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A Synthesis of Biaryls *via* Nickel(0)-Catalyzed Cross-Coupling Reaction of Chloroarenes with Phenylboronic Acids

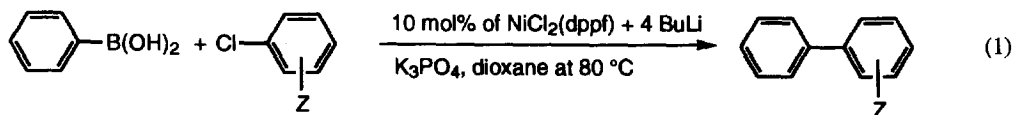
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Abstract: The cross-coupling reaction of phenylboronic acid with chloroarenes to give biaryls was carried out in high yields at 80 °C in the presence of the nickel(0) catalyst and K₃PO₄ (3 equivs) in dioxane. The nickel(0) catalyst prepared *in situ* from NiCl₂(dppf) (10 mol%) and four equivalents of BuLi was recognized to be most effective. The reaction can be applicable for a wide range of chloroarenes having an electron-withdrawing or an electron-donating group such as 4-CN-, 4-CHO, 2- or 4-CO₂Me, 4-COMe, 4-NHAc, 3- or 4-Me, and 3- or 4-OMe, and 4-NH₂. Copyright © 1996 Elsevier Science Ltd

The palladium-catalyzed cross-coupling reaction of arylboronic acids with aryl halides or triflates gives biaryls. High yields have been achieved with many substrates having various functional groups on either coupling partners, when using aryl bromides, iodides, or triflates as an electrophile.¹ Chloroarenes are an economical and easily available, but they have been rarely used for the palladium-catalyzed cross-coupling reaction of arylboronic acids because of the oxidative addition of chloroarenes is too slow to develop the catalytic cycle.² However, chloroarenes have been an efficient substrate for the nickel-catalyzed cross-coupling reaction with Grignard reagents developed by Kumada and Tamao.³ The recent report by Percec also demonstrated the efficiency of nickel catalyst for the cross-coupling reaction of less reactive arenesulfonates with arylboronic acids.⁴

Herein, we wish to report the use of the nickel catalyst for the cross-coupling reaction of chloroarenes with arylboronic acids (Eq. 1). Phenylboronic acids reacted in high yields with both chloroarenes having an electron-withdrawing and an electron-donating group.



Z = 4-CN, 4-CHO, 2- or 4-CO₂Me, 4-COCH₃, 4-NHAc, 3- or 4-CH₃, 3- or 4-OMe, 4-NH₂

The reaction conditions were optimized at 80 °C using 3-chlorotoluene and 1.1 equiv of phenylboronic acid (Table 1). The highly active nickel(0) catalysts were *in situ* prepared by treating the nickel chloride complexes with four equivalents of BuLi at room temperature.⁵ The nickel chloride

Table 1. Reaction Conditions for the Cross-Coupling of 3-Chlorotoluene^a

entry	catalyst ^b	solvent	base	products and yields (%) ^c	
				3-phenyltoluene	biphenyl
1	NiCl ₂ (dppf)	dioxane	K ₂ CO ₃	24	10
2	NiCl ₂ (dppf)	dioxane	K ₂ CO ₃ / H ₂ O	70	2
3	NiCl ₂ (dppf)	dioxane	Cs ₂ CO ₃	80	4
4	NiCl ₂ (dppf)	dioxane	K ₃ PO ₄	89	6
5	NiCl ₂ (dppf)	dioxane	K ₃ PO ₄ / H ₂ O	76	3
6	NiCl ₂ (dppf)	dioxane	CsF ^d	85	4
7	NiCl ₂ (dppf)	dioxane	KOH/H ₂ O	8	2
8	NiCl ₂ (dppf)	DME	K ₃ PO ₄	76	6
9	NiCl ₂ (dppf)	benzene	K ₃ PO ₄	69	6
10	NiCl ₂ (dppe)	dioxane	K ₃ PO ₄	18	16
11	NiCl ₂ (dppp)	dioxane	K ₃ PO ₄	32	7
12	NiCl ₂ (dppb)	dioxane	K ₃ PO ₄	56	16
13	NiCl ₂ (PPh ₃) ₂	dioxane	K ₃ PO ₄	77	9

^aAll reactions were carried out in 5 ml of solvent at 80 °C for 24 h using phenylboronic acid (1.1 mmol), 3-chlorotoluene (1.0 mmol), base (3.0 mmol) and the nickel(0) catalyst (0.10 mmol).

^bThe nickel(II) chloride complexes were reduced with BuLi to the nickel(0) species, just prior to use for the next cross-coupling reaction. Dppf, dppe, dppp and dppb abbreviate 1,1'-bis(diphenylphosphino)-ferrocene, 1,2-bis(diphenylphosphino)ethane, 1,2-bis(diphenylphosphino)propane, and 1,2-bis(diphenylphosphino)butane.


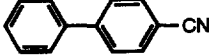
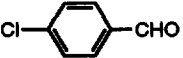
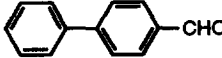
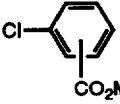
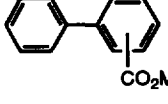
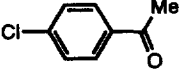
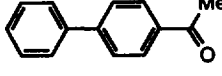
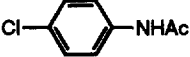
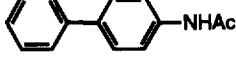
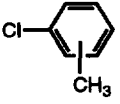
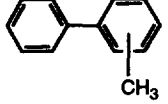
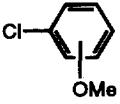
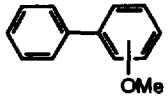

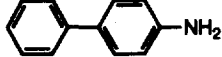
^cGC yields based on 3-chlorotoluene. ^dFour equivs of CsF was used.

complexes themselves or their reduction with zinc dust resulted in lower yields.

The palladium-catalyzed cross-coupling reaction of arylboronic acid with bromo- or iodoarenes can be best carried out in the presence of an aqueous base such as sodium carbonate; however, the arylnickel(II) intermediates produced in the catalytic cycle seem to be rather sensitive to water because higher yields were obtained when using anhydrous bases such as cesium carbonate, potassium phosphate, or cesium fluoride suspended in dioxane (entries 3, 4 and 6). The yields increased as the solubility (entries 1-3) or the basicity increased (entries 1 and 4), but strong bases such as sodium hydroxide reversely decreased the rate of the coupling, similarly to the palladium-catalyzed reaction¹ (entry 7). Although the effect of ligand is not obvious at present, the catalytic activity strongly depended on the phosphine ligands on nickel chloride decreasing in the order of dppf > PPh₃ > dppb > dppp > dppe (entries 4, and 10-13). The products were contaminated with some biphenyl formed from either the oxidative addition through a charge transfer process⁶ or the coupling with a phenyl group on the dppf ligand.⁷ However, the formation of 3,3'-dimethylbiphenyl derived from the homocoupling of 3-chlorotoluene was less than 1% in each case.

The results of the nickel(0)- or palladium(0)-catalyzed cross-coupling reaction of phenylboronic acid with representative chloroarenes are summarized in Table 2. The reaction with chloroarenes having an electron-withdrawing group, such as 4-CN, 4-CHO, 2- or 4-CO₂Me, and 4-COCH₃, gave excellent

Table 2. Synthesis of Biaryls via the Cross-Coupling Reaction with Chloroarenes^a

entry	chloroarene	catalyst/ time (h)	product	yield (%) ^b	
				Ph-Ar	Ph-Ph
1		NiCl ₂ (dppf)/16		74	3
2		Pd(PPh ₃) ₄ /16		80	6
3		NiCl ₂ (dppf)/16		93	3
4		NiCl ₂ (dppf)/16		2-	89 ^c
5				4-	96
6		NiCl ₂ (dppf)/16		98	3
7		Pd(PPh ₃) ₄ /16		64	8
8		NiCl ₂ (dppf)/16		81	4
9		NiCl ₂ (dppf)/24		3-	89
10		Pd(PPh ₃) ₄ /16		3-	3
11		NiCl ₂ (dppf)/24		4-	69
12		Pd(PPh ₃) ₄ /16		4-	< 1
13		NiCl ₂ (dppf)/24		3-	94
14		Pd(PPh ₃) ₄ /16		3-	< 1
15		NiCl ₂ (dppf)/24		4-	83
16		Pd(PPh ₃) ₄ /16		4-	< 1
17		NiCl ₂ (dppf)/48		89 ^c	-

^aThe nickel-catalyzed reactions were carried out by the procedure shown in the text. The palladium-catalyzed reactions were conducted in DME/H₂O at 80 °C for 16 h using phenylboronic acid (1.1 equiv), chloroarenes (1 equiv), Na₂CO₃ (3 equivs) and Pd(PPh₃)₄ (3 mol%).

^bGC yields based on chloroarenes. ^cIsolated yields by chromatography.

yields of biaryls with the nickel(0) catalyst, often exceeding 95% (entries 1, 3-6). The palladium(0) catalyst gave equally good results for such chloroarenes (entries 2 and 7); however, the reaction with methyl or methoxy substituted chlorobenzenes was extremely slow which resulted in early catalyst decomposition precipitating palladium-black (entries 10, 12, 14 and 16). For the substrates having an electron-donating group, the more nucleophilic nickel(0) catalyst provided definitively superior results. High yields were readily achieved for 3-methyl- (σ , - 0.07), 4-methyl- (σ - 0.17), 4-methoxy- (σ , - 0.27), and even 4-aminochlorobenzene (σ , - 0.66) (entries 9, 11, 15, and 17).⁸ The formations of biphenyl in those nickel-catalyzed reactions were in a range of 2 to 7 per cents.

Representative procedure: A solution of BuLi in hexane (0.4 mmol) was added to a solution of NiCl₂(dppf) (0.1 mmol) in dioxane (4 ml) at room temperature to give a red solution of nickel(0) complex. After being stirred for 10 min, phenylboronic acid (1.1 mmol), K₃PO₄ (3.0 mmol), a chloroarene (1.0 mmol), and an additional dioxane (2 ml) were added to the flask. The reaction mixture was stirred at 80 °C for the period indicated in the Table 2. The product was isolated by chromatography over silica gel.

References and Notes

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