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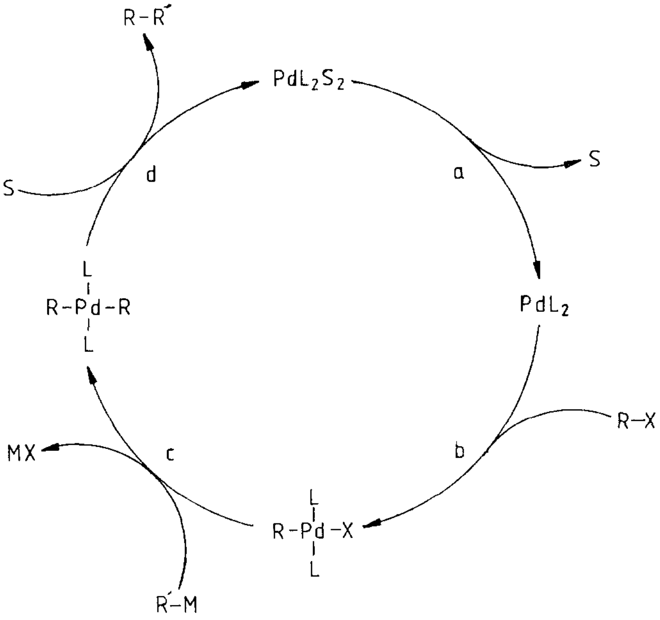
NEW DEVELOPMENTS IN PALLADIUM CATALYSED CROSS COUPLING: THE COUPLING OF ALKYL IODIDES WITH ALKYL GRIGNARD REAGENTS

Paul L. Castle and David A. Widdowson*
Department of Chemistry, Imperial College, London SW7 2AY

Summary - The species generated by the in situ reduction of 1,1'-bis(diphenylphosphino)ferrocenepalladium dichloride is an effective catalyst for the cross coupling of alkyl iodides with alkyl Grignard reagents.

The palladium catalysed cross coupling reaction between an organic halide and an organo-main group metal is a powerful and widely used method for carbon-carbon bond formation between sp and/or sp^2 centres[1]. The commonly accepted mechanism for this process[1,2] is given in the Scheme.



(L = phosphine ligand; S = phosphine ligand or solvent; X = halogen.)

Scheme

Recently, Kumada has shown[3] that alkylmetals (Mg or Zn) can be coupled with aryl halides (sp^3 - sp^2 coupling) via the catalytic use of 1,1'-bis(diphenylphosphino)ferrocenepalladium dichloride ($dppfPdCl_2$). The dppf ligand suppresses β-elimination in the final intermediate (**3**, LL = dppf, R = Aryl) and thereby maximises the yield of the reductive elimination product. We now report a new extension of this reaction to unsymmetrical sp^3 - sp^3 coupling, a process which is not readily achieved by conventional organic synthetic methods, and thereby considerably expand the generality and utility of the process.

Two problems needed to be overcome. Firstly, the oxidative addition (Step b) to form (2), which is normally prohibitively slow for alkyl halides[4], must be activated and secondly, β-elimination in the alkyl-palladium intermediate (2) [as well as (3)] must be inhibited[3]. This question had been partly answered by Kumada[3], but it was not known at the outset whether or not β-elimination was inhibited sufficiently by dppf for the initial adduct (2, LL = dppf, R = alkyl) to exist until Step c could occur. In order to promote Step b, the oxidative addition, a palladium catalyst containing only weakly coordinating ligands, other than one dppf was desirable[5]. We find that prior reduction of $dppfPdCl_2$ with 2 equivalents of DIBAL[6] in THF as solvent produces a catalyst which effects the required reaction. The results of a series of couplings is given in the Table.

Runs 1 - 2 demonstrate that a catalysed coupling can occur in the reverse sense (alkyl iodide/arylmagnesium) to the Kumada work[3]. β-Elimination is of course not possible here and for a higher iodide (Runs 3 - 5), elevated temperatures were necessary (Run 4), but the oxidative addition did occur in moderate yield (53%) and most importantly, even at these temperatures, no hexadecene derived from β-elimination was observed. We have already shown[7] that the transition state for the formation of diorganopalladium intermediates (**3**) is susceptible to steric inhibition and in accord with this, when the aryl Grignard reagent of Runs 3 - 5 was replaced with a primary alkylmagnesium (Runs 6 - 8), the yields improved to 80 - 91%. The use of a more sterically demanding sec-alkylmagnesium (Run 9) or sec-alkyl iodide (Run 10) gave slightly reduced coupling yields (63 and 69% respectively) and the secondary - secondary coupling (Run 11) even more so (37%). In this latter case, the product could have arisen from homo - coupling of the Grignard reagent[8], but in the absence of added iodide (Run 12), no dicyclohexyl was produced.

In a control experiment in the absence of catalyst (Run 5), no coupling products were detectable and the iodide was recovered unchanged. The use of 5 mole % of catalyst appears to be optimum and the yield did not improve on increasing the catalyst concentration to 10%.

Palladium reactions are frequently highly chemoselective[1] and in exemplification of this, the extension of the coupling reaction to functionalised alkanes is in hand.

TABLE

Cross Coupling Reactions.

Run	Reactants			T (°C)	t (h.)	Products (%)[a]		
	R'MgBr	RI	Cat. (mol.%)			RR'	RI	R'R'[b]
1	4-MeOC_6H_4MgBr	MeI	2	0	16	74	-[c]	4
2	4-MeOC_6H_4MgBr	MeI	2	21[d]	36	88	-	9
3	4-MeOC_6H_4MgBr	$n\text{-}C_{16}H_{33}I$	2	21	16	-	81[e]	28
4	4-MeOC_6H_4MgBr	$n\text{-}C_{16}H_{33}I$	2	67[f]	16	53	18	5
5	4-MeOC_6H_4MgBr	$n\text{-}C_{16}H_{33}I$	0	67	16	-	97[g]	5
6	$Ph(CH_2)_3MgBr$	EtI	5	21	16	87	-	-
7	$Ph(CH_2)_3MgBr$	$n\text{-}C_6H_{13}I$	5	67	16	91	-	-
8	$Ph(CH_2)_3MgBr$	$n\text{-}C_6H_{13}I$	5	67	16	80	6	-
9	$c\text{-}C_6H_{11}MgBr$	$n\text{-}C_6H_{13}I$	5	67	16	63	19	-
10	$n\text{-}C_6H_{13}MgBr$	$c\text{-}C_6H_{11}I$	5	67	16	69	16	-
11	$c\text{-}C_6H_{11}MgBr$	$c\text{-}C_6H_{11}I$	5	67	16	37	53	-
12	$c\text{-}C_6H_{11}MgBr$	--	5	67	16	-	-	-

a. Isolated yields of major products, relative yields determined by g.l.c. analysis, no olefins from β-elimination reactions were detectable.

b. This arises by homo-coupling when Grignard reagent formation is incomplete.

c. No detectable yield.

d. Ambient temperature.

e. Also detected: 4-bromoanisole (37%).

f. Refluxing THF solution.

g. Also detected: anisole (83%), the product of proton quenching of unreacted Grignard reagent.

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