Palladium Catalysts for Cross-Coupling of Ortho-Substituted Aryl Triflates with Grignard Reagents

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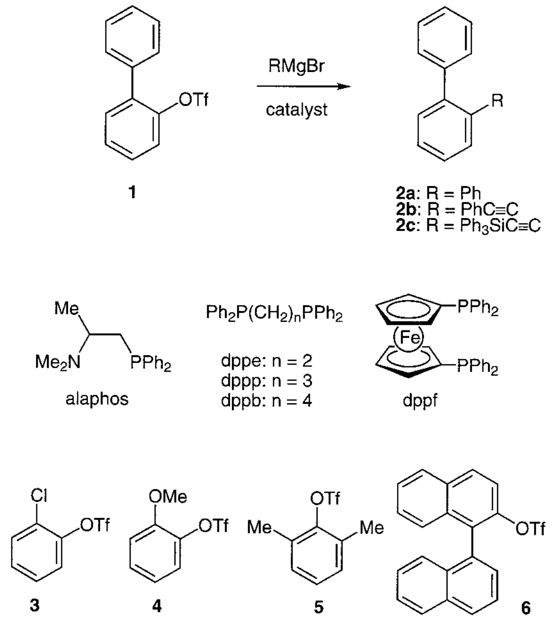
Received 14 November 1996

Abstract: Dichloro[(2-dimethylamino)propyldiphenylphosphine]palladium ($PdCl_2$(alaphos)) and dichloro[1,3-bis(diphenylphosphino)-propane]palladium ($PdCl_2$(dppp)) were found to be much more effective catalysts than $PdCl_2(PPh_3)_2$ and other palladium complexes for cross-coupling of sterically congested aryl triflates with aryl and alkynyl Grignard reagents.

During our recent studies on enantioposition-selective cross-coupling of aryl ditriflates with the Grignard reagents,[1] it was found that the palladium complexes coordinated with β-(dimethylamino)alkyldiphenylphosphines are highly effective as catalysts for the Grignard cross-coupling of aryl triflates containing sterically bulky groups at ortho-position. Here we wish to report the effects of phosphine ligands on the catalytic activity of the palladium-catalyzed cross-coupling of sterically congested aryl triflates with aryl and alkynyl Grignard reagents, the ligand effects being different from those observed for the cross-coupling of non-congested aryl halides or triflates.[2,3]



Scheme

In a typical experiment (Scheme), to a mixture of 2-phenylphenyl triflate (**1**) (1.0 mmol), dichloro[(2-dimethylamino)propyldiphenylphosphine]palladium ($PdCl_2$(alaphos)) (0.05 mmol), and lithium bromide (1.0 mmol) in ether was added phenylmagnesium bromide (2.0 mmol) in ether at 0 °C, and the mixture was stirred at 30 °C for 3 h. Acidic hydrolysis and preparative TLC on silica gel gave 95% yield of 1,2-diphenylbenzene (**2a**) (entry 1 in Table 1). The reaction was much slower with the palladium catalysts coordinated with triphenylphosphine ligands, $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$, which gave **2a** in low yields after a prolonged reaction time (entries 2 and 3), though the triphenylphosphine-palladium complexes have been often used for the cross-coupling of aryl halides with several organometallic reagents.[2] The cross-coupling was also slow with dichloro[1,1'-bis(diphenylphosphino)-ferrocene]palladium ($PdCl_2$(dppf)), which is one of the most effective catalysts for the Grignard cross-coupling of aryl bromides and the related reactions[4] (entry 4). Of the palladium catalysts containing α,ω-bis(diphenylphosphino)alkanes (entries 5-7), dichloro[1,3-bis(diphenylphosphino)propane]palladium ($PdCl_2$(dppp)) was most catalytically active, a little more active than $PdCl_2$(alaphos), in the reaction with the phenyl Grignard reagent to give **2a** in 97% yield. The chemical yield of **2a** obtained with $PdCl_2$(alaphos) or $PdCl_2$(dppp) shown above is higher than that obtained by the reaction of **1** with phenylboronic acid in the presence of $Pd(PPh_3)_4$ (entry 9).[5] For the cross-coupling with alkynyl Grignard reagents, $PdCl_2$(alaphos) was found to be the only catalyst giving high yields of the alkynylation products (**2b**: 93%, **2c**: 99%) (entries 10, 15). Other palladium or nickel complexes were all much less catalytically active than $PdCl_2$(alaphos) for the alkynylation (entries 11-14).

Table 1. Effects of Phosphine Ligands on the Cross-Coupling of Aryl Triflate **1** with Grignard Reagents[a)]

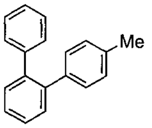
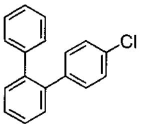
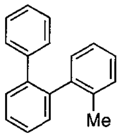
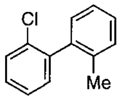
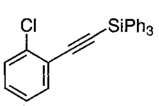
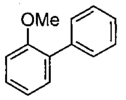
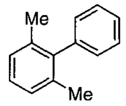
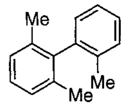
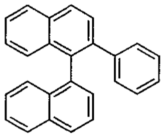
entry	catalyst	Grignard	time (h)	yield (%) of **2**[b)]
1	$PdCl_2$(alaphos)	PhMgBr	3	95 (**2a**)
2	$PdCl_2(PPh_3)_2$	PhMgBr	24	25 (**2a**)
3	$Pd(PPh_3)_4$	PhMgBr	24	2 (**2a**)
4	$PdCl_2$(dppf)	PhMgBr	24	10 (**2a**)
5	$PdCl_2$(dppe)	PhMgBr	14	93 (**2a**)
6	$PdCl_2$(dppp)	PhMgBr	1	97 (**2a**)
7	$PdCl_2$(dppb)	PhMgBr	3	95 (**2a**)
8	$NiBr_2(PPh_3)_2$	PhMgBr	24	97 (**2a**)
9[c)]	$Pd(PPh_3)_4$	$PhB(OH)_2$	24	67 (**2a**)
10	$PdCl_2$(alaphos)	PhC≡CMgBr	6	93 (**2b**)
11	$PdCl_2(PPh_3)_2$	PhC≡CMgBr	24	30 (**2b**)
12	$PdCl_2$(dppp)	PhC≡CMgBr	6	0 (**2b**)
13	$PdCl_2$(dppf)	PhC≡CMgBr	24	3 (**2b**)
14	$NiBr_2(PPh_3)_2$	PhC≡CMgBr	6	0 (**2b**)
15	$PdCl_2$(alaphos)	$Ph_3SiC≡CMgBr$	10	99 (**2c**)

a) The cross-coupling was carried out with 2 equiv of Grignard reagent in the presence of 1 equiv of LiBr and 5 mol % palladium catalyst at 30 °C. In ether (entries 1-8). In ether/toluene = 5/1 (entries 10-14). In ether/toluene = 3/1 (entry 15). b) Isolated yield by silica gel chromatography. c) In the presence of K_3PO_4 in refluxing dioxane.

The high catalytic activity observed here for $PdCl_2$(alaphos) is ascribed, at least partly, to the high basicity of the alaphos ligand which is a chelating ligand with a trialkylamino group and an alkyldiphenylphosphino group. The high basicity will accelerate the oxidative addition of sterically congested aryl triflate to a palladium(0) species. The oxidative addition is one of the key steps in the catalytic cycle of the transition metal-catalyzed cross-coupling reactions.[2] Higher basicity of α,ω-bis(diphenylphosphino)alkanes than PPh_3 or dppf may be also related to the higher catalytic activity of the palladium complexes of dppe, dppp, and dppb than those of triarylphosphines.

The palladium catalysts, $PdCl_2$(alaphos) and $PdCl_2$(dppp), were also effective for the reaction of 2-phenylphenyl triflate (**1**) with some other aryl Grignard reagents (entries 1-7, in Table 2). The triflate group in **1** was successfully substituted with 4-methylphenyl, 4-chlorophenyl, and 2-methylphenyl groups by use of these palladium catalysts. The nickel complex $NiBr_2(PPh_3)_2$ can not be used for the cross-coupling of aryl triflates or Grignard reagents containing chloride on the aromatic ring, the chloride being reactive towards the nickel-catalyzed cross-coupling leading to polymeric products (entries 5, 10).[6] The sterically congested aryl triflates **3-6**, which contain substituents at ortho-position(s) also underwent the cross-coupling with phenyl, 2-methylphenyl, and triphenylsilylethynyl Grignard reagents to give the corresponding cross-coupling products in high yields by use of $PdCl_2$(alaphos) or $PdCl_2$(dppp) catalyst.

Table 2. Cross-Coupling of Aryl Triflates with Grignard Reagents[a]

entry	triflate	R in RMgBr	catalyst	product	time (h)	yield (%)[b]
1	**1**	4-MeC$_6$H$_4$	PdCl$_2$(alaphos)		4	93
2		4-MeC$_6$H$_4$	PdCl$_2$(dppp)		1	92
3		4-ClC$_6$H$_4$	PdCl$_2$(alaphos)		2	92
4		4-ClC$_6$H$_4$	PdCl$_2$(dppp)		1	91
5		4-ClC$_6$H$_4$	NiBr$_2$(PPh$_3$)$_2$		1	5
6		2-MeC$_6$H$_4$	PdCl$_2$(alaphos)		3	92
7		2-MeC$_6$H$_4$	PdCl$_2$(dppp)		1	93
8	**3**	2-MeC$_6$H$_4$	PdCl$_2$(alaphos)		4	84[c]
9		2-MeC$_6$H$_4$	PdCl$_2$(PPh$_3$)$_2$		24	66[c]
10		2-MeC$_6$H$_4$	NiBr$_2$(PPh$_3$)$_2$		1	19[c]
11[d]		$Ph_3SiC{\equiv}C$	PdCl$_2$(alaphos)		14	99
12	**4**	Ph	PdCl$_2$(alaphos)		5	95
13		Ph	PdCl$_2$(dppp)		1	97
14		Ph	PdCl$_2$(PPh$_3$)$_2$		24	12
15	**5**	Ph	PdCl$_2$(dppp)		14	94[e]
16		2-MeC$_6$H$_4$	PdCl$_2$(dppp)		18	65[e]
17	**6**	Ph	PdCl$_2$(dppp)		14	91

a) The cross-coupling was carried out with 2 equiv of Grignard reagent in ether in the presence of 1 equiv of LiBr and 5 mol % palladium catalyst at 30 °C. b) Isolated yield by silica gel chromatography. c) Contaminated with a small amount of 2,2'-dimethylbiphenyl and the yield was calibrated by ^{1}H NMR. d) Solvent is ether/toluene = 3/1. e) GLC yield.

Acknowledgment. This work was supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture of Japan.

References and Notes

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