tl_2CO_3 gave yields of 5% and 2% respectively. This suggests that in these room temperature reactions it is essential for water to solubilise the base for efficient reaction.

Solvent effects. As a matter of course the reaction was performed in a variety of solvents (Table 3).

Table 3. Effect of Solvent



Entry	Solvent	Yield/%[a]
1	DMA	92
2	DMF	68
3	DMPU	51
4	dioxane	48
5	NMP	40
6	benzene	30
7	DME	10

[a] Isolated yields of pure products as judged by 1H nmr, based on iodobenzene

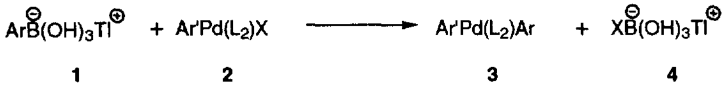
It is clear from the solvents screened that dimethylacetamide (DMA) gave good yield of coupled product. We can offer no reason why DMA gave far better yields than DMF or DMPU. Solvent polarity is not an issue as the dielectric constants for DMA, DMF and DMPU are all similar (38.9,[21] 38.3,[21] 36.1[22] respectively) and that of dioxane, which gives a yield very similar to DMPU (compare entries 3 and 4) is only 2.2.[21]

These results established a reliable room temperature coupling protocol requiring DMA as solvent and 1.5 mole equivalent of 10% aqueous TlOH. This amount of base contradicts a recent result that suggested for an efficient process to occur 2 mole equivalents of base are required.[23] One equivalent of base to activate the boronic acid (equation 1) and another equivalent required to neutralise the boric acid produced as a coupling byproduct (equation 2). It is well accepted that aryl boronic acids form borate complexes with hydroxide ion[24] and that this complex is more reactive in the transmetallation reaction.[25]

$$\mathrm{ArB(OH)_2} + \overset{\ominus}{\mathrm{O}}\mathrm{H} \longrightarrow \mathrm{Ar}\overset{\ominus}{\mathrm{B}}\mathrm{(OH)_3} \qquad (1)$$

$$\mathrm{B(OH)_3} + \overset{\ominus}{\mathrm{O}}\mathrm{H} \longrightarrow \overset{\ominus}{\mathrm{B}}\mathrm{(OH)_4} \qquad (2)$$

As we have less than two mole equivalents of base in our system and achieve a high yield this suggests that one equivalent of base is needed to activate the boronic acid, but another whole equivalent is not necessarily required to form the byproduct. Addition of 1 mole equivalent of NaBr to our room temperature reaction decreased the yield to 62%. As thallium(I) halides are sparingly soluble in water[26] we interpret this result as effectively removing one mole equivalent of TlOH from the reaction, giving sodium hydroxide and thallium(I) bromide. This would leave 0.5 mole equivalents of TlOH behind to perform the coupling. From our experiments investigating different bases we know NaOH gives poor yields of coupled products (Table 1, entry 4). In addition we also looked at using phenyl triflate in this procedure and obtained no yield of biaryl in the prescence of 1.5 molar equivalent of LiCl, NaCl or KBr[27] (incidentally nor without[28]). These results suggest a modified reaction scheme where the reaction between the borate complex **1** and the Pd(II) intermediate **2**, formed from the oxidative additon of Pd(0) to the aryl halide (Ar'X), produces the biaryl Pd(II) complex **3** and a thallium halogen borate complex **4**, that we believe is insoluble (equation 3). Our room temperature procedure produces a heavy precipitate but despite efforts we have been unable to acertain its exact composition.

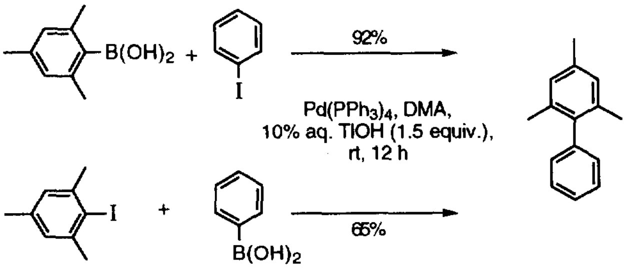


$$\underset{\mathbf{1}}{Ar\overset{\ominus}{B}(OH)_3Tl^{\oplus}} + \underset{\mathbf{2}}{Ar'Pd(L_2)X} \longrightarrow \underset{\mathbf{3}}{Ar'Pd(L_2)Ar} + \underset{\mathbf{4}}{X\overset{\ominus}{B}(OH)_3Tl^{\oplus}} \qquad (3)$$

Boron species. In our new procedure we found that the boronic acid function gave superior yields in comparison to di-*n*-butyl or tri-methylene glycol boronic acid esters (92% versus 84% and 72% respectively). In a control experiment we stirred mesitylboronic acid tri-methylene glycol ester with TlOH in DMA and found after 12 hours that we could isolate a 75% yield of the corresponding boronic acid. It would seem that the boronic acid is the active species in these coupling reactions.

The steric environment of the boronic acid in the coupling partner was probed by performing the coupling of phenyl boronic acid with mesityl iodide (Scheme 1).

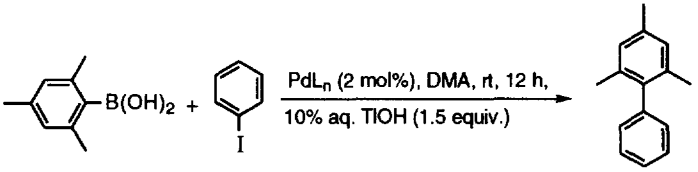
Scheme 1. Comparison of Steric Effects on Boronic Acid Coupling Partner



It seems that the more stercically hindered boronic acid gives a better yield and suggests that either the oxidative addition is rate determining or that the transmetallation step is sensitive to the steric environment of the oxidative addition product.

Ligand Effects: The mechanistic details of transition metal catalysed cross coupling reactions are still under investigation. The electronic and steric character of the ligands and the degree of coordination around the metal can all influence the success of the reaction. We assayed a host of conventional ligands in our standard reaction to probe the steric and electronic requirements of the palladium catalyst. The active catalysts were generated by mixing two or four equivalents of the required ligand with tris(dibenzylideneacetone)dipalladium chloroform.[29] Our results are summarised in table 4. Phosphine ligand free Suzuki type biaryl couplings at 65 °C have recently been published and give good yields.[30] However conducting this reaction as below with no ligand resulted in no yield of product.

Table 4. Effect of Palladium Catalyst



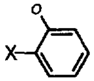
Entry	Ligand	Yield/%[a]	
		n=2	n=4
1	PPh_3	61	97
2	$AsPh_3$	17	51
3	tri-2-furylphosphine	32	85
4	n-Bu_3P	0	0
5	$(MeO)_3P$	0	0
6	$Ph_2P(CH_2)_2PPh_2$	30[b]	76[c]
7	dppf[d]	0[b]	0[c]

[a] Isolated yields of pure products as judged by 1H nmr, based on iodobenzene.
[b] n=1. [c] n=2. [d] dppf = 1,1'-bisdiphenylphosphinoferrocene.

In the accepted catalytic cycle of these types of transition metal coupling reactions, the oxidative addition requires an electron rich metal so that oxidation will be favourable.[31] Conversely the transmetallation presumably requires an electron-deficient palladium for the nucleophilic aryl boronate to attack the metal centre. Evidence would suggest that transmetallation is the rate determining step in cross couplings of synthetic interest.[32] Both oxidative addition and reductive elimination require ligand dissociation,[33] but the strong donor ligands, that are good at stabilising the Pd(0) intermediates, should dissociate less readily. Consequently the best ligands in a typical cross coupling reaction achieve a compromise between donor and dissociation ability. Coordinately unsaturated catalysts should have faster turnover rates if ligand dissociation is not intimately inolved in the rate determining step. In our experiments coordinately saturated catalysts performed much better (compare columns n=2 and n=4 in Table 4). Coordinately unsaturated catalysts may also suffer from catalyst decomposition, although this is normally thermal in nature.[29,34] It has been suggested that tri-2-furylphosphine ligands and especially triphenylarsine ligands accelerate the rate of certain coupling reactions due to their lower bond dissociation energies with respect to the Pd-PPh_3 bond and hence their greater ability to dissociate during the rate determining transmetallation step.[35] We see no such effect in our experiments and a chelate ligand (dppe) still gives good yields of coupled products. If ligand dissociation was intimately involved in the rate determining step of our reactions then the chelate effect should significantly reduce the effectiveness of the reaction. Presumably dppf (entry 7) has too large a bite angle to achieve efficient chelation. Our results suggest that if the transmetallation step is rate determining in this Suzuki type biaryl coupling then this step probably proceeeds via a one step associative mechanism[36] in which the aryl boronate **1** forms an unstable pentacoordinated intermediate upon attack of the initial oxidative addition product **2** which then releases the halide leaving group to give the diaryl palladium (II) intermediate **3**. This scenario would not require dissocaition of a ligand. It was pleasing to note that the combination of $Pd_2(dba)_3$ and 4 mole equivalents of triphenylphosphine gave a near quantitative yield of coupled product. For practical purposes we believe tetrakis(triphenylphosphine)palladium (0) would suit most purposes.

Electronic and Steric Effects of Aryl Halide Coupling Partner. To determine the scope of the coupling procedure substituted aromatic halides were coupled with mesityl boronic acid under our room temperature reaction conditions (Table 5).

Table 5. Synthesis of biaryls

Entry	Aryl halide	Yield/%[a]
		
1	X=Br, *p*=NO_2	77
2	X=Br, *p*=OMe	90
3	X=I, *p*=OMe	71
4	X=I, *p*=Cl	61
5	X=I, *p*=CO_2Me	73
		
6	X=Br, *o*=NO_2	83
7	X=I, *o*=NO_2	78
8	X=I, *o*=OMe	49
9	X=I, *o*=CO_2Me	35
10	X=Br, *o*=Me	10

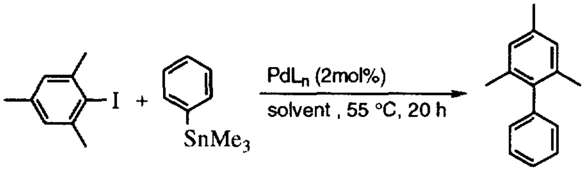
[a] Isolated yields of pure products based on aryl halides employed.

The coupling reaction was little affected by electron withdrawing or donating substituents (entries 1-5). The yield of coupled product between methyl-4-iodobenzoate and mesityl boronic acid (entry 5) was comparable to known mild procedures involving heat (81%),[12] indicating that under these ambient conditions there was little hydrolysis of the base sensitive ester functionality. The yields for the formation of tri-*ortho* substituted biaryls were moderate to good. An *o*-nitro substituent does not affect yields (entry 6), whereas *o*-methoxy and *o*-methylcarboxylate gave only moderate yields entries 8 and 9 respectively) and peculiarly an *o*-methyl substituent had a very delitirious affect on yield (entry 10). This suggests a subtle balance of sterics and electronics at this position. Disappointingly attempts to form tetra-*ortho*-substituted biaryls using this modification were unsuccessful.[37]

MODIFICATIONS OF STILLE TYPE BIARYL COUPLINGS

Following on from the report that a large rate acceleration (typically 10^2-10^3 over triphenylphosphine based catalysts) in the Stille reaction between aryl halides or triflates and vinyl stannanes can be observed by employing tri-2-furylphosphine or triphenylarsine ligands,[35] we investigated whether there could be a similar effect in biaryl couplings. Again we were interested in sterically hindered couplings so our probe reactions were conducted between iodomesitylene and phenyltrimehthylstannane. In direct contrast to our Suzuki studies the corresponding coupling reaction between mesityltrimethylstannane and iodobenzene was unproductive under the reaction conditions we employed. It was quickly ascertained that insignificant yields were obtained at room temperature and so conducted our experiments at a nominal 55 °C. We compared the yields of coupled product from using saturated and unsaturated palladium catalysts generated from tris(dibenzylideneacetone)dipalladium chloroform and either tri-2-furylphosphine, triphenylarsine or triphenylphosphine ligands in a range of solvents (Table 6).

Table 6. Ligand Effects in Stille Biaryl Coupling Reaction



Entry	Ligand	Solvent	Yield/%[a]	
			n=2	n=4
1	PPh$_3$	DMF	21	0
2	tri-2-furylphosphine	DMF	27	31
3	AsPh$_3$	DMF	25	24
4	PPh$_3$	NMP	23	0
5	tri-2-furylphosphine	NMP	27[b]	31
6	AsPh$_3$	NMP	21	29
7	tri-2-furylphosphine	THF	10	0
8	AsPh$_3$	THF	0	0
9	PPh$_3$	DMA	15	-
10	tri-2-furylphosphine	DMA	23	-
11	AsPh$_3$	DMA	25	-
12	tri-2-furylphosphine	DMF	-	19[c]
13	tri-2-furylphosphine	DMF	-	40[b,d]

[a]Crude yield from 1H NMR nmr room temperature. [b]Isolated yield. [c]Room temperature reaction. [d]CuI (1 mol equiv.) additive.

These results show that the the tri-2-furylphosphine and triphenylarsine ligands gave sligtly improved conditions over triphenylphosphine. Within experimental error there did not seem to be much difference in yield when using coordinately unsaturated or saturated catalysts with the tri-2-furylphosphine or triphenyl arsine ligands, although a dramatic effect was noted with triphenylphosphine (entries 1 and 4). The best reaction (entry 2, n=4) was repeated at room temperature to give a much decreased yield (entry 12, 19% compared to entry 2, 31%). In an attempt to improve the yield and in line with observations by others,[38] additives such as CuO, CuI, and Ag_2O, were incorporated into the reaction mixture. Only the incorporation of CuI improved the yield to a maximum of 40% isolated yield of biaryl compound (entry 13). At this point the investigation was halted as although the new ligands gave improved yields over triphenylphosphine, this procedure could not compete with the Suzuki chemistry.

CONCLUSIONS

The present study has more fully documented our previous observation of a Suzuki coupling procedure for certain hindered biaryls at room temperature.[15] The use of TlOH as base, in DMA, with hindered boronic acids gave good to moderate yields of biaryls. Boronic acids were found to be the best partners in this procedure as the corresponding esters required hydrolysis under the reaction conditions, which was comparable with the rate of the coupling reaction at room temperature. Two mole equivalents of base are not required, indicating that the nature of the thallium counter ion may play a role in this reaction, either forming insoluble thallium halide salts or **4**. The ligand effects suggested that dissociation of ligand during the reaction does not play an important role in the success of the reaction.

Investigation of Stille type biaryl couplings revealed that this process does not significantly benefit from the use of tri-2-furylarsine and triphenylarsine ligands as documented for vinyltrimethylstannanes.[35] In the light of these results it would seem that Suzuki type biaryl couplings provide the mildest procedure for preparing hindered biaryls in comparison to Stille type biaryl couplings.

EXPERIMENTAL

All reactions were performed under an oxygen-free atmosphere of nitrogen. Thin layer chromatography was carried out using Merck 5554 60F silica gel coated aluminium plates and visualisation was effected using ultra-violet light or by development using iodine, potassium permanganate solution or ceric ammonium molybdate solution. Flash chromatography[39] was performed on BDH silica gel for flash chromatography (40-63μm). ^1H and ^{13}C NMR spectra were recorded at 250 and 63 MHz respectively in $CDCl_3$ unless otherwise stated. Coupling constants are given in Hz. Elemental analyses were obtained in the Department of Chemistry at the University of Sheffield. Reagents and solvents were purified prior to use when necessary according to established procedures.[40] THF was distilled from K/benzophenone ketyl, Et_2O from Na/benzophenone ketyl, CH_2Cl_2 and Et_3N were distilled from CaH. Thallium (I) hydroxide was precipitated from a solution of thallium (I) formate and potassium hydroxide,[17] isolated as a yellow crystalline solid and immediately made into a 10% aqueous degassed solution. After ~1 week a precipitate would develop in the solution and yields were affected. Consequently degassed solutions were kept for no longer than 1 week. CAUTION: thallium is very toxic and all manipulations were carried out in an efficient fume cupboard and nitrile gloves were worn at all times.

Tetrakis(triphenylphosphine)palladium(0) and tris(dibenzylideneacetone)dipalladium(0) chloroform were prepared according to the procedures of Coulson[41] and Ishii[29] respectively. Mesitylboronic acid was prepared from the hydrolysis of the product from the addition of mesitylmagnesium bromide to tri-*n*-butyl borate.[42] Phenyl- and mesityl- trimethyl tin were prepared by transmetallation of the corresponding Grignard reagents with trimethyltin chloride.

Representative Coupling Procedure for TlOH Promoted Room Temperature Suzuki Type Biaryl Coupling

To a solution of $Pd(PPh_3)_4$ (0.02 mmol) and mesitylboronic acid (1.1 mmol) in DMA (6 ml) was added 10% aq. TlOH (3.5 ml) and aryl halide (1 mmol) under nitrogen. The heterogeneous reaction was allowed to stir overnight (~12 h) at room temperature. The biaryl was extracted with benzene, washed with brine and dried over $MgSO_4$. Purification was by conventional silica gel chromatography.

Base effects. The representative procedure was followed with the substitution of the appropriate 10% aqueous base solution.

Stoichiometry of TlOH. The representative procedure was followed with the substitution of the appropriate percentage solution of TlOH (3.5 ml).

Solvent effects. The representative procedure was followed with the substitution of the appropriate solvent.

Boron species. The representative procedure was followed with the substitution of phenylboronic acid (1.1 mmol) and iodomesitylene (1 mmol).

Ligand effects. A mixture of $Pd_2(dba)_3.CHCl_3$ (0.02 mmol), iodobenzene (1 mmol), mesitylboronic acid (1.1 mmol) and ligand (0.08 mmol for Pd:L = 1:2, or 0.16mmol for Pd:L = 1:4) were dissolved in DMA (6 ml) under nitrogen and stirred for 5 mins before the addition of 10% aq. TlOH (3.5 ml) under nitrogen. The reaction was stirred for 12 h before being worked up by the standard method above.

Data for Biaryls[43]

Only given for biaryls with no spectroscopic data in the literature.

2,4,6-trimethylbiphenyl

Isolated as colourless oil. 1H NMR δ 7.51-7.33 (3H, m); 7.15 (2H, dd, J=8.0, 1.5); 6.89 (2H, s), 2.43 (3H, s, *p*-CH_3); 2.10 (6H, s, 2x*o*- CH_3), MS (EI^+), 196 (M+), 181 (-CH_3), 165 (-2xCH_3), 152, 115, 77. $C_{15}H_{16}$ requires 196.1252 found 196.1261. υ_{max} (thin film) 3057, 3021, 2948, 2918, 2857, 1613, 1475, 1442, 1376, 1071 cm^{-1}.

2,4,6-trimethyl-2'-nitro biphenyl (Table 5, entry 6)

Isolated as yellowish crystals (mp. 47 °C), 1H NMR δ 7.98 (1H, dd, J= 8.0, 0.6); 7.65 (1H, td, J=8.7, 1.0); 7.50 (1H, td, 8.7, 1.0); 7.19 (1H, dd, J= 8.0, 0.6); 6.92 (2H, s); 2.30 (3H, s, *p*- CH_3); 1.93 (6H, s, 2x*o*- CH_3), MS (EI^+) 241 (M+), 226 (-CH_3), 210 (-O_2), 194, 179 , 165, 121 , 89, 76, $C_{15}H_{15}NO_2$ requires 241.1102, found 241.1111. υ_{max} (thin film) 3088, 2863, 1585, 1528, 1463, 1436, 1361, 1294, 1258, 1148, 1042 cm^{-1}.

2,4,6-trimethyl-2'-methoxy biphenyl (Table 5, entry 8)

Isolated as a colourless solid, mp 59°C, 1H NMR δ 7.24 (2H, m); 6.92 (2H, m); 6.37 (2H, s); 3.65 (3H, s, OCH_3), 2.25 (3H, s, *p*- CH_3); 1.89 (6H, s, 2x*o*- CH_3). MS (EI+) 226 (M^+), 211 (- CH_3), 195 (-OCH_3), 180, 165, 152, 105, 92, $C_{16}H_{18}O$ requires 226.1357, found 226.1367. ν_{max} 2993, 2953, 2834, 1608, 1584, 1572, 1515, 1468, 1459, 1286, 1245, 1174 cm^{-1}.

2,4,6-trimethyl-biphenyl-2'-carboxylic acid methyl ester (Table 5, entry 9)
Isolated as a white solid mp. 110 °C. 1H-NMR δ 7.77 - 7.56 (2H, m); 7.49 - 7.42 (2H, m); 6.95 (2H, s,); 3.62 (3H, s, OCH_3); 2.32 (3H, s, *p*- CH_3); 1.92 (6H, s, 2x*o*-CH_3). MS (EI+) 254 (M^+), 239 (-CH_3), 223 (-OCH_3), 195 (-$COOCH_3$), 180, 165, 119, 104. ν_{max} (thin film) 3034, 1718, 1609,1285, 1265, 1189, 1002 cm^{-1}.

2,4,6-trimethyl-2'-methylbiphenyl (Table 5, entry 10)
Isolated as colourless oil. 1H NMR δ 7.51-7.33 (2H, m); 7.21 (2H, m); 6.89 (2H, s), 2.45 (3H, s, *p*- CH_3); 2.15 (3H, s, *o*-CH_3); 2.08 (6H, s, 2x*o*- CH_3), MS (EI^+), 210 (M+), 195 (-CH_3), 180 (-2xCH_3), 148, 124, 77. ν_{max} (thin film) 3055, 3018, 2935, 2865, 1603, 1469, 1354, 1074 cm^{-1}.

General Procedure for Investigations into Stille Biaryl Coupling
Iodomesitylene (1 mmol), tris(dibenzylideneacetone) dipalladium(0) chloroform (0.02mmol) and ligand (0.08 mmol for Pd:L = 1:2, or 0.16mmol for Pd:L = 1:4) were dissolved in solvent (5ml) and the mixture stirred, under nitrogen at room temperature, for 30 minutes to preform the palladium/ligand complex. To the resulting bright yellow solution was then added phenyltrimethylstannane (1.1 mmol) and the reaction mixture sparged with nitrogen for a minute before being heated in an oil bath at 55°C for a period of 20 h. The now black reaction mixture was then allowed to cool before treatment with a 10% aqueous solution of potassium fluoride (5ml). After stirring for a further 30 m the reaction mixture was partitoned between ethyl acetate and water. The organic phase was then separated, washed sequentially with water and brine, filtered through celite®(if necessary) and dried over Na_2SO_4. Removal of solvent *in vacuo* yielded a brown oil. Percentage yield was calculated by ^{1}H NMR spectroscopy, through examination of the integral ratio for the *o*-CH_3 signals of the product (δ 2.10) and the starting material (δ 2.46). Isolation of pure biaryl as a colourless oil, if required, could be effected by column chromatography on silica, eluting with light petrol.

ACKNOWLEDGEMENTS

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