Synthesis of Biaryls via a Nickel(0)-Catalyzed Cross-Coupling Reaction of Chloroarenes with Arylboronic Acids

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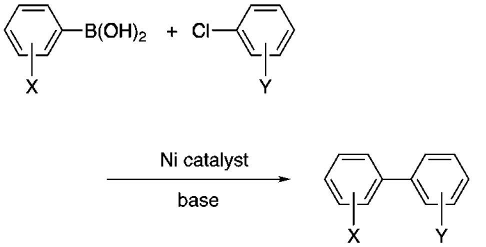
The cross-coupling reaction of arylboronic acid with chloroarenes to give biaryls was carried out in high yields at 70−80 °C in the presence of a nickel(0) catalyst and K_3PO_4 (3 equiv) in dioxane or benzene. The nickel(0) catalyst in situ prepared from $NiCl_2 \cdot L$ (L = dppf, 2PPh$_3$) (3−10 mol %) and 4 equiv of BuLi at room temperature was recognized to be most effective. The reaction can be applicable to a wide range of chloroarenes having an electron-withdrawing or an electron-donating group such as 4-NC, 4-CHO, 2- or 4-CO_2Me, 4-COMe, 4-NHAc, 4-Me, 4-OMe, 4-NH_2, and 4-NMe_2. The Hammett's plot of the substituent effect of chloroarenes revealed that the reaction involves a rate-determining oxidative addition of chloroarenes to the nickel(0) complex.

The palladium-catalyzed cross-coupling reaction of arylboronic acids with aryl halides or triflates gives biaryls.[1] High yields have been achieved with many substrates having various functional groups on either coupling partner, when using aryl bromides, iodides,[2] or triflates[3] as an electrophile. Chloroarenes are an economical and easily available substrate, but they have been rarely used for the palladium-catalyzed cross-coupling reaction of arylboronic acids because the oxidative addition of chloroarenes to palladium(0) is too slow to develop the catalytic cycle. Thus, the palladium catalysts have been limitedly used for activated chloroarenes such as chloropyridines,[4] (chloroarene)chromium tricarbonyl,[5] and chloroarenes having an electron-withdrawing group.[6] The superiority of trialkylphosphines as the ligand for palladium catalysts, e.g., $^iPr_3P$, $Cy_2PCH_2CH_2PCy_2$, and $^iPr_2PCH_2CH_2CH_2P^iPr_2$ (dippp), was demonstrated by Milstein and Hiyama on the carbonylation and the formylation of chloroarenes,[7] and the cross-coupling reaction with organosilanes.[8] However, chloroarenes have been an efficient substrate for the nickel-catalyzed cross-coupling reaction with Grignard reagents developed by Kumada and Tamao.[9] The recent report by Percec also demonstrated the efficiency of a nickel catalyst for the cross-coupling reaction of less reactive arenesulfonates with arylboronic acids.[10] Herein, we wish to report the use of the nickel catalyst for the cross-coupling between arylboronic acids and chloroarenes (eq 1).[11,12]



(1)

The nickel(0) complexes, in situ prepared from $NiCl_2 \cdot$(dppf) (dppf abbreviate 1,1′-bis(diphenylphosphino)ferrocene) or $NiCl_2 \cdot 2PPh_3$ and *n*-BuLi (4 equiv), was recognized to be an efficient catalyst, thus allowing the selective coupling with both chloroarenes having an electron-withdrawing and an electron-donating group.

Reaction Conditions

The effects of catalysts and their ligands were studied at 80 °C in the presence of K_3PO_4 (3 equiv) and a 3 mol % of nickel(II) chloride phosphine complex using the reaction between phenylboronic acid (1.1 equiv) and 3-chlorotoluene (Table 1).

[⊗] Abstract published in *Advance ACS Abstracts,* October 15, 1997.

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[9] (a) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374−4376. (b) Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958−1969. For reviews, see: (c) Tamao, K. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon: New York, 1991; Vol. 3, p 435. (d) Farina, V. *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Hegedus, L. S., Eds.; Pergamon: New York, 1995; Vol. 12, p 161.

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[12] It was recently reported that the similar reaction can be carried out at 95 °C without the reduction the nickel(II) chloride complex: Indolese, A. F. *Tetrahedron Lett.* **1997**, *38*, 3513.

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Table 1. Effects of Catalysts and Ligands on the Cross-Coupling Reaction of Phenylboronic Acids with 3-Chlorotoluene[a]

entry	catalyst	ligand (equiv)	reducing agent	time/h	yield/%[b]
1	$NiCl_2$(dppf)		none	8	59 (2)
2	$NiCl_2$(dppf)		Zn	8	73 (2)
3	$NiCl_2$(dppf)		DIBAH	8	90 (3)
4	$NiCl_2$(dppf)		BuLi	8	89 (2)
5	$NiCl_2$(dppf)	dppf (1)	BuLi	8	41 (2)
6	$NiCl_2$(dppf)	dppf (1)	BuLi	24	92 (3)
7	$NiCl_2$(dppf)	PPh_3 (2)	BuLi	16	93 (4)
8	$NiCl_2$(dppf)	$AsPPh_3$ (2)	BuLi	24	89 (2)
9	$NiCl_2$(dppf)	$SbPPh_3$ (2)	BuLi	24	89 (5)
10	$NiCl_2$(dppe)[c]		BuLi	16	54 (8)
11	$NiCl_2$(dppp)[d]		BuLi	16	61 (6)
12	$NiCl_2$(dppb)[e]		BuLi	16	33 (8)
13	$NiCl_2(PPh_3)_2$		BuLi	16	33 (8)
14	$NiCl_2(PPh_3)_2$	PPh_3 (2)	BuLi	16	84 (5)

[a] All reactions were carried out in dioxane (6 mL) at 80 °C using phenylboronic acid (1.1 mmol), 3-chlorotoluene (1.0 mmol), $K_3PO_4 \cdot nH_2O$ (3 mmol), catalyst (0.03 mmol), and an additional ligand shown in the table. The nickel catalyst was *in situ* reduced to the Ni(0) complex with BuLi (0.12 mmol) or DIBAH (0.12 mmol), prior to use the coupling reaction. [b] GC yields based on 3-chlorotoluene and the yields of biphenyl were shown in the parentheses. [c] Dppe is 1,2-bis(diphenylphosphino)ethane. [d] Dppp is 1,3-bis(diphenylphosphino)propane. [e] Dppb is 1,4-bis(diphenylphosphino)butane.

Table 2. Reaction Conditions for the Ni(dppf)-Catalyzed Coupling Reaction of Phenylboronic Acids with 3-Chlorotoluene[a]

entry	solvent	base	temp/°C	time/h	yield/%[b]
1	dioxane/H_2O	$K_3PO_4 \cdot nH_2O$	80	8	0
2	dioxane	$K_3PO_4 \cdot nH_2O$	80	8	89 (2)
3	dioxane	$K_3PO_4 \cdot nH_2O$	80	24	89 (4)
4	dioxane	Na_2CO_3	80	16	11 (5)
5	dioxane	Cs_2CO_3	80	16	trace
6	dioxane	CH_3CO_2Na	80	16	3 (1)
7	dioxane	CsF	80	16	13 (1)
8	DMF	$K_3PO_4 \cdot nH_2O$	100	16	2 (2)
9	THF	$K_3PO_4 \cdot nH_2O$	67	24	55 (6)
10	DME	$K_3PO_4 \cdot nH_2O$	80	24	67 (9)
11	benzene	$K_3PO_4 \cdot nH_2O$	80	24	69 (5)

[a] All reactions were carried out in 6 mL of solvent using phenylboronic acid (1.1 mmol), 3-chlorotoluene (1.0 mmol), base (3 mmol), and $NiCl_2$(dppf) (0.03 mmol). The $NiCl_2$(dppf) was *in situ* reduced to the Ni(0) complex with BuLi (0.12 mmol) prior to use for the next coupling reaction. [b] GC yields based on 3-chlorotoluene and the yields of biphenyl were shown in the parentheses.

The highly active nickel(0) catalysts were in situ obtained by treating the nickel chloride complexes with 4 equiv of *n*-BuLi at room temperature (entry 4).[12] The reduction with DIBAH similarly gave good results (entry 3), but low yields resulted in the reaction with the nickel chloride complexes themselves or their reduction with zinc dust (entries 1 and 2). The catalytic activity strongly depended on the phosphine ligands decreasing in the order of dppf > dppp > dppe > dppb ∼ PPh_3 (entries 4 and 10−13). The nickel(0) complexes are highly reactive, but they are a very labile species slowly decomposing on prolonged reaction times. Thus, the use of higher concentration of the catalyst was apparently advantageous to achieve high yields; however, a 3 mol % catalyst similarly gave high yields of cross-coupled products when an additional phosphine ligand was added to $NiCl_2$(dppf) or $NiCl_2(PPh_3)_2$. Although the addition of 1 equiv of dppf to $NiCl_2$(dppf) slowed the reaction rate (entry 5), a 92% yield was easily obtained after 24 h at 80 °C (entry 6). The addition of 2 equiv of triphenylphosphine, -arsine, and -antimony also gave good results (entries 7−9). A combination of 2 equiv of PPh_3 and $NiCl_2(PPh_3)_2$ allowed the use of an economical and readily available nickel catalyst based on triphenylphoshine (entry 14).

The reaction was accompanied with some biphenyl arising from the homocoupling of phenylboronic acid. The yield of biphenyl was less than 5% in most cases, but it improved when the cross-coupling resulted in low yields (entries 10, 11, and 13). However, the homocoupling of 3-chlorotoluene was not observed.

The $NiCl_2$(dppf)-catalyzed reaction between phenylboronic acid and 3-chlorotoluene was carried out at 80 °C using various bases and solvents (Table 2).

The palladium-catalyzed cross-coupling reaction of arylboronic acid with bromo- or iodoarenes can be best conducted in the presence of an aqueous base such as sodium carbonate or potassium phosphate.[1] However, aqueous bases should be avoided because the arylnickel(II) species involved in the catalytic cycle seem to be rather sensitive to water (entry 1). Finally, potassium phosphate suspended in dioxane was recognized to be the most effective to complete the reaction within 8 h (entries 2 and 3). The yields increased as the basicity increased (entries 2−6), but lower yields resulted in strong bases such as sodium hydroxide. Cesium fluoride is a mild base, accelerating the palladium-catalyzed cross-coupling reaction of organoboronic acids,[13] but it was, unfortunately, not effective for the nickel-catalyzed reaction (entry 7). Higher yields can be obtained in less polar solvents such as dioxane, DME, and benzene (entries 8−11).

Scope and Limitation

The results of the nickel(0)-catalyzed cross-coupling reaction of arylboronic acid with representative chloroarenes are summarized in Table 3.

The $NiCl_2$(dppf)-catalyzed reaction with chloroarenes having an electron-withdrawing group, such as 4-CN, 4-CHO, 2- or 4-CO_2Me, and 4-$COCH_3$, gave excellent yields of biaryls, often exceeding 90% (entries 1−6). However, the reaction completely failed for 4-chloronitrobenzene (entry 7). The catalyst may lose its activity by the formation of a stable (nitroso)nickel(II) species because the reaction of nitrobenzene with $Ni(PPh_3)_4$ gives nitrosobenzene and triphenylphosphine oxide.[14] For the substrates having an electron-donating group, a 3 mol % of catalyst is not sufficient to complete the reaction. Although the addition of 1 equiv dppf to $NiCl_2$(dppf) improved the yields, the best results can be more conveniently achieved by using a 10 mol % of the catalyst (entries 10 and 11).

Heteroatoms which coordinate to transition metals often retard the cross-coupling reactions of organometallics.[15] 7-Chloroindole and 2-chlorothiophene smoothly coupled with phenylboronic acid (entries 12 and 17), but 2-chloroquinoline was strongly resistant to the reaction (entries 13 and 14). A combination of $NiCl_2(PPh_3)_2$ (3 mol %) and 2 equiv of PPh_3 exceptionally gave a high yield of 2-phenylquinoline (entry 15).

Various functionalized arylboronic acids can be used for the cross-coupling reaction. However, arylboronic

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(14) Serman, R. S.; Kochi, J. K. *Inorg. Chem.* **1980**, *19*, 248−254.

(15) Yang, Y. *Synth. Commun.* **1989**, *19*, 1001−1004.

Table 3. Synthesis of Biaryls *via* the Nickel(0)-Catalyzed Cross-Coupling of Arylboronic Acids with Chloroarenes[a]

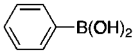
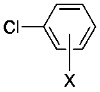
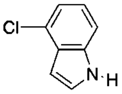
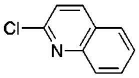
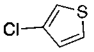
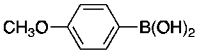
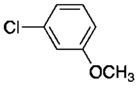
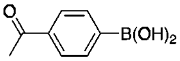
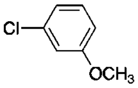
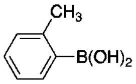
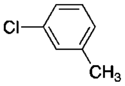
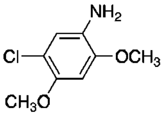
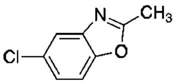
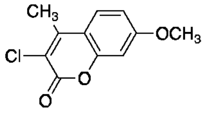
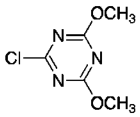
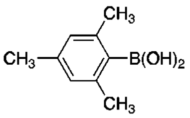
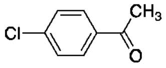
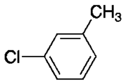
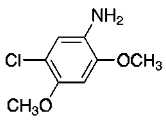
entry	arylboronic acid	chloroarenes		reaction conditions	yield/%[b]
1			X=4-CN	$NiCl_2$(dppf)/dioxane/80 °C/6 h	74
2			X=4-$COCH_3$		96
3			X=4-CHO		89
4			X=4-CO_2CH_3		87
5			X=3-CO_2CH_3	$NiCl_2$(dppf)/dioxane/80 °C/8 h	96
6			X=2-CO_2CH_3	$NiCl_2$(dppf)/dioxane/80 °C/12 h	(63) (89)^c
7			X=4-NO_2	$NiCl_2$(dppf)/dioxane/80 °C/16 h	0
8			X=4-$NHCOCH_3$	$NiCl_2$(dppf)/dioxane/80 °C/8 h	81
9			X=4-OCH_3	$NiCl_2$(dppf)/dioxane/80 °C/16 h	82
10			X=4-NH_2	$NiCl_2$(dppf)/dioxane/80 °C/24 h	(90)^c
11			X=4-$N(CH_3)_2$	$NiCl_2$(dppf)/dioxane/80 °C/24 h	(85)^c
12				$NiCl_2$(dppf)/dioxane/80 °C/16 h	80
13				$NiCl_2$(dppf)/dioxane/80 °C/24 h	28, 59^c
14				$NiCl_2$(dppf)/dppf/dioxane/80 °C/24 h	36
15				$NiCl_2(PPh_3)_2$/2 PPh_3/dioxane/80 °C/24 h	90
16				$NiCl_2$(dppf)/dioxane/80 °C/24 h	39, 88^c
17				$NiCl_2$(dppf)/dppf/dioxane/80 °C/24 h	86
18				$NiCl_2$(dppf)/dioxane/80 °C/16 h	91
19				$NiCl_2$(dppf)/dioxane/80 °C/20 h	36^c
20				$NiCl_2$(dppf)/DME/80 °C/24 h	77^c
21				$NiCl_2$(dppf)/dioxane/80 °C/16 h	30
22				$NiCl_2$(dppf)/dppf/dioxane/80 °C/16 h	91
23				$NiCl_2(PPh_3)_2$/2 PPh_3/dioxane/80 °C/16 h	92
24				$NiCl_2$(dppf)/dppf/dioxane/80 °C/16 h	(92)
25				$NiCl_2$(dppf)/dppf/dioxane/80 °C/16 h	(90)

Table 3 (Continued)

entry	arylboronic acid	chloroarenes	reaction conditions	yield/%[b]
26			$NiCl_2$(dppf)/dppf/dioxane/80 °C/16 h	(20)
27			$NiCl_2$(dppf)/dppf/benzene/70 °C/16 h	(82)
28			$NiCl_2$(dppf)/2 $SbPh_3$/benzene/70 °C/16 h	(90)
29			$NiCl_2$(dppf)/dppf/dioxane/80 °C/16 h	(25)
30			$NiCl_2$(dppf)/2 $SbPh_3$/benzene/70 °C/16 h	(46)
31			$NiCl_2$(dppf)/dppf/benzene/70 °C/16 h	(33) (69)[c]
32			$NiCl_2$(dppf)/dppf/benzene/70 °C/16 h	(78)
33			$NiCl_2$(dppf)/dpppf/dioxane/80 °C/16 h	30
34			$NiCl_2$(dppf)/2 PPh_3/benzene/70 °C/16 h	42
35			$NiCl_2$(dppf)/2 $SbPh_3$/benzene/70 °C/16 h	70
36			$NiCl_2$(dppf)/2 $SbPh_3$/benzene/70 °C/16 h	(22)

[a] All reactions were carried out under argon using arylboronic acid (1.1 equivs), chloroarene (1 equiv), K_3PO_4•nH_2O(3 equivs) and $NiCl_2$(dppf) (3 mol%), unless otherwise noted. $NiCl_2$(dppf) was reduced with BuLi (4 equivs) in the presence of an additinal ligand.

[b] GC yields based on chloroarenes and isolated yields are in the parentheses.

[c] 10 mol% of $NiCl_2$(dppf) was used.

acids having electron-withdrawing groups often resulted in low yields due to the C−B bond cleavage with the base.[2c,16] For example, the cross-coupling of 4-acetylphenylboronic acid with 3-methoxychlorobenzene gave only 36% of biary accompanied with a large amount of acetophenone, even in the presence of 10 mol % of $NiCl_2$(dppf) (entry 19). For such arylboronic acids, 1,2-dimethoxyethane (DME) was a better solvent than dioxane because the hydrolytic protodeborylation is rather slow in DME (entry 20).

The nickel-catalyzed cross-coupling reaction is more sensitive to the steric hindrance of both arylboronic acids and chloroarenes than the palladium-catalyzed reaction. Presumably, this is partly due to the shorter bond lengths of Ni−C and Ni−Cl than that of the palladium complexes. However, *ortho*-monosubstituted arylboronic acids, such as *o*-tolylboronic acid, readily coupled with various chloroarenes having *ortho*-monosubstituents or heteroatoms (entries 21−31). The use of an additional phosphine ligand apparently gave better results in most cases. It is interesting that benzene was advantageous over dioxane for chloroarenes sensitive to bases, whereas the inorganic base is insoluble in such solvent (entries 27−31). It was more difficult to achieve high yields in the reaction of mesitylboronic acid due to its large steric hindrance in the transmetalation step. Although the presence of an electron-withdrawing group allowed a very smooth coupling (entry 32), the reactions were extremely slow for electron rich chloroarenes. A combination of $NiCl_2$(dppf) and Ph_3Sb[17] in benzene was found to be effective in the reaction with 3-methylchlorobenzene (entry 35), but all attempts at the arylation of *ortho*-substituted chloroarenes were unsuccessful (for example 36). Thus, it can be rather difficult to achieve high yields in the synthesis of *ortho* trisubstituted biaryls by the nickel-catalyzed reaction.

Mechanism

The nickel-catalyzed cross-coupling reaction of Grignard reagents with organic halides was extensively studied by Kumada and Tamao.[9] The unique mechanism[18] proceeding through the oxidative addition, transmetalation, and reductive elimination has been a guide to the theoretical fundamentals and the synthetic applications to other cross-coupling reactions of organozinc,[19] -stannanes,[20] -boron,[1] and -silicones[21] with the palladium catalysts (Figure 1).

The nickel(II) chloride phosphine complexes are readily reduced to the nickel(0) species by treatment with BuLi[22] or other various organometallics via a transmetalation

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(16) Kuvilla, H. G.; Nahabedian, K. V. *J. Am. Chem. Soc.* **1961**, *83*, 2159, 2164 and 2167. Kuvila, H. G.; Reuwer, J. F.; Mangravite, J. A. *J. Am. Chem. Soc.* **1964**, *86*, 2666.

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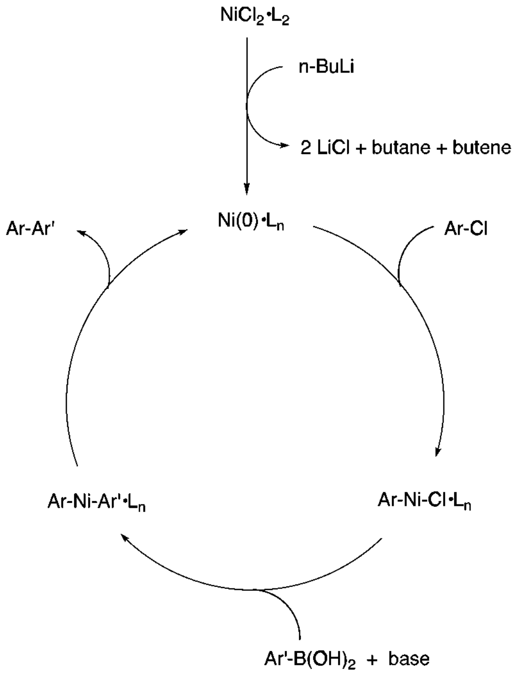

Figure 1. Catalytic cycle.

and reductive elimination or β-hydride elimination sequence. The electron-rich nickel(0) complexes thus obtained are highly reactive, undergoing the oxidative addition to various chloroarenes. The addition of substituted chloroarenes to $Ni(PPh_3)_4$ reported by Casser[23] exhibited a unique Hammett's correlation suggesting two different mechanisms in the regions of electron-donating groups and -withdrawing groups (the dotted lines in Figure 3). The reactivity linearly increased by electron-withdrawing groups with $\sigma > 0.23$ ($\rho = 8.6$), but it was quite insensitive to the electron-donating substituents with $\sigma < 0.23$ ($\rho = 0.59$). The results are in sharp contrast to the substitution effect in the oxidative addition of chloroarenes to the palladium(0) complex which revealed a linear correlation to σ^- in a range of -0.26 to 1.126 ($\rho = 5.2$).[24] Thus, chloroarenes having electron-donating groups, even 4-amino- (σ, -0.66) and 4-(dimethylamino)chlorobenzene (σ, -0.83), exhibit a quite similar reactivity to chlorobenzene itself in the reaction with the nickel(0) complexes, whereas the palladium-catalyzed reaction is greatly retarded by such substituents. The yields of biaryls in the palladium- and nickel-catalyzed cross-coupling reactions of phenylboronic acid with substituted chloroarenes are shown in Table 4.

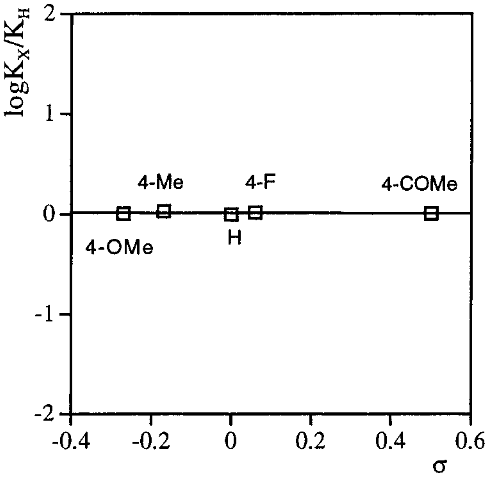

Figure 2. Effect of substituents on arylboronic acids.

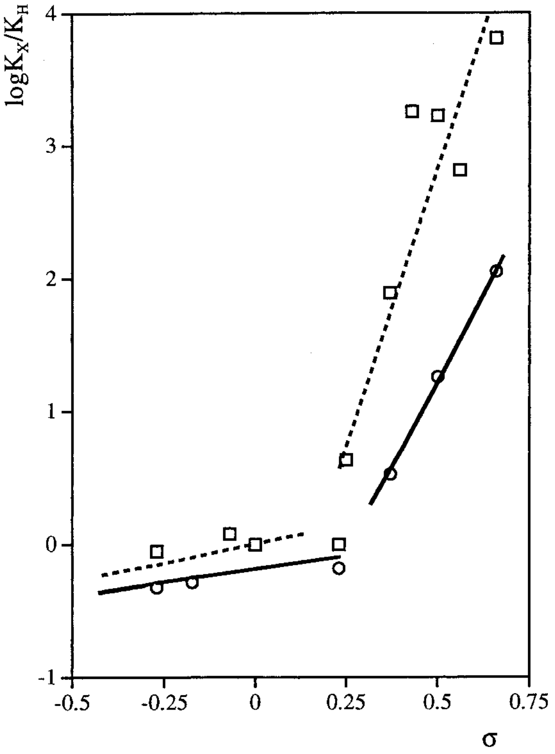

Figure 3. Effects of substituents on chloroarenes (Table 6). The solid lines (○) show the effect on the present reaction, and the dotted lines (□) indicate the correlation in the oxidative addition of ArCl to $Ni(PPh_3)_4$ reported by Casser.

The palladium-catalyzed reaction was limitedly used for the substituents with $\sigma > 0.45$, whereas all substituents in a range of -0.83 to 0.66 well accommodated the nickel-catalyzed reaction.

The effects of substituents on arylboronic acids and chloroarenes are shown in Figures 2 and 3.

The nucleophilicity of aryl groups on the boron atom may affect the rates of either transmetalation or reductive elimination,[25] but the two steps did not determine the total reaction rate because the relative reactivity was quite insensitive to the substituents on arylboronic acids (Figure 2). Thus, K_3PO_4 suspended in dioxane has sufficient basicity to assist the transmetalation step, the mechanism of which is, however, not yet obvious at

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(18) The nickel-catalyzed reaction; (a) Morrell, D. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1975**, *97*, 7262–7270. The palladium-catalyzed reaction: (b) Ozawa, F.; Kurihara, K.; Fujimori, M.; Hidaka, T.; Toyoshima, T.; Yamamoto, A. *Organometallics* **1989**, *8*, 180–188. For general reviews: (c) Kochi, J. K. *Organometallic Mechanisms and Catalysis*; Academic: New York, 1978. (d) Hartley, F. R.; Patai, S. *The Chemistry of Metal–Carbon Bond*; Wiley: New York, 1985; Vol. 3. (e) Hegedus, L. S. *Organometallics in Organic Synthesis*; Schlosser, M., Ed.; Wiley: New York, 1994; p 383.

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(22) The treatment of the nickel(II) chloride complexes with n-BuLi (3 equiv) gives the corresponding nickel(0) complexes with evolution of 1-butene, butane, and octane.[18a]

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Table 4. Palladium- *versus* Nickel-Catalyzed Cross-Coupling of Phenylboronic Acid with Chloroarenes

			yield/%	
entry	substituent	σ^a	$Pd(PPh_3)_4{}^b$	$NiCl_2(dppf)^c$
1	4-C≡N	0.66	80	74
2	$4\text{-}COCH_3$	0.50	64	96
3	$4\text{-}CO_2CH_3$	0.45	40	87
4	$3\text{-}OCH_3$	0.12	<1	72
5	$3\text{-}CH_3$	−0.07	<1	89
6	$4\text{-}NMe_2$	−0.83	0	85^d

[a] Hammett constant. [b] A mixture of $PhB(OH)_2$ (1.1 mmol), ArCl (1 mmol), Na_2CO_3 (1.5 mmol), and $Pd(PPh_3)_4$ (0.03 mmol) in aqueous DME was heated at 80 °C for 16 h. [c] A mixture of $PhB(OH)_2$ (1.1 mmol), ArCl (1 mmol), $K_3PO_4 \cdot nH_2O$ (3 mmol), and $NiCl_2(dppf)$ (0.03 mmol) in dioxane was heated at 80 °C for 16 h. [d] A 10 mol % of $NiCl_2(dppf)$ was used.

present. The rate-determining role of the oxidative addition step in the reaction of chloroarenes with arylboronic acids was suggested by the plot of the relative reactivity of substituted chloroarenes to the σ constants. A small change in the rate constants ($\rho = 0.74$) in a range of −0.27 to 0.06 and a high electronic effect ($\rho = 5.26$) in 0.37 to 0.66 were characteristic of the correlation observed in the oxidative addition of chloroarenes to $Ni(PPh_3)_4$[23] (Figure 3).

The catalytic processes exhibited a strong dependence on the ligands utilized for the catalyst. The ligands may affect all three steps involved in the catalytic cycle, but the catalysts which accelerate the rate-determining step will be desirable. It was reported that alkylphosphines are superior to triarylphosphines on the oxidative addition of chloroarenes to the palladium(0) complexes,[7,8] and the nucleophilicity of the metal center increases upon the decrease of the P−M−P angle in the bis(phosphine)-palladium(0) or -platinum(0) complex.[26] However, alkylphosphines such as $NiCl_2(P^iPr_3)_2$ and $NiCl_2(\text{tricyclohexylphosphine})_2$ were less effective than triarylphosphines. The nickel catalysts based on dppf apparently gave better results than the dppe or dppp complexes (Table 1), that can be reverse to the order of nucleophilicity of the metal center.[26] Thus, the effect of ligands can be attributable to their ability to stabilize the labile nickel(0) species during the cross-coupling reaction. Indeed, the use of 10 mol % of the catalyst or an additional ligand to 3 mol % of $NiCl_2 \cdot L_2$ always gave higher yields than $NiCl_2(dppf)$ itself, and they were essential for sterically hindered or electron-rich chloroarenes (Table 3).

The cross-coupling reaction catalyzed by palladium or nickel complexes often affords unexpected byproducts including the homocoupling products of electrophiles and organometallics. The reaction of Grignard reagents has suffered from the homocoupling resulting from the metal−halogen exchange.[9,27] The metathesis of RMX to R_2M and MX_2 (M = Ni, Pd) produced both dimers of electrophiles and organometallics.[28] The oxidative addition of the metal−carbon bonds to the low-valent transition-metals[29] or their oxidation with oxygen or other oxidizing sources[30] has been another route leading to the dimer of organometallics. Exchange of metal- and phosphine-bound aryls produced the coupling products of organometallics with the aryl groups on the phosphine ligands.[31] The formation of the dimer of electrophiles was reported in the oxidative addition of organic halides to nickel(0) complexes via an electron-transfer mechanism.[32] Although there are many probable processes to give the byproducts, arylboronic acids undergo a clean cross-coupling reaction by the nickel catalyst. The observed byproducts were the dimers of arylboronic acids in less than 2%. The mechanism is not obvious at present; however, the process may not involve the oxidative addition of the C−B bond to the nickel(0) complex[29] because the reaction between phenylboronic acid and the Ni(0)dppf did not produce biphenyl at 80 °C for 16 h in the presence of K_3PO_4 (3 equiv). The coupling with electron-rich chloroarenes was often contaminated with very small amounts of arene resulting from the displacement of chlorine with the hydrogen atom, but the formation of the chloroarene dimers were less than 1%.[32]

Experimental Section

All experiments were carried out under an argon atmosphere. THF, DME, dioxane, and benzene were distilled from benzophenone ketyl.

Reagents. The reaction of $NiCl_2 \cdot 6H_2O$ with a commercially available phosphine ligand in benzene at 50 °C gave the nickel chloride complexes with dppf (1,1′-bis(diphenylphosphino)-ferrocene), dppe ($Ph_2PCH_2CH_2PPh_2$), dppp ($Ph_2PCH_2CH_2CH_2PPh_2$), dppb ($Ph_2PCH_2CH_2CH_2CH_2PPh_2$), and triphenylphosphine.[33] Chloroarenes purchased from Aldrich were distilled or recrystalized before use. Phenylboronic acid was obtained from Strem Chemical, and other arylboronic acids were prepared by the reported procedures.[34] $K_3PO_4 \cdot nH_2O$ from Nakarai Chem. Co. was used directly.

Caution. *The alkaline hydrogen peroxide oxidation of organoboron compounds is a convenient way to remove the residual organoboron species remaining in the reaction mixture. However, the addition of hydrogen peroxide to the mixtures containing nickel catalyst should be absolutely avoided because the nickel forms an explosive nickel peroxide.*

Effect of Catalyst and Ligand (Table 1). The flask was charged with $NiCl_2 \cdot L$ (L = dppf, dppe, dppp, dppb, and 2 PPh_3) (0.03 mmol) and then flushed with argon. The catalyst was dissolved in dioxane (6 mL) and treated with *n*-BuLi in hexane (0.12 mmol) at room temperature for 10 min to give a solution of the nickel(0) complex. Phenylboronic acid (1.1 mmol), $K_3PO_4 \cdot nH_2O$ (3 mmol), 3-chlorotoluene (1.0 mmol), and an additional ligand shown in Table 1 (0.03 mmol of dppf or 0.06 mmol of other monodentate ligands) were added to the flask. The reaction mixture was stirred at 80 °C during the period shown in Table 1. The reduction with zinc powder was in situ

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(30) The mixture of arylboronic acids, $Pd(OAc)_2$, and Na_2CO_3 in aqueous ethanol catalytically gives symmetrical biaryls and phenols on exposure to air.[35] The reaction may involve the oxidation of the palladium(0) complexes to the Pd(II)(OH)OOH.[36]

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carried out by directly heating the all mixture at 80 °C. The yields of biphenyl and 3-methylbiphenyl were analyzed by GC.

Effects of Base and Solvents (Table 2). The flask was charged with $NiCl_2(dppf)$ (0.03 mmol) and solvent (6 mL). The catalyst was reduced with *n*-BuLi in hexane (0.12 mmol) at room temperature for 10 min. Phenylboronic acid (1.1 mmol), a base (3 mmol), and 3-chlorotoluene (1.0 mmol) were added to the flask. The reaction mixture was then stirred at the temperature and during the period shown in Table 2.

Representative Procedure (Table 3). The following procedure for the cross-coupling of 2-methylphenylboronic acid with 4-amino-2,4-dimethoxychlorobenzene is representative (entry 24). A 50 mL-flask was charged with $NiCl_2(dppf)$ (0.021 g, 0.03 mmol) and dppf (0.018 g, 0.03 mmol) and flushed with argon. The catalyst was dissolved in dioxane (6 mL) and then reduced with *n*-BuLi (1.6 M, 0.075 mL, 0.12 mmol) at room temperature for 10 min to give a solution of nickel(0) complex. 2-Methylphenylboronic acid (0.15 g, 1.1 mmol), $K_3PO_4 \cdot nH_2O$ (0.636 g, 3 mmol), and 4-amino-2,4-dimethoxychlorobenzene (0.188 g, 1 mmol) were added through the neck of the flask keeping a slow stream of argon. The mixture was stirred at 80 °C for 16 h. The product was extracted with ether, washed with brine, and dried over $MgSO_4$. Chromatography over silica gel with hexane/ethyl acetate = 2/1 gave 0.220 g (91%) of the corresponding biaryl: ^1H NMR δ 2.15 (s, 3 H), 3.54 (broad s, 2 H), 3.67 (s, 3 H), 3.91 (s, 3 H), 6.54 (s, 1 H), 6.55 (s, 1 H), 7.15−7.25 (m, 4 H),; MS, *m/e* 115 (15), 168 (13), 196 (29), 197 (34), 213 (10), 228 (52), 243 (M^+, 100), 244 (18); exact mass calcd for $C_{15}H_{16}O_2N$ 243.1259, found 243.1231.

The following biaryls were synthesized by the above general procedure.

2-Phenylquinoline: ^1H NMR δ 7.44−7.60 (m, 4 H), 7.70−7.75 (m, 1 H), 7.82 (d, 1 H, J = 8.1 Hz), 7.87 (d, 1 H, J = 8.8 Hz), 8.15−8.25 (m, 4 H); MS, *m/e* 76 (9), 102 (24), 128 (6), 151 (4), 176 (7), 204 (81), 205 (M^+, 100); exact mass calcd for $C_{15}H_{11}N$ 205.0892, found 205.0899.

7-Phenylindole: IR 3375 cm^{-1}; ^1H NMR δ 6.72 (m, 1 H), 7.18−7.50 (m, 6 H), 7.71 (m, 2 H), 8.18 (broad s, 1 H); MS, *m/e* 117 (10), 139 (4), 154 (32), 165 (38), 193 (M^+, 100); exact mass calcd for $C_{14}H_{11}N$ 193.0892, found 193.0882.

2-Methyl-6-(2-methylphenyl)benzoxazole: ^1H NMR δ 2.26 (s, 3 H), 2.66 (s, 3 H), 7.22−7.29 (m, 5 H), 7.49 (d, 1 H, J = 8.3 Hz), 7.59 (d, 1 H, J = 1.7 Hz); MS, *m/e* 152 (32), 153 (43), 154 (29), 167 (32), 181 (42), 222 (25), 223 (M^+, 100); exact mass calcd for $C_{15}H_{13}ON$ 223.0997, found 223.0979.

3-(2-Methylphenyl)-4-methyl-7-methoxycoumarin: ^1H NMR δ 2.16 (s, 3 H), 2.17 (s, 3 H), 3.89 (s, 3 H), 6.80−6.50 (m, 2 H), 7.11 (d, 1 H, J = 7.1 Hz), 7.15−7.25 (m, 3 H), 7.57 (d, 1 H, J = 8.7 Hz); MS, *m/e* 165 (27), 178 (6), 194 (5), 221 (5), 237 (24), 252 (5), 263 (38), 265 (100), 280 (M^+, 62); exact mass calcd for $C_{18}H_{16}O_3N$ 280.1100, found 280.1120.

2-(2-Methylphenyl)-4,6-dimethoxy-1,3,5-triazine: ^1H NMR δ 2.70 (s, 3 H), 4.10 (s, 6 H), 7.20−7.40 (m, 3 H), 8.10 (d, 1 H, J = 8.1 Hz); MS, *m/e* 116 (85), 159 (31), 173 (4), 216 (100), 231 (M^+, 16); exact mass calcd for $C_{12}H_{13}O_2N_3$ 231.1008, found 231.1027.

Palladium- *versus* Nickel-Catalyzed Cross-Coupling (Table 4). The palladium-catalyzed cross-coupling reactions were carried out by the following general procedure. The flask was charged with phenylboronic acid (1.1 mmol), $Pd(PPh_3)_4$ (0.03 mmol), and Na_2CO_3 (3 mmol) and flushed with argon. DME (3 mL), water (0.5 mL), and a chloroarene (1 mmol) were added, and the mixture was then stirred for 16 h at 80 °C.

Table 5. Relative Reactivity of Substituted Arylboronic Acids to 3-Methoxychlorobenzene

$XC_6H_4B(OH)_2$ X =	$YC_6H_4B(OH)_2$ Y =	yield/%[a]	yield/%[b]	rel rate (Y/X)
H	4-CH_3CO	13.6	17.6	1.29
4-CH_3	4-F	15.1	19.8	1.31
H	4-CH_3	19.5	20.8	1.07
H	4-CH_3O	20.9	28.3	1.36

[a] Yields of $3\text{-}CH_3OC_6H_4C_6H_4X$. [b] Yields of $3\text{-}CH_3OC_6H_4C_6H_4Y$.

Table 6. Relative Reactivity of Substituted Chloroarenes to 3-Methoxyphenylboronic Acid

XC_6H_4Cl X =	YC_6H_4Cl Y =	yield/%[a]	yield/%[b]	rel rate (Y/X)
3-CO_2CH_3	4-CN	1.6	51.1	31.9
H	4-$COCH_3$	4.2	76.6	18.2
H	3-CO_2CH_3	21.1	69.4	3.27
4-F	4-CH_3	40.7	30.2	0.742
4-F	4-OCH_3	23.3	29.2	1.25
H	4-CH_3	37.2	18.4	0.495
H	4-OCH_3	38.8	18.5	0.495

[a] Yields of $3\text{-}CH_3OC_6H_4C_6H_4X$. [b] Yields of $3\text{-}CH_3OC_6H_4C_6H_4Y$.

For the nickel-catalyzed reactions, see the entries 1−11 in Table 3.

Effect of Substituents on Arylboronic Acid (Figure 2). The cross-coupling reaction in dioxane did not give a good correlation due to the hydrolytic protodeboration of arylboronic acids. Thus, all the reactions were carried out in DME. $NiCl_2(dppf)$ (0.045 mmol) in DME (6 mL) was treated with *n*-BuLi in hexane (0.108 mmol) at room temperature for 10 min. Two arylboronic acids (1.65 mmol of $XC_6H_4B(OH)_2$ and 1.65 mmol of $YC_6H_4B(OH)_2$), K_3PO_4 (45 mmol), and 3-methoxychlorobenzene (1.5 mmol) were successively added to the above catalyst solution. The mixture was stirred for 3 h at 80 °C. The relative reactivity was estimated from the yields of two biaryls. The same reaction was repeated three times, and their averages are shown in Table 5.

Effect of Substituents on Chloroarenes (Figure 3). To a solution of $NiCl_2(dppf)$ (0.045 mmol) in dioxane (6 mL) was added *n*-BuLi in hexane (0.18 mmol) at room temperature. 3-Methoxyphenylboronic acid (1.65 mmol), K_3PO_4 (4.5 mmol), and two chloroarenes (1.5 mmol of XC_6H_4Cl and 1.5 mmol of YC_6H_4Cl) were added, and the mixture was then stirred for 3 h at 80 °C. The same reaction was repeated three to four times, and their yields were averaged to give the relative reactivity (Table 6).

Supporting Information Available: Copies of NMR spectra of biaryls (23 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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