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Selective Mono-Alkylation and Arylation of Dichlorobenzenes by Palladium-Catalyzed Grignard Cross-Coupling

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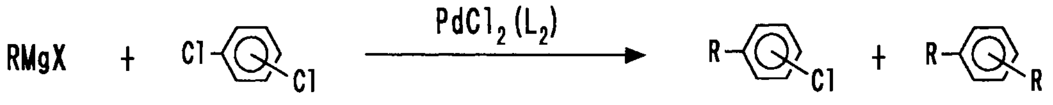
Palladium(II)-phosphine complexes, especially $PdCl_2(dppf)$ where dppf stands for 1,1'-bis(diphenylphosphino)ferrocene, are effective catalysts for the cross-coupling of Grignard reagents with dichlorobenzenes to produce selectively mono-alkylated and arylated benzenes. The addition of ligands is also effective for the cross-coupling of Grignard reagents containing a β-hydrogen(s).

Since Kumada$^{1)}$ and Corriu$^{2)}$ reported in 1972 nickel-catalyzed Grignard cross-coupling with alkenyl and aryl halides, wide applications of this coupling reaction have been developed. Although the selective mono-alkylation and arylation of aromatic polyhalides are one of the most attractive and useful reactions for which Grignard cross-coupling would be used, there have been only a few reports related to this subject. The Grignard cross-coupling of dichlorobenzene using conventional nickel catalysts usually gave dialkylated benzenes predominantly.$^{1,3)}$ Recently, it was reported that $[NiCl(triphos)]PF_6$ was used as a catalyst for Grignard cross-coupling with dichlorobenzenes to mainly give mono-alkylated benzenes.$^{4)}$ It has also been reported that $Ni(acac)_2$ is effective for mono-alkylation of trichlorobenzene.$^{5)}$ But they did not always give satisfactory selectivities. Mono-alkylation and arylation of bromochlorobenzene,$^{6,7)}$ fluoroiodobenzene,$^{7)}$ dibromobenzene$^{8)}$ have been achieved by palladium-catalyzed Grignard cross-coupling, but such halides, especially mixed halides, are not readily available. One of the limitations of the reaction using palladium is that aryl chloride is generally unable to undergo oxidative addition to palladium(0),$^{9)}$ and so various modified methods were proposed.$^{10)}$ The most desirable combination, palladium catalyst and dichlorobenzene, has not yet been realized.

We now wish to report that palladium catalyzed Grignard cross-coupling with dichlorobenzenes gives rise to the selective formation of mono-alkylated and arylated benzenes: The essential factor for the success was the high concentration of the Grignard reagent and high reaction temperature.

In a typical procedure, to a mixture of *m*-dichlorobenzene (100 mmol), $PdCl_2(dppf)$ (50×10^{-3} mmol) and dppf (50×10^{-3} mmol) was added a solution of *n*-propylmagnesium chloride (50 mmol ; 1.8 M) in THF at room temperature under nitrogen atmosphere. The mixture was



1 **2** **3** **4**

Table 1. Cross-Coupling of RMgX with Dichlorobenzenes a)

1 b)	2	Catalyst c)	Additive c)	Temp d)	Time	Yield/% e)		
				°C	h	**3**	**4**	others
MeMgCl	*m*-	PdCl$_2$(dppf)	-	70 f)	15	7		
MeMgCl	*m*-	PdCl$_2$(dppf)	-	105	1	93	2	
MeMgCl	*m*-	PdCl$_2$(dppb)	-	105	2	88	1	
MeMgCl	*m*-	PdCl$_2$(dppp)	-	105	8	89(82)	1	
MeMgCl	*m*-	PdCl$_2$(PPh$_3$)$_2$	-	105	8	56	2	12 g)
PhMgCl	*o*-	PdCl$_2$(dppf)	-	95	2	79	2	4 h)
PhMgCl	*m*-	PdCl$_2$(dppf)	-	95	1	85	4	2 h)
EtMgBr	*m*-	PdCl$_2$(dppb)	-	85	15	21	1	20 i)
EtMgBr	*m*-	PdCl$_2$(dppf)	-	85	15	34	1	18 i)
EtMgBr	*m*-	PdCl$_2$(dppb)	dppb	85	18	73	1	1 i)
n-PrMgCl	*o*-	PdCl$_2$(dppf)	dppf	85	18	68		
n-PrMgCl	*m*-	PdCl$_2$(dppf)	dppf	85	18	84 j)	1	3 i)
n-PrMgCl	*p*-	PdCl$_2$(dppf)	dppf	85	25	80		
i-PrMgCl	*m*-	PdCl$_2$(dppf)	dppf k)	85	15	42 l)	1	10 i)
n-OcMgCl	*m*-	PdCl$_2$(dppf)	dppf m)	85	12	88(80)		

a) **1**/**2**/Catalyst/Additive = 1/2/10^{-3}/10^{-3} (molar ratio), unless otherwise noted.

b) 1.8 - 3.3 M. Acid-base titration after being prepared in THF.

c) dppf = 1,1'-bis(diphenylphosphino)ferrocene. dppb = 1,4-bis(diphenylphosphino)-butane. dppp = 1,3-bis(diphenylphosphino)propane.

d) Reflux in THF. e) Determined by GLC using an internal standard based on the Grignard reagent, isolated yield by fractional distillation in parenthesis.

f) No reflux. g) Yield of 3,3'-dichlorobiphenyl. h) Yield of biphenyl.

i) Yield of chlorobenzene. j) No *i*-propylated isomer was detected.

k) **1**/Additive = 1/0.2x10^{-3} (mol/mol). l) A *n*-propylated isomer (2%) was detected.

m) **1**/Additive = 1/0.5x10^{-3} (mol/mol).

refluxed at 85 °C for 18 h, and then hydrolyzed. The yield of products was determined by GLC analysis using an internal standard.

Representative results are summarized in Table 1. Several characteristic features are as follows. (1) Temperatures should be maintained at higher than 80 °C to occur smoothly, therefore high concentrations (1.8 - 3.3 M) of Grignard reagent were used. The yield of mono-alkylated and arylated products formed was in the range of 42 - 93%. In all cases disubstituted products were formed in the range of less than several per cent. (2) $PdCl_2(dppf)$ was found to be the most effective catalyst for this reaction. The activity of the palladium catalysts was in the order of $PdCl_2(dppf)$ > $PdCl_2(dppb)$ > $PdCl_2(dppp)$ > $PdCl_2(PPh_3)_2$. (3) Cross-coupling of dichlorobenzenes with methyl and phenyl Grignard reagents gave satisfactory results. (4) In contrast, using $PdCl_2(dppf)$ in the cross-coupling of Grignard reagents bearing a β-hydrogen(s) gave lower yields, for the main reduction and isomerization must have occurred by β-hydride elimination of the alkylmetal species in the catalytic cycle. The yield, however, could be dramatically improved by an addition of proper amount of bidentate phosphine in the reaction using bidentate phosphine-palladium complex as a catalyst to suppress such side reactions. The addition of dppf was the most effective in the reaction using $PdCl_2(dppf)$. In Fig. 1, the yields for the cross-coupling of *n*-propylmagnesium chloride and *i*-propylmagnesium chloride with *m*-dichlorobenzene are plotted versus the molar ratio of dppf to $PdCl_2(dppf)$. The yield increased linearly with the molar ratio in the range of 0 - 0.4, and then generally gave a flat line in the range of 0.4 - 1 for the cross-coupling of *n*-propylmagnesium chloride. For the cross-coupling of *i*-propylmagnesium chloride, a 0.2 molar ratio gave the highest yield, which was reproducible.

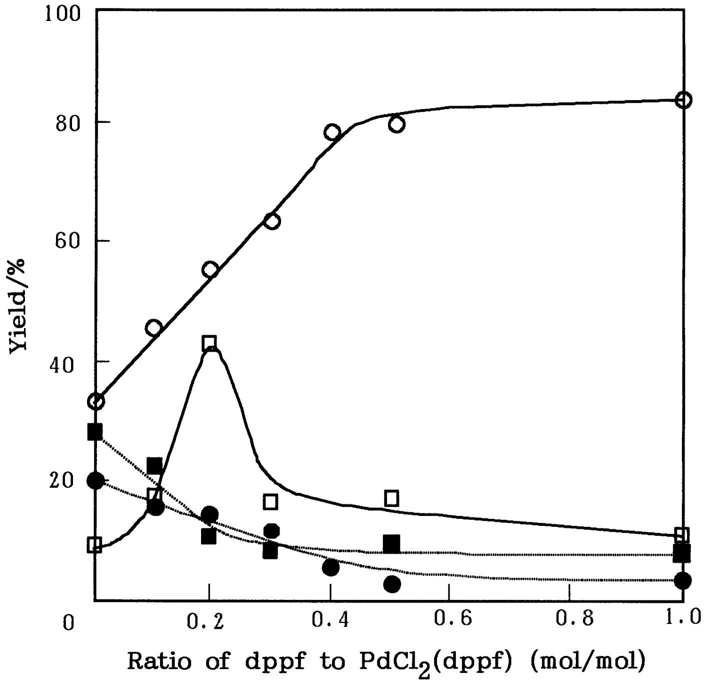


Fig. 1. Effect of dppf added in cross-coupling using $PdCl_2(dppf)$ as a catalyst[a)]

a) **1**/**2**/$PdCl_2(dppf)$/dppf = $1/2/10^{-3}/n\times10^{-3}$ (molar ratio).

b) Cross-coupling of *n*-PrMgCl with *m*-dichlorobenzene. ○:*m*-Chloro-*n*-propylbenzene. ●:Chlorobenzene.

c) Cross-coupling of *i*-PrMgCl with *m*-dichlorobenzene. □:*m*-Chloro-*i*-propylbenzene. ■:Chlorobenzene.

Based on the proposed catalytic cycle[3,11,12] for cross-coupling reaction, the followings are the summary of conclusion. Firstly, the oxidative addition of aryl chloride to palladium(0) species is presumably the rate-determining step, so that temperatures higher than 80 °C were necessary for this reaction to surmount this step. The resulting monosubstituted mono-chlorobenzene should be much less reactive than dichlorobenzene due to the electron-donating nature of the introduced organic group. Secondly, the order of ligand activity is similar to that proposed in a previous paper,[12] which is ascribed to its large P-Pd-P angle. Finally, the addition of ligands is remarkably effective for the cross-coupling using Grignard reagent bearing a β-hydrogen(s) to suppress any side reactions including β-hydride elimination. Although the reaction rate was not determined, it seemed to decrease with an increase of the added ligands. It is premature to draw a conclusion, but with these results it is suggested that an excess of ligand might block the vacant site of the palladium species to prevent the process of oxidative addition of dichlorobenzene to palladium(0) as well as β-hydride elimination of the alkyl moiety on the metal.

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