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Unsymmetrical Biaryl Synthesis: An Approach to Natural Highly Functionalised Biaryls via Palladium Catalysed Coupling

David A. Widdowson* and Ying-Zhi Zhang

Department of Chemistry, Imperial College, London SW7 2AY

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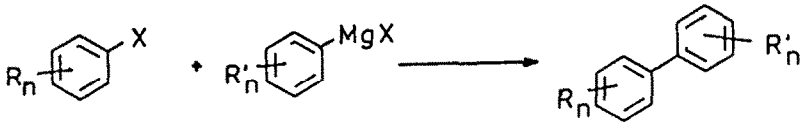
Abstract - The synthetic utility of the palladium catalysed cross-coupling reaction of aryl iodides and bromides with aryl Grignard reagents has been explored with respect to the polyoxygenated and polyalkylated arenes found in nature. High yields of unsymmetrical biaryls are obtained, free of symmetrical byproducts. The method will tolerate a limit of two ortho-substituents in the biaryl system with a preference for the 2 groups to be on the arylmagnesium ring. Transition state models of the potential rate determining steps are discussed with respect to this preference.

Highly functionalised, unsymmetrical biaryls are widespread in nature[1] and are an important constituent of many medicinals[2] but the classical methods for biaryl synthesis[3] are rarely applicable to them with any efficiency. Nickel[4] and other metal[5] catalysis has been used to good effect in cross coupling but in general has proved to be less versatile than palladium[6]. The use of the palladium catalysed cross coupling reaction[7], with a predictably high tolerance of oxygen functionality[8], is therefore particularly attractive and we proposed to develop a programme of synthesis of biaryl lignans and related species using this coupling.

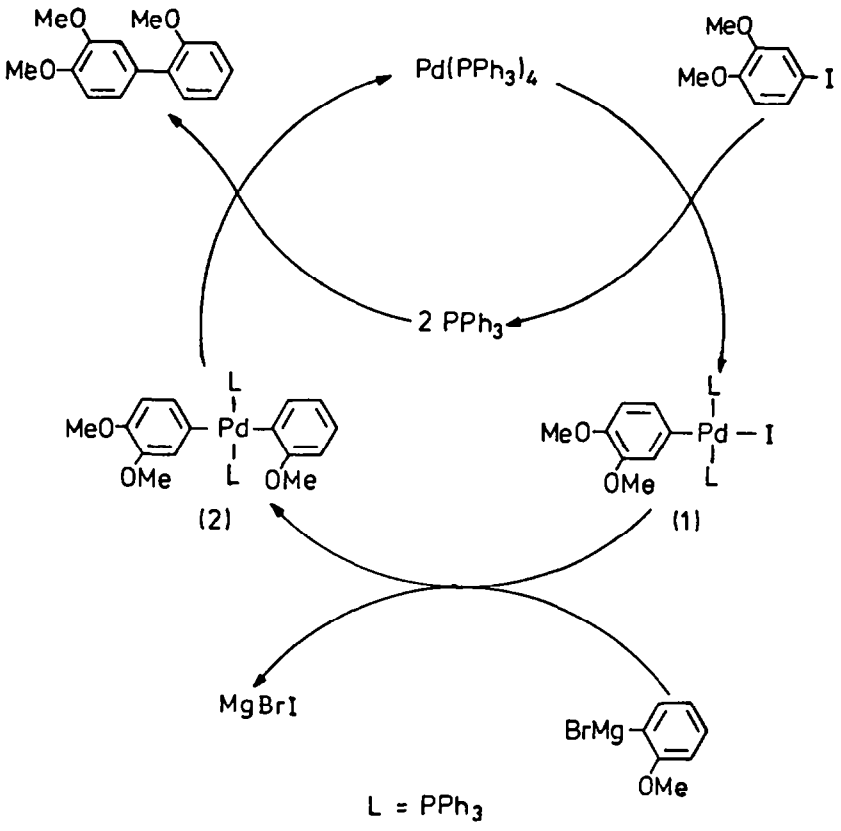
SCHEME 1



The palladium catalysed cross coupling reaction of aryl (Scheme 1) and alkenyl halides with Grignard reagents and other organometallic species has been described for simple systems[7], yet little is known of the scope of this reaction. The generally accepted overall sequence is given in Scheme 2[9]. It was a necessary prerequisite for this programme that the synthetic limits of the process be determined. We report here the results of that study.

Three aspects of the reaction required evaluation: 1, the rate determining step in Scheme 2 for unhindered arenes is usually the initial oxidative addition of the aryl halide to the palladium(0) species[10] and this process is accelerated by electron withdrawing groups on the aryl ring. It was important, therefore, to determine the feasibility of using the electron rich rings characteristic of many natural products; 2, palladium is coordinated relatively weakly by oxygen[11] and no problems were anticipated with such functionality either adjacent to or remote from the reacting centres, but

SCHEME 2



softer, more strongly coordinating heteroatoms could inhibit the reaction and we sought to assess to some extent, the tolerance of the process to amines and nitrogen heterocycles; 3, the mechanism of the metathesis step, (1 --> 2), is not known with certainty but it may be presumed, by precedent from related reactions[12], to be an associative process involving a rather congested transition state (3 or 4, see below). The coupling could therefore be particularly susceptible to steric retardation by ortho-substituents on the aryl rings.

Reactions between aryl bromide or iodide and aryl Grignard reagent were carried out in THF, either at reflux or at ambient temperature, depending on the reactivity of the halide, using tetrakistriphenylphosphinepalladium[13] as catalyst. The results are displayed in the Table.

Initially, we repeated some reported couplings[9]; in our hands biphenyl was formed in 70% isolated yield (Run 1) and 2-methoxybiphenyl in 97% yield (Run 4). It is immediately apparent that the reaction is not adversely affected by remote alkoxy substituents on the aryl halide partner (Runs 2, 3) and the isolated yields could even be enhanced (up to 97%) by the presence of a 2-alkoxy group in the Grignard reagent (Runs 3, 4, 5). The presence of nitrogen, either remote from (Run 6) or adjacent to (Runs 7, 13) the reacting centre was not deleterious to yields and there is no apparent problem of nitrogen coordination although strongly coordinating groups such as 2-dimethylaminomethyl- were not tested in this system[14].

Table

Synthesis of Biaryls[a]

Run	ArX	Ar'MgX	Temp (°C)	Ar-Ar' Isolated Yield (%)
1	PhI	PhMgBr	20	70
2	3,4-$(MeO)_2C_6H_3I$	PhMgBr	20	53
3	3,4-$(MeO)_2C_6H_3I$	2-$MeOC_6H_4MgBr$	20	70
4	PhI	2-$MeOC_6H_4MgBr$	20	97
5	PhBr	2-$MeOC_6H_4MgBr$	65	92
6	4-$Me_2NC_6H_4Br$	2-$MeOC_6H_4MgBr$	65	62
7	4-$MeOC_6H_4I$	1-Me-2-Li-indole	65	68
8	PhI	2,4,6-$Me_3C_6H_2MgBr$	20	70[b]
9	3,4-$(MeO)_2C_6H_3I$	2,4,6-$Me_3C_6H_2MgBr$	20	20[b]
10	3,4-$(MeO)_2C_6H_3I$	2,4,6-$Me_3C_6H_2MgBr$	20	68[b,c]
11	2-MeC_6H_4Br	2-$MeOC_6H_4MgBr$	65	8
12	2-MeC_6H_4Br	2-$MeOC_6H_4MgBr$	65	39[d]
13	2-$Me(Me_3Si)NC_6H_4I$[e]	2-$MeOC_6H_4MgBr$	20	66[d,f]

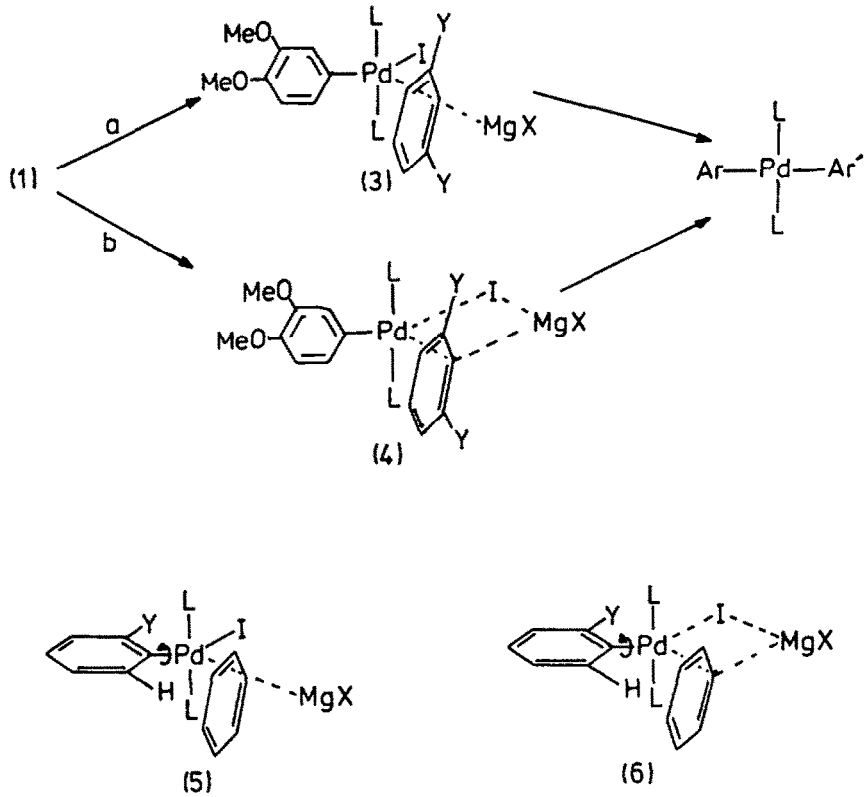
[a] 0.02 equivalents of catalyst, unless otherwise stated.
[b] solvent: THF/HMPA 10:1.
[c] 0.1 equivalents of catalyst.
[d] 1 equivalent of catalyst.
[e] generated *in situ*, see Experimental.
[f] the isolated product was desilylated.

Mesitylmagnesium bromide cross coupled with 2-unsubstituted aryl halides without undue difficulty (Runs 8, 9, 10) although it was advantageous to add 10% HMPA to the solvent (Runs 8, 9) and increase the catalyst concentration (Run 10). However, the yield dropped considerably when 2 *ortho* substituents on different rings were present (Run 11) and only became synthetically useful when a stoichiometric amount of palladium catalyst was added (Runs 12, 13). Attempts to prepare tri- or tetra-*o*-substituted biaryls all failed.

These observations can be rationalised by a more detailed consideration of the steps in Scheme 2. The oxidative addition is known to be very tolerant of *ortho* substitution[8] and because of the congestion involved, the rate limiting step, for *o*-functionalised arenes, is likely to become the metathesis of Grignard reagent and arylpalladium iodide or the reductive elimination.

Two limiting pathways for the former can be envisaged (Scheme 3). Both involve distorted bipyramidal transition states, either the S_E2(open) process [Scheme 3a, transition state (3)] or the S_E2(cyclic) mechanism [Scheme 3b, transition state (4)]. The side-on approach of the aryl group in either process would minimise interaction of the incoming *ortho* substituents [Y in (3) and (4)] with the apical ligands and render the process relatively insensitive to these substituents although clearly, one substituent is preferable to two. If this step is rate limiting, then the key to the limitations of the coupling process lies in the functionality on aryl group of the initial oxidative addition complex (1). An *o*-unsubstituted aryl ligand has a low barrier to rotation in transition

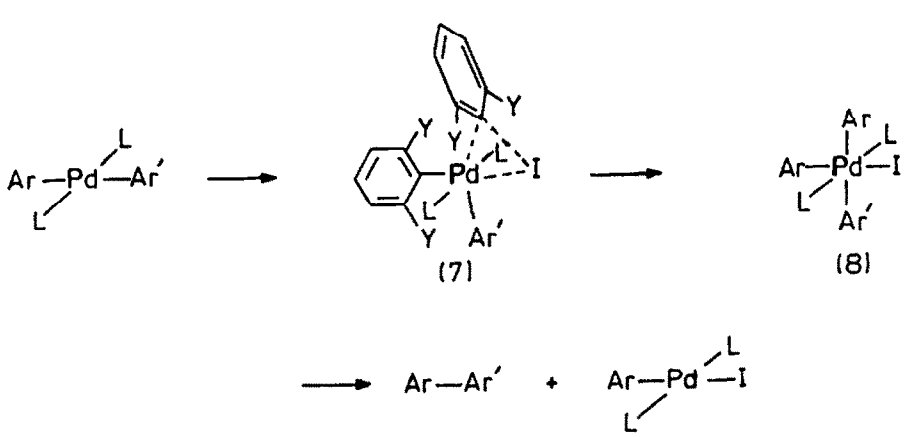
SCHEME 3



metal complexes[16] and it is reasonable to assume in (3) and (4) also. In these conformations there is minimal interaction of the aryl ligand with the incoming arylmagnesium and the reaction would proceed smoothly. However, an ortho substituent [Y in (5) and (6)] on the aryl ring of (1) would interact strongly with the apical ligands[17] and the expected preferred conformations in the transition state would be as in (5) and (6). These conformations would produce serious interaction between the ortho substituents of the aryl ligand and the face of the incoming arene and inhibit reaction, even when the interacting group is only the remaining hydrogen [as in (5) or (6)].

If the reductive elimination (Scheme 4) is the rate determining step then the associative mechanism proposed by Stille for similar reactions[18] would apply analogous conformational constraints on the Ar-Pd bonds. Here, the key step would be the oxidative addition of the second aryl halide molecule via a distorted octahedral transition state (such as 7) to give the Pd^{IV} intermediate (8). The criticality of the o-functionalisation of this partner is shown in (7) and is analogous to that of the metathesis reaction. However, the Stille mechanism (Scheme 4) would require a dependence on both partners in the cross coupling since either Ar (from aryl halide) or Ar' (from arylmagnesium) could interact with the incoming aryl halide, depending on the orientation of the approach. Since the reaction is principally dependent on the o-substitution of one partner, the aryl halide, either the reductive elimination is not rate determining or the Stille mechanism is not operative in this case.

SCHEME 4



Although our results do not allow an absolute distinction to be made between all the possibilities, the transition state models (5) and (6) do accurately predict the observed aryl substitution dependence of the coupling. The synthetic potential of the cross coupling reaction is thus defined; judicious choice of the reaction partners will allow the synthesis of a wide range of polyfunctionalised biaryls with no apparent limitation on the number of m- and p- substituents, provided that no more than two ortho substituents are present, preferably both in the ring of the arylmagnesium component. Two o-substituents in the aryl halide prohibit reaction.

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Experimental.

Melting points were determined on a Kofler hot stage apparatus. Flash chromatography was carried out on Kieselgel 60 H and gravity column chromatography on aluminium oxide (basic) Brockmann Grade I or BDH silica gel MFC. Thin layer chromatography was carried out on Merck Kieselgel $^{19}GF_{254}$ plates or Aluminium Oxide F_{254} (Type E) plates. Solvents were purified by literature methods[19].

Tetrakistriphenylphosphinepalladium(0).- This was prepared in 92% yield according to the method of Coulson[13]. The product was thoroughly dried in vacuo to mp 112-114°C (dec) [lit[13] mp 116°C (dec)] and stored under nitrogen at -15°C.

General Procedure for Cross Coupling Reactions.

Method A - non-nitrogenous reactants.- The palladium catalyst (0.115g, 0.1 mmol) was added to a solution of aryl halide (5 mmol) in THF (5 ml) under nitrogen. A solution of the Grignard reagent, prepared in the usual way from aryl halide (7.5 mmol) and magnesium turnings (8 mmol) in THF (5 ml), was added dropwise to the mixture under reflux (or other conditions as indicated in Table 1). The resulting slurry was evaporated under reduced pressure to remove THF. Ether (~ 20 ml) and 1M hydrochloric acid (~ 10 ml) were added until the solids just dissolved. The aqueous layer was separated and extracted with ether (2 x 10 ml). The combined ether layers were washed with water until the washings were neutral, dried ($MgSO_4$), and the ether removed under reduced pressure. The residue was purified by chromatography.

Method B - nitrogenous reactants.- The mixture, at the end of the reaction carried out as before, was evaporated under reduced pressure. Ether (~ 10 ml) and 1N hydrochloric acid (~ 10 ml) were added until the residual solids just dissolved. The ether layer was extracted with 1N hydrochloric acid (2 x 10 ml). 1N Aqueous sodium hydroxide was added to the combined aqueous layers until precipitation was complete. The product was extracted with ether (3 x 10 ml) and the combined ethereal extracts washed with water until the washings were neutral. The ether solution was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by chromatography.

Biphenyl.- Method A, colourless crystals (70%, lit[9] 70 - 82%), mp 68-69°C (lit[20] mp 70°C).

3,4-Dimethoxybiphenyl.- Method A, colourless crystals (53%), mp 68-69°C (lit[21] mp 70°C).

2,3',4'-Trimethoxybiphenyl.- Method A, colourless oil (70%), δ ($CDCl_3$) 3.70 (3H, s), 3.78 (6H, s), 6.70-7.25 (7H, m); m/z 244 (M^+, 100%), 229, 198. Found: C, 73.49; H, 6.75; calc for $C_{15}H_{16}O_3$: C, 73.73; H, 6.61%.

2-Methoxybiphenyl.- Method A, colourless oil (97% from iodobenzene, 92% from bromobenzene); δ ($CDCl_3$) 3.75 (3H, s), 6.80-7.55 (9H, m); m/z 184 (M^+, 100%), 169, 141. Found: C, 84.98; H, 6.74; calc for $C_{13}H_{12}O$: C, 84.78; H, 6.52%.

4'-(N,N-Dimethylamino)-2-methoxybiphenyl.- Method B, yellow oil (62%), δ ($CDCl_3$) 2.95 (6H, s), 3.80 (3H, s), 6.75-7.55 (8H, m); m/z 227 (M^+, 100%), 212, 198. Found: C, 78.96; H, 7.56; N, 6.13; calc for $C_{15}H_{17}NO$: C, 79.25; H, 7.54; N, 6.17%.

THF (~ 40 ml). The mixture was refluxed for 4 h before a preformed mixture [4-iodoanisole (2.11 g, 9 mmol) and tetrakistriphenylphosphinepalladium (0.57 g, 0.5 mmol) in THF (20 ml) stirred for 30 min] was added dropwise. The mixture was refluxed for a further 2 h. Most of the THF was removed under reduced pressure and the residue diluted with ether (40 ml) and washed with water (2 x 30 ml). The ether layer was dried ($MgSO_4$) and concentrated to give an oil (2.96 g). Column chromatography gave 2-(4-methoxyphenyl)-1-methylindole (1.29 g, 68%), mp 118-120°C, δ ($CDCl_3$) 3.75 (3H, s), 3.87 (3H, s), 6.55 (1H, s), and 6.90-7.80 (8H, m); ν_{max} (neat) 3040, 3000, 2950, 2930, 2830, 1600, 1570, 1550 cm^{-1}; m/z 237 (M^+, 100%), 222, 206. Found: C, 80.97; H, 6.30; N, 5.77; $C_{16}H_{15}NO$ requires: C, 80.97; H, 6.38; N, 5.91%.

2,4,6-Trimethylbiphenyl.- Method A, modified by the use of 10% HMPA/THF as solvent; colourless oil (70%, lit[9] 64%), δ($CDCl_3$) 2.0 (6H, s), 2.30 (3H, s), 6.90-7.40 (7H, m); m/z 196(M^+, 100%), 181, 165.

3',4'-Dimethoxy-2,4,6-trimethylbiphenyl.- Method A, modified by the use of 10% HMPA/THF as solvent; colourless needles (20% or 68%, see Table), mp 98-100°C, δ ($CDCl_3$) 1.95 (6H, s), 2.25 (3H, s), 3.75 (3H, s), 3.82 (3H, s), 6.55-6.90 (5H, m); m/z 256 (M^+, 100%), 241, 128. Found: C, 79.36; H, 8.24; calc for $C_{17}H_{20}O_2$: C, 79.64; H, 7.87%.

2-Methoxy-2'-methylbiphenyl.- Method A, colourless oil (8% or 39% see Table), δ ($CDCl_3$) 2.15 (3H, s), 3.75 (3H, s), 6.90-7.40(8H, m); m/z 198 (M^+, 100%), 183, 168, 167. Found: C, 84.57; H, 7.34; calc for $C_{14}H_{14}O$: C, 84.80; H, 7.12%.

2-Methoxy-2'-(N-methylamino)biphenyl.- Method B, modified by starting with the in situ generation of 2-iodo-N-methyl-N-trimethylsilylaniline (see below) and by the use of a stoichiometric amount of catalyst. The 2-methoxy-2'-(N-methylamino)biphenyl had mp 140-142°C (from CH_2Cl_2/petroleum ether), δ ($CDCl_3$) 2.80 (3H, s), 3.75 (3H, s), 4.15 (1H, br s), 6.65-7.30 (8H, m); ν_{max} (CCl_4) 3440, 3080, 2938, 2820, 1590, 1510 cm^{-1}; m/z 213 (M^+, 100%), 182, 166. Found: C, 78.58; H, 7.05; N, 6.37; $C_{14}H_{15}NO$ requires: C, 78.83; H, 7.09; N, 6.57%.

2-Iodo-N-methyl-N-trimethylsilylaniline.- Ethylmagnesium bromide (1 mmol), prepared in the usual way from ethyl bromide and magnesium turnings in THF, was added dropwise during 5 min to a solution of 2-iodo-N-methylaniline (2.33 g, 1 mmol) in THF (10 ml). The mixture was refluxed for 8 h then trimethylchlorosilane (0.12 g, 1.1 mmol) was added and the mixture refluxed for a further 8 h. IR analysis showed the absence of an N-H group. The resulting solution was used directly in the cross coupling reaction.

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