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Ni-catalyzed cross-coupling reaction of aryl chlorides with arylboronic acids in IPA without using a reducing reagent

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Abstract—The coupling reaction of aryl chlorides with arylboronic acids was successfully performed in isopropanol (IPA) by using $[NiCl(Ph_2PCH_2CH_2OH)_2(H_2O)]Cl$ (**5**), a cationic Ni(II)-complex, as a precatalyst in the absence of a reducing agent. The coupling reaction proceeded smoothly under mild conditions to provide biaryls in satisfactory to excellent yields, and formation of the undesired dechlorination products of aryl chlorides was completely prevented.

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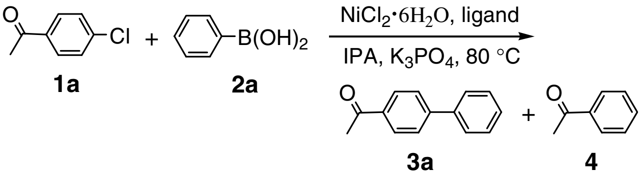
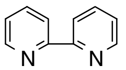
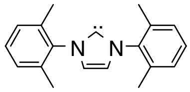
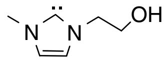
Suzuki cross-coupling reaction has become one of the most useful methods for the construction of C–C bonds.[1] During the past decade, Pd catalysts have been used commonly for the cross-coupling of organoboron compounds with organic halides or pseudo-halides, such as aryl bromide,[1] iodides,[1] and triflates[2] as well as sulfonates.[3] However, the more easily accessible aryl chlorides have been rarely employed as coupling partners in palladium-catalyzed Suzuki coupling because the oxidative addition of C–Cl bond to Pd(0) species is usually difficult.[4] In 1996, Miyaura and co-workers reported the first example of Ni(0)-catalyzed cross-coupling of aryl chlorides with arylboronic acids.[5] Since then, several examples have been reported by other research groups.[6] However, the use of Ni(II) complexes as precatalysts often needs to combine an activating agent such as Zn or BuLi to generate Ni(0) species in situ to achieve high efficiency of the catalysts.[5,6a,c] More recently, Fu and coworker reported an impressive result that the coupling reaction of unactivated alkyl halides with arylboronic acids could be performed by using NiI_2-NaHDMS catalyst system in isopropanol (IPA).[7] IPA has recently attracted considerable interest as a solvent in this type of coupling reaction because it is readily available and inexpensive with low toxicity.[8] During our continuous research on Suzuki coupling reaction,[9] we attempted to

Table 1. Ligand effect in the Ni(II)-catalyzed cross-coupling of 4-chloroacetophenone (**1a**) with phenylboronic acid (**2a**)[a]



Entry	Ligand	Yield (%) of **3a**[b]	Yield (%) of **4**[b]
1	PPh_3	14	46
2	$P(OPh)_3$	43	41
3	$O{=}PPh_3$	19	12
4	PCy_3	0	97
5	NPh_3	16	16
6	Pyridine	36	7
7		0	0
8	DPPF	0	0
9	DPPF	6	58
10	$Ph_2PCH_2CH_2OH$	99	0
11	$Ph_2PCH_2CH_3$	40	56
12		0	0
13		9	22

[a] Reaction conditions: 4-chloroacetophenone (0.5 mmol), phenylboronic acid (1.5 equiv), K_3PO_4 (2.0 equiv), $NiCl_2{\cdot}6H_2O$ (3 mol %), ligand (12 mol % for monodentate ligand; 6 mol % for bidentate ligand), IPA (2 mL), 80 °C, 12 h.

[b] GC yield based on 4-chloroacetophenone.

Keywords: Nickel catalyst; Suzuki coupling; Aryl chloride; Isopropanol.

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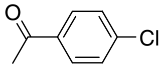
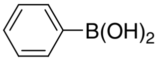
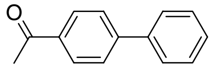
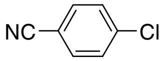
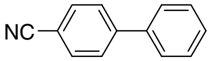
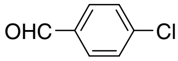
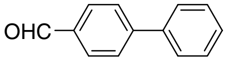
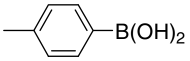
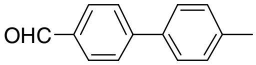
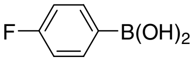
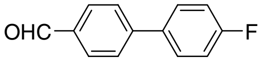
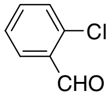
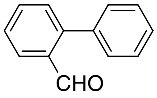
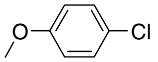
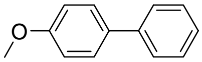
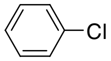
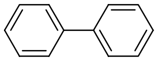
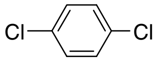
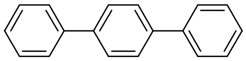
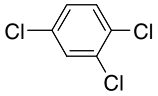
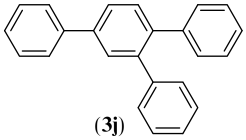
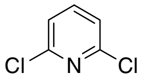
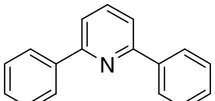
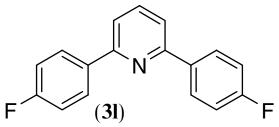
use IPA as a solvent for Ni(II)-catalyzed coupling reaction of aryl chlorides with arylboronic acids in the absence of a reducing agent, and found that the cross-coupling reaction proceeded smoothly in the presence of [NiCl($Ph_2PCH_2CH_2OH$)$_2$(H_2O)]Cl (**5**) to provide the desired products in satisfactory to excellent yields. Herein our results are reported.

The influence of various ligands in a model reaction of 4-chloroacetophenone (**1a**) with phenylboronic acid

Table 2. Ni(II)-catalyzed cross-coupling of aryl chlorides (**1**) with arylboronic acids (**2**)[a]

Entry	Aryl chloride (**1**)	Ar–B(OH)$_2$ (**2**)	Product (**3**)	Time (h)	Yield (%)[b]
1	 (**1a**)	 (**2a**)	 (**3a**)	12	99
2	 (**1b**)	(**2a**)	 (**3b**)	4	99
3	 (**1c**)	(**2a**)	 (**3c**)	4	91
4	(**1c**)	 (**2b**)	 (**3d**)	6	91
5	(**1c**)	 (**2c**)	 (**3e**)	6	93
6	 (**1d**)	(**2a**)	 (**3f**)	4	88
7	 (**1e**)	(**2a**)	 (**3g**)	12	63
8	 (**1f**)	(**2a**)	 (**3h**)	12	54
9[c]	 (**1g**)	(**2a**)	 (**3i**)	18	60
10[d]	 (**1i**)	(**2a**)	 (**3j**)	24	58
11	 (**1j**)	(**2a**)	 (**3k**)	6	70
12[c]	(**1j**)	(**2a**)	(**3k**)	4	96
13[c]	(**1j**)	(**2c**)	 (**3l**)	4	92

[a] All reactions were carried out under nitrogen at 80 °C for the period indicated in the table using aryl chloride (0.5 mmol), arylboronic acid (1.5 equiv), K_3PO_4 (2.0 equiv), IPA (2.0 mL) and Ni-complex **5** (3 mol %), unless otherwise noted. The reaction progress was monitored by TLC.

[b] Isolated yields.

[c] 3.0 equiv of **2a** or **2c** was used.

[d] 4.5 equiv of **2a** was used.

(**2a**) using IPA as a solvent was examined, and the results are shown in Table 1. When PPh_3[10] was used as a ligand, the desired coupling product 4-phenylacetophenone (**3a**) was obtained only in 14% yield, and a large amount (46%) of dechlorination product acetophenone (**4**), was afforded (Table 1, entry 1). The use of $P(OPh)_3$ and $O{=}PPh_3$ gave coupling product **3a** in 43% and 19% yield, along with dechlorination product **4** in 41% and 12% yield, respectively (entries 2 and 3). When the reaction was performed in the presence of an electron-rich ligand PCy_3,[11] the undesired compound **4** was obtained as the sole product in 97% yield (entry 4). The employment of nitrogen-containing ligands such as triphenylamine, pyridine, and 2,2′-bipyridine,[12] also failed to give the desired coupling product **3a** in high yield, and the starting materials were recovered in large amounts (entries 5–7). Although the P-containing bidentate ligands, bis(diphenylphosphino)ethane (DPPE)[13] and 1,1′-bis(diphenylphosphino)ferrocene (DPPF),[14] were also investigated, the results were not satisfactory (entries 8 and 9). Interestingly, when the ligand $Ph_2PCH_2CH_2OH$[9] was utilized, the desired biaryl **3a** was obtained in almost quantitative yield (99%, entry 10). However, an attempt to use $Ph_2PCH_2CH_3$ in place of $Ph_2PCH_2CH_2OH$ in the coupling reaction resulted in failure, giving the desired product **3a** only in 40% yield (entry 11). Finally, we examined electron-rich N-heterocyclic carbene ligands,[15] but the reaction did not proceed or gave trace amounts of the desired product **3a** even when the N-heterocyclic carbene ligand bearing hydroxyethyl moiety was used (entries 12 and 13). The above results indicated that among the ligands screened, $Ph_2PCH_2CH_2OH$ was the most effective ligand to promote this coupling in IPA, suggesting that both the electron-richness and the hydroxyethyl moiety of this ligand play important roles in the catalyst system. Therefore, we chose $Ph_2PCH_2CH_2OH$ as a ligand to carry out the coupling reaction of other aryl chloride substrates with arylboronic acids in IPA by using nickel catalyst.

Because the ligand $Ph_2PCH_2CH_2OH$ exists as liquid at room temperature, it is not easy to handle it in a small scale. Therefore, Ni(II)-complex containing $Ph_2PCH_2CH_2OH$ was prepared and used for the cross-coupling reaction (Table 2), and the X-ray crystal structure of Ni(II)-complex is shown in Figure 1. It clearly shows a cationic structure of $[NiCl(Ph_2PCH_2CH_2OH)_2(H_2O)]Cl$ (**5**).[16] In the molecular structure of complex **5**, two $Ph_2PCH_2CH_2OH$ ligands chelate to nickel and one chlorine anion as well as one water molecule coordinate to the same nickel atom, and another Cl^- is located as a counter ion.

The coupling reaction of aryl chlorides (**1a**–**c**) bearing an electron-withdrawing group, such as 4-$COCH_3$, 4-CN, and 2- or 4-CHO, with phenylboronic acid gave biaryls in excellent yields ranging from 88% to 99% (Table 2, entries 1–3 and 6). The coupling reaction of **1c** with 4-methylphenylboronic acid (**2b**) or 4-fluorophenylboronic acid (**2c**) also afforded the corresponding biaryls in excellent yields (**3d**: 91%, entry 4; **3e**: 93%, entry 5). 4-Chloroanisole (**1e**) and chlorobenzene (**1f**) reacted with **2a** to give the coupling products **3g** and **3h** in moderate yields (63% and 54%, respectively, entries 7 and 8). The results were in accordance with the common understanding that an electron-withdrawing group in aromatic ring accelerates the process of metal (Pd or Ni) insertion into the C–Cl bond. When the coupling reaction of 1,4-dichlorobenzene (**1g**) with 3 equiv of **2a** was performed, the bis-coupled product **3i** was afforded in 60% yield (entry 9), accompanied with mono-coupled product, 4-chlorobiphenyl, in 12% yield. The further attempt by using 1,2,4-trichlorobenzene (**1i**) revealed that tri-coupling product **3j** was obtained as the major product (58%, entry 10) along with mono- and di-coupling products in total 15% yield. Interestingly, when 2,6-dichloropyridine (**1j**) was treated with 1.5 equiv of **2a**, bis-coupled product, 2,6-diphenylpyridine (**3k**), was obtained as the sole product in 70% yield (entry 11). This result was consistent with that of the literature.[17] The coupling reaction of **1j** with 3.0 equiv of **2a** gave **3k** in a high yield (96%, entry 12). Furthermore, the coupling reaction of **1j** with 3.0 equiv of **2c** gave the desired bis-coupled product **3l** also in a high yield (92%, entry 13).[18]

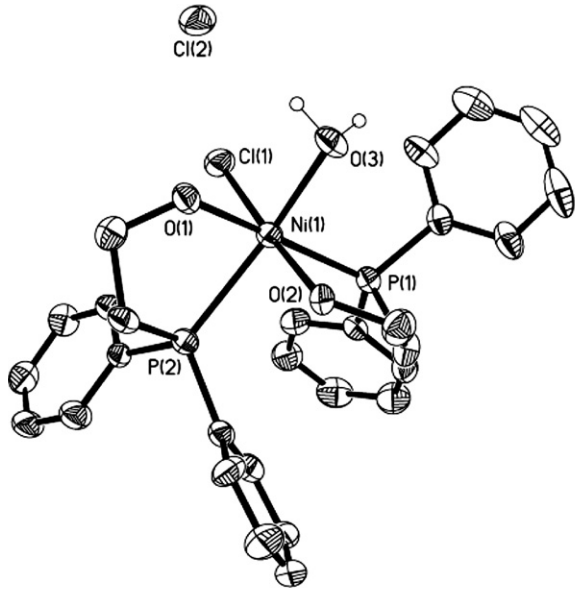


Figure 1. Crystal structure of complex **5**.

When the Ni-catalyzed cross-coupling reaction of aryl chlorides with arylboronic acids was performed in IPA, the major impediment was the intervention of a facile dechlorination pathway, which competed with the desired cross-coupling. In our procedure developed, Ni(II)-$Ph_2PCH_2CH_2OH$ complex can be utilized as a precatalyst without use of any reducing agent to provide biaryls in satisfactory to excellent yields, and the undesired dechlorination reaction was completely prevented. The reason why $Ph_2PCH_2CH_2OH$, a simple ligand, promoted the Ni-catalyzed coupling of aryl chlorides with arylboronic acids in IPA exclusively has not yet been clarified at present. However, it seems that the OH group of $Ph_2PCH_2CH_2OH$ in the intermediate, $ArNi(Ph_2PCH_2CH_2OH)_2Cl$, coordinates to boron atom of arylboronic acid to facilitate intramolecular transmetalation between boron and chlorine.[19]

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9. Guo, M.-P.; Jian, F.-F.; He, R. *Tetrahedron Lett.* **2005**, *46*, 9017–9020.
10. PPh_3 was an effective ligand for Ni-catalyzed cross-coupling of aryl chlorides with arylboronic acids in dioxane, toluene or THF. See: (a) Ref. 6e; (b) Ref. 6k.
11. PCy_3 has been utilized as a effective ligand for Ni-catalyzed coupling of aryl tosylates and aryl chlorides with arylboronic acids in THF or dioxane. See: (a) Ref. 6h; (b) Zim, D.; Lando, V. R.; Dupont, J.; Monterio, A. L. *Org. Lett.* **2001**, *3*, 3049–3051.
12. $NEt_3$and 2,2′-bipyridine have been used as ligands instead of phosphines, for Ni-catalyzed coupling of aryl halides with arylboronic acids in dioxane. See: Ref. 6d.
13. DPPE can be used as a ligand for Ni-catalyzed coupling of aryl chlorides, aryl mesylates or aryl sulfonates with arylboronic acids in dioxane/H_2O or dioxane. See: (a) Ref. 6c; (b) Ref. 6g.
14. A numbers of papers have demonstrated that DPPF is more effective ligand for Ni-catalyzed coupling of aryl chlorides or aryl mesylates with arylboronic acids in dioxane, toluene or THF. See: (a) Ref. 5; (b) Refs. 6a,b; (c) Ueda, M.; Saitoh, A.; Oh-tani, S.; Miyaura, N. *Tetrahedron* **1998**, *54*, 13079–13086; (d) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1060–1065.
15. Recently, N-heterocyclic carbenes have attracted considerable attention as an efficient ligand for Pd or Ni-catalyzed Suzuki coupling. See: (a) Ref. 4. (b) Ref. 61.
16. The complex $[NiCl(Ph_2PCH_2CH_2OH)_2(H_2O)]Cl$ (**5**) was prepared by the following procedure: A solution of $NiCl_2 \cdot 6H_2O$ (0.48 g, 2.0 mmol) dissolved in minimum amounts of ethanol was added to a solution of $Ph_2PCH_2CH_2OH$ (1.01 g, 4.4 mmol) in 50 mL of ether, and after the reaction mixture with grape color was stirred for 16 h, a lot of green solid formed. The resulting mixture was filtered to produce green solid. Recrystallization of the crude product from ethanol/ether afforded **5** as green crystals (0.73 g, 60% yield). MS (API-ES): *m*/*z*: 517.1 $[M–H_2O–2Cl–H]^+$; Anal. Calcd for $C_{28}H_{32}Cl_2NiO_3P_2$: C, 55.30; H, 5.30. Found: C, 55.72; H, 5.50. X-ray crystallographic analysis was carried out on a Rigaku AFC7R diffractometer using a rotating anode with graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). Crystal data for **5**: $C_{28}H_{32}Cl_2NiO_3P_2$, $M = 608.10$, space group: monoclinic, $C2/c$, $a = 17.8864(11)$ Å, $b = 8.5177(6)$ Å, $c = 38.512(3)$ Å, $\alpha = 90.00(0)°$, $\beta = 102.164(3)°$, $\gamma = 90.00(0)°$, $V = 5735.7(7)$ Å,[3] $T = 273(2)$ K, $Z = 8$, $D_c = 1.399\ \mathrm{g\ cm^{-3}}$, $\mu = 1.002\ \mathrm{mm^{-1}}$, goodness of fit = 1.020, $R_1\ [I > 2\sigma(I)] = 0.0499$, $wR_2 = 0.1260$. Selected bond distances (Å) and angles (°) are shown as follows: Ni(1)–O(1) 2.109(5), Ni(1)–O(2) 2.149(5), Ni(1) –O(3) 2.125(5), Ni(1)–Cl(1) 2.331(2), Ni(1)–P(1) 2.360(2), Ni(1)–P(2) 2.469(2), O(1)–Ni(1)–O(3) 82.0(2), O(1)–Ni(1)–O(2) 86.7(2), O(3)–Ni(1)–O(2) 84.0(2), O(1)–Ni(1)–Cl(1) 91.15(15), O(3)–Ni(1)–Cl(1) 91.67(16), O(2)–Ni(1)–Cl(1) 175.36(14), O(1)–Ni(1)–P(1) 168.35(15), O(3)–Ni(1)–P(1) 93.86(16), O(2)–Ni(1)–P(1) 82.01(15), Cl(1)–Ni(1)–P(1) 99.89(8), O(1)–Ni(1)–P(2) 80.31(15), O(3)–Ni(1)–P(2) 158.57(17), O(2)–Ni(1)–P(2) 83.01(13), Cl(1)–Ni(1)–P(2) 100.71(8), P(1)–Ni(1)–P(2) 101.07(8). Atomic coordinates, other bond lengths, and other angles and the other important parameters have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication, CCDC No. 626494. Copies of this information can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1233-336033 or e-mail: deposit@ccdc.cam.ac.uk).
17. Siclair, D. J.; Sherburn, M. S. *J. Org. Chem.* **2005**, *70*, 3730–3733.
18. General procedure for the coupling of aryl chlorides with arylboronic acids: A mixture of aryl chloride (0.5 mmol), arylboronic acid (0.75 mmol), potassium phosphate (1.0 mmol), complex **5** in 2 mL of IPA was stirred at 80 °C under a nitrogen atmosphere for 4–24 h. The reaction progress was monitored by TLC, and aryl chloride disappeared after 2–24 h. When the reaction completed, the mixture was cooled to room temperature, then was filtered by a short silica gel column to afford a crude product. Further purification of the product was performed by a chromatography on silica gel column [petroleum ether (60–90 °C)/ethyl acetate = 100:0 to 20:1].
19. Son, S. U.; Kim, S. B.; Reingold, J. A.; Carpenter, G. B.; Sweigart, D. A. *J. Am. Chem. Soc.* **2005**, *127*, 12238–12239.