Homocoupling of Aryl Halides Using Nickel(II) Complex and Zinc in the Presence of Et_4NI. An Efficient Method for the Synthesis of Biaryls and Bipyridines[1)]

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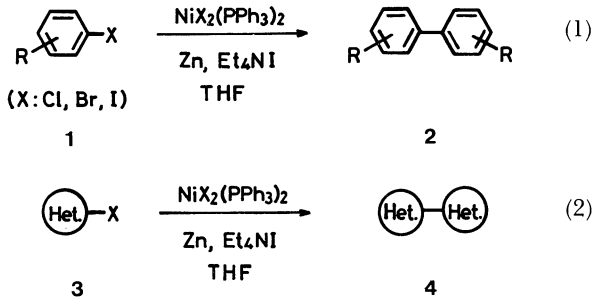
(Received July 18, 1989)

Reduction of $NiX_2(PPh_3)_2$ with zinc in the presence of Et_4NI gives a nickel catalyst which has been proven to be useful for the coupling of aryl halides. This nickel catalyst can be prepared in THF without an additional triphenylphosphine and is effective for the homocoupling of aryl chlorides, bromides, and iodides to produce biaryls and bipyridines in good yields. The reported new approach provides a simple access to novel derivatives of biaryls and bipyridines.

The nickel-catalyzed homocoupling of aryl halides[2)] has received considerable attention in recent years, because the reaction proceeds under very mild conditions as compared with the classical Ullmann conditions to give the corresponding biaryls in relatively good yields, and because many functional groups such as aldehyde or ketone do not interfere in the coupling of halides. The yield of biaryls in the coupling reaction has been found to be dependent on a suitable choice of zerovalent nickel complexes, solvents, and additives such as iodide, bromide, or triphenylphosphine. Semmelhack's early investigation on this coupling was carried out using stoichiometric amounts of air-sensitive bis(1,5-cyclooctadiene)nickel(0) in *N*,*N*-dimethylformamide (DMF).[3)] Kende[4)] has demonstrated that an effective coupling of aryl bromides and iodides proceeds by stoichiometric amounts of $Ni(PPh_3)_4$[5)] which is generated in situ in DMF from $NiCl_2(PPh_3)_2$, PPh_3, and zinc [the molar ratio=1:2:1]. Kumada and Tamao[6)] improved Kende's method and presented that the coupling reaction proceeds catalytically using 5 molar% of nickel(II) complex and stoichiometric amounts of zinc in the presence of excess PPh_3 in DMF. Because of the wide applicability of this nickel-catalyzed coupling reaction, many alternative methods, improvements and modifications have been reported up to date.[7–15)]

Recently, we have reported an efficient homocoupling of organic halides using an active nickel complex[16)] which is generated in situ by reduction of $NiX_2(PPh_3)_2$ with zinc in the presence of Et_4NI. This active nickel complex is effective for the coupling of aryl halides to produce biaryls in good to high yields. Many groups have reported that iodide ion causes an acceleration of the nickel-catalyzed coupling reactions.[6,8,9,11,13–15)] However, our method reported in this paper possesses several advantages: (a) no additional PPh_3 is necessary for the preparation of the catalyst; (b) tetrahydrofuran (THF) can be employed as solvent instead of DMF; (c) the coupling of aryl chlorides proceeds smoothly under the reaction conditions. Thus, the present study describes the efficient method for the preparation of biaryls and bipyridines.



Results and Discussion

Synthesis of Biaryls. We initially studied the reductive coupling of bromobenzene with $NiX_2(PPh_3)_2$ and zinc in the presence of Et_4NI (Eq. 3 and Table 1). The nickel-catalyzed coupling of bromobenzene in various solvents (50 °C, 2 h) proceeds smoothly in the presence of 1 equiv of Et_4NI to give biphenyl in good yields. Nickel-catalyzed coupling of aryl halides was reported to proceed smoothly only in the dipolar aprotic solvents such as DMF,[3,4,6)] *N*,*N*-dimethylacetamide,[14)] hexamethylphosphoric triamide (HMPA),[8)] and *N*-methyl-2-pyrrolidone,[8)] because these solvents can play a role as donor ligands which stabilize the

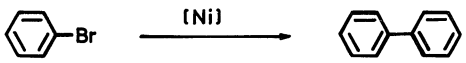


Table 1. Coupling of Bromobenzene with $NiX_2(PPh_3)_2$ and Zn in the Presence of Et_4NI[a)]

Catalyst	Solvent	Isolated yield/%
$NiCl_2(PPh_3)_2$	THF	92
$NiBr_2(PPh_3)_2$	THF	94
$NiI_2(PPh_3)_2$	THF	94
$NiBr_2(PPh_3)_2$	DMF	84
$NiBr_2(PPh_3)_2$	CH_3CN	88
$NiBr_2(PPh_3)_2$	Acetone	80

a) Bromobenzene (10 mmol), $NiX_2(PPh_3)_2$ (1 mmol), Zn (15 mmol), and Et_4NI (10 mmol) were used, and reactions were carried out at 50 °C for 2 h.

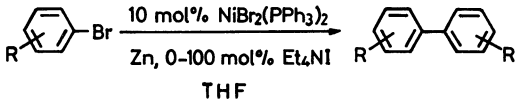
Table 2. Coupling of Aryl Bromides with $NiBr_2(PPh_3)_2$ and Zinc in the Presence or Absence of Et_4NI[a)]

Substrate R	Et_4NI/mol%	Time/h	Yield/%
H	0	1.5	75
H	10	1.5	99
H	50	1.5	96
H	100	2	94
p-COOMe	0	5	85
p-COOMe	10	4	90
p-COOMe	50	4.5	86
p-COOMe	100	4	86
p-OMe	0	8	61
p-OMe	10	4	72
p-OMe	50	2.5	73
p-OMe	100	1.5	66
o-COOMe	0	24	68
o-COOMe	20	24	79
o-COOMe	100	24	90

a) Aryl bromide (5 mmol), $NiBr_2(PPh_3)_2$ (0.5 mmol), and Zn (7,5 mmol) were used, and reactions were carried out at 50 °C in THF.

intermediate and facilitate the coupling reaction. However, our results demonstrate the coupling reaction to take place cleanly in THF, acetonitrile, and acetone, when the reaction is carried out in the presence of Et_4NI.

In order to clarify the effect of Et_4NI, we examined the coupling reactions of aryl bromides using $NiBr_2(PPh_3)_2$ and zinc in the presence or absence of Et_4NI (Eq. 4 and Table 2). Although the nickel-catalyzed



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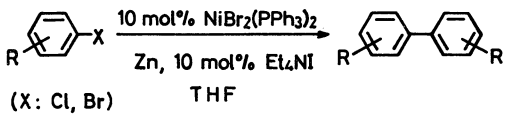
coupling of benzyl chloride in the absence of Et_4NI gives bibenzyl in a very low yield,[16a)] the reaction of aryl bromides produces biaryls without Et_4NI in moderate yields and 10 mol% of Et_4NI is effective enough to raise the yields of biaryls except for *o*-substituted derivatives which may be delayed the reaction rate due to the steric repulsion. In the case of iodobenzene, the nickel-catalyzed coupling gave biphenyls either in the presence or absence of Et_4NI in high yields.

Taking into account the results shown in Table 2, we carried out the coupling of *p*- and *m*-substituted aryl halides using $NiBr_2(PPh_3)_2$ and zinc in THF in the presence of 10 mol% of Et_4NI (Eq. 5 and Table 3).



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The *p*- and *m*-substituted aryl bromides gave the corresponding biaryls in good to high yields except for *p*-chlorobromobenzene. Substituent groups such as aldehyde, ketone, and ester are unreactive to nickel species under the reaction conditions. However, *p*-chlorobromobenzene resulted in the formation of oligomers and polymer,[13,16c)] and gave no 4,4′-dichlorobiphenyl. Therefore, the reactivity of aryl chlorides with the active nickel complex may be comparable to that of aryl bromides. As shown in Table 3, the coupling of *p*- and *m*-substituted aryl chlorides proceeds in a similar manner as that of aryl bromides and produces biaryls in good yields. In the case of *p*-methoxy or *p*-methoxy-*m*-methyl derivative, the formation of 4-methoxy- or 3-methyl-4-methoxybiphenyl was observed as a by-product in 10—15% yield.

Table 3. Coupling of Aryl Halides Having *p*- and/or *m*-Substituents with $NiBr_2(PPh_3)_2$ and Zinc in the Presence of 10 mol% of Et_4NI[a)]

Substrate R	Substrate X	Time/h	Yield/%
p-CH_3	Br	4	89
p-$COCH_3$	Br	20	71
p-CHO	Br	20	75
m-$COOCH_3$	Br	20	85
p-OCH_3	Cl	20	67
p-CH_3	Cl	5	81
p-$COCH_3$	Cl	20	73
p-CHO	Cl	20	70
p-$COOCH_3$	Cl	20	85
m-$COOCH_3$	Cl	20	81
p-OCH_3, *m*-CH_3	Cl	20	57

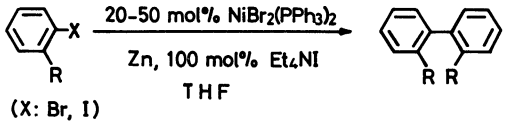
a) Aryl halide (5 mmol), $NiBr_2(PPh_3)_2$ (0.5 mmol), Zn (7.5 mmol), and Et_4NI (0.5 mmol) were used, and reactions were carried out at 50 °C in THF.

Table 4. Coupling of *o*-Substituted Aryl Halides with $NiBr_2(PPh_3)_2$ and Zinc in the Presence of 1 equiv of Et_4NI[a)]

Substrate R	Substrate X	$NiBr_2(PPh_3)_2$/mol%	Time/h	Yield/%
OCH_3	Br	50	46	81
CH_3	Br	20	5	83
$COOCH_3$	Br	20	24	90
Cl	I	20	3	56

a) Aryl halide (5 mmol), $NiBr_2(PPh_3)_2$ (1—2.5 mmol), Zn (7.5 mmol), and Et_4NI (5 mmol) were used, and reactions were carried out at 50 °C in THF.

For the reaction of *o*-substituted aryl halides (Eq. 6 and Table 4), 20—50 mol% of $NiBr_2(PPh_3)_2$, 1.5 molar

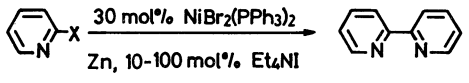


(6)

equiv of Zn and 1 equiv of Et_4NI were employed. As shown in Table 4, the coupling of aryl halides gave the corresponding biaryls in good yields except for *o*-chloro derivative. However, the stability of 2,2′-dichlorobiphenyl under the reaction conditions may be attributable to steric inhibition of the oxidative addition to nickel.

Synthesis of Bipyridines. There is growing interest in the chemistry of bipyridines, because of their importance as ligands for the preparation of metal complexes bearing catalytic activity, novel structure, and host-guest interaction.[17-20] Although many synthetic methods of bipyridines have been known so far, the most convenient method for the synthesis of bipyridine derivatives seems to be the coupling of halopyridines using transition metal catalysts such as copper halides,[21] palladium catalysts,[22] or nickel complexes.[23]

In agreement with this prospect, the coupling of halopyridines proceeds smoothly under similar reaction conditions described in the preceding section (Eqs. 7 and 8). Since bipyridines tend to make stable



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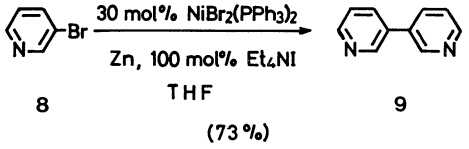

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complexes with nickel, 0.3 equiv of $NiBr_2(PPh_3)_2$ was used for the coupling of halopyridines in the presence of excess amounts of zinc as a reducing metal. As shown in Table 5, the reaction of 2-halopyridines (**5** and **7**) with the nickel complex prepared from $NiBr_2(PPh_3)_2$, zinc, and Et_4NI is slower than that of chloro- or bromobenzene, but the effect of Et_4NI was remarkable. Thus, 2,2′-bipyridine (**6**) was obtained from 2-bromopyridine (**5**) in 72% yield in the presence of an equimolecular amount of Et_4NI, but only in 3% yield in the presence of 10 mol% of this compound. The homocoupling of 2-chloropyridine (**7**) under similar conditions in the presence of 1 equiv of Et_4NI also gave 2,2′-bipyridine (**6**) in 60% yield.

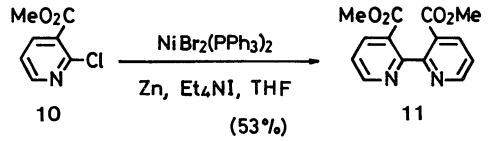
Table 5. Coupling of 2-Halopyridines (**5** and **7**) with $NiBr_2(PPh_3)_2$ and Zinc in the Presence of Et_4NI[a]

Substrate	X	Et_4NI/ mol%	Time/h	Yield of **6**/%
5	Br	10	20	3
5	Br	50	20	24
5	Br	100	20	72
7	Cl	100	30	60

a) 2-Halopyridine (10 mmol), $NiBr_2(PPh_3)_2$, Zn (15 mmol), and Et_4NI (1—10 mmol) were used, and reactions were carried out at 50 °C in THF.

In the case of 3-bromopyridine (**8**), the reaction of **8** under similar conditions used for **5** and **7** afforded 3,3′-bipyridine (**9**) in 73% yield.

The coupling reaction is also applicable to substituted halopyridines, and carbonyl groups are unreactive to the nickel complex (Eqs. 9—11). Thus, methyl 2-chloronicotinate (**10**) and methyl 5-bromonicotinate (**12**) gave the corresponding bipyridines **11** and **13** in 53 and 69% yields, respectively. 2-Chloro-6-methoxypyridine (**14**) gave 6,6′-dimethoxy-2,2′-bipyridine (**15**) in 90% yield.



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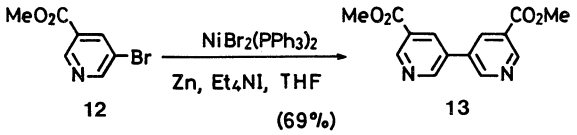

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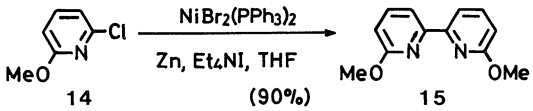
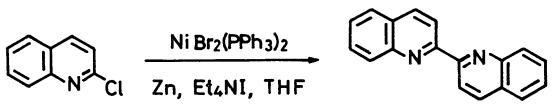


(11)

Furthermore, homocoupling of haloquinolines proceeds smoothly to give biquinolines (Eqs. 12—14). Thus, the coupling of 2-chloro-, 3-bromo-, and 4-chloroquinolines (**16**, **18**, and **20**) afforded the corresponding biquinolines **17**, **19**, and **21** in 84, 61, and 77% yields, respectively.



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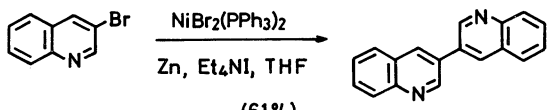

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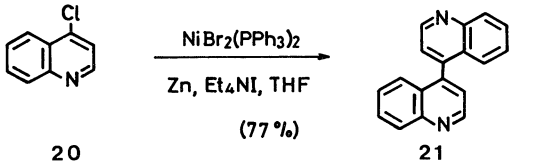
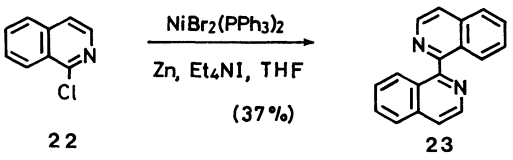


(14)

Biisoquinolines were prepared in very low yields by treating the appropriate bromoisoquinolines with copper under the conditions of the Ullmann reaction.

In addition, the synthetic methodology for access to biisoquinolines is still very limited. Nickel-catalyzed coupling can be also applied to the synthesis of biisoquinolines (Eqs. 15 and 16). Thus, the coupling of 1-chloro- and 4-bromoisoquinolines (**22** and **24**) gave 1,1′- and 4,4′-biisoquinolines (**23** and **25**) in 37 and 60% yields, respectively. Reaction of 1-chloroisoquinoline (**22**) with the nickel catalyst proceeds very fast at 50 °C and the reaction at 30 °C for 4 h also produces **23** in 31% yield.



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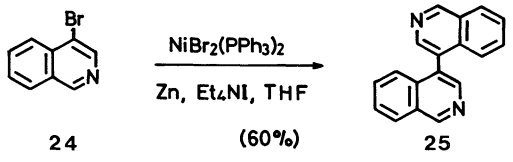


(16)

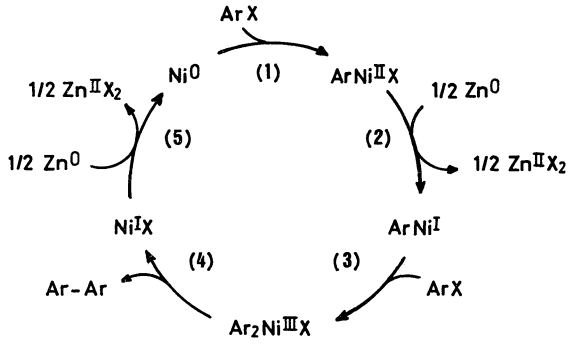
Mechanism. Several reaction mechanisms have been proposed for the nickel-catalyzed coupling of aryl halides. The most simple and intelligible mechanism involves the oxidative addition of aryl halides to zerovalent nickel (Eq. 17), followed by methathesis to diarylnickel(II) species and nickel halides (Eq. 18). Reductive elimination from diarylnickel(II) species gives biaryls and regenerates nickel(0) (Eq. 19). However, the formation of diarylnickel(II) species via methathesis has not been demonstrated in detail and is still controversial.

$$ArX + Ni^0 \longrightarrow ArNi^{II}XL_2 \quad (17)$$

$$2ArNi^{II}XL_2 \longrightarrow Ar_2Ni^{II}L_2 + Ni^{II}X_2L_2 \quad (18)$$

$$Ar_2Ni^{II}L_2 \longrightarrow Ar\text{-}Ar + Ni^0 \quad (19)$$

Recently, a new mechanism, which involves nickel(I) and nickel(III) species as the intermediates, has been postulated by two groups (Scheme 1).[14,24] The proposed key steps are the zinc-mediated or electrochemical reduction of $ArNi^{II}X$ to $ArNi^{I}$ (step 2). Oxidative addition of $ArNi^{I}$ to aryl halides (step 3), followed by reductive elimination yields biaryls (step 4). The nickel-catalyzed aryl coupling in the presence of Et_4NI in THF can be also explained by a similar mechanism which involves $ArNi^{I}$ and $Ar_2Ni^{III}X$ species. Tsou and Kochi suggested a radical chain process which involves the oxidative addition of ArX to $Ni^{I}X$ to produce $ArNi^{III}X_2$.[25] However, the reaction of bromobenzene with 1 equiv of $NiI(PPh_3)_3$ in THF at 50 °C produced biphenyl only in very low yield (<1%).[26]



Scheme 1.

Although Colon already reported an effective method for nickel-catalyzed coupling of aryl halides,[14] there are some differences between Colon's method and our conditions described here. At first, Colon reported that the coupling of aryl halides with nickel complex proceeds in the order chloride>bromide≥iodide. However, aryl halides react with nickel complex by our method in the order iodide≫bromide>chloride. The reaction of a 1:1 mixture of iodobenzene and chlorobenzene with the nickel catalyst, which was generated in situ from $NiBr_2(PPh_3)_2$, zinc, and Et_4NI in THF, was monitored (Fig. 1). The reaction between iodobenzene and the nickel catalyst occurred in the first step, and most of chlorobenzene remained unreacted until iodobenzene had been consumed. After 45 min, a large portion of iodobenzene reacted, and chlorobenzene began to react with the nickel catalyst. After 90 min, the coupling reaction was completed, and the formation of biphenyl reached to nearly maximum. Under similar conditions,

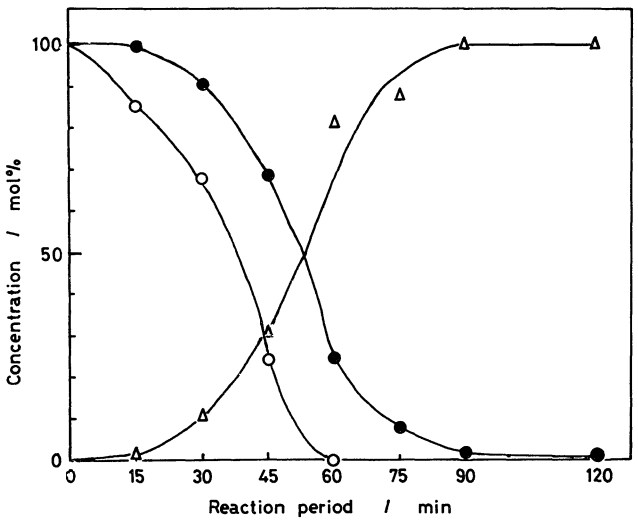


Fig. 1. Time dependence of the reaction components of the coupling for a mixture of iodobenzene (25 mmol) and chlorobenzene (25 mmol) with $NiBr_2(PPh_3)_2$ (5 mmol) and zinc (75 mmol) in the presence of Et_4NI (50 mmol) in THF (75 ml) at 40 °C. Plots of the observed molar concentrations of iodobenzene (○), chlorobenzene (●), and biphenyl (△) vs. time.

bromobenzene reacted somewhat faster than chlorobenzene. Interestingly, chlorobenzene was consumed in the presence of iodobenzene more smoothly compared with the reaction of chlorobenzene alone.

Colon reported the acceleration of the nickel-catalyzed aryl-coupling with halide ions such as bromide or iodide. Although iodide accelerates coupling reactions markedly, no acceleration with bromide was observed in our case. Thus, the reaction of bromobenzene with the nickel catalyst prepared from $NiBr_2(PPh_3)_2$ and zinc in the presence of Et_4NBr in THF occurs at the same rate at which the reaction of bromobenzene with the in situ generated $Ni(PPh_3)_4$ proceeds in THF.

Tamao and Kumada explained the role of iodide as a bridging ion between nickel and zinc in the electron-transfer processes.[6] The acceleration of the reaction caused by iodide was reported for the case of an activated nickel powder which is free from zinc.[11] In addition, the UV and ^{31}P NMR spectra of the active nickel catalyst described in this article were different from those of $Ni(PPh_3)_3$.[5] Therefore, iodide may play an important role for the acceleration of the coupling as a bridging ligand, although it is difficult to detect the true activated state or species.

For the homocoupling of *m*- or *p*-substituted aryl halides, the presence of 10 mol% of iodide ion is enough to produce biaryls, presumably owing to the recyclable use of iodide. However, 1 equiv of iodide is required for the reactions of either *o*-substituted aryl halides or halopyridines.

Most useful in our method is that the nickel-catalyzed coupling proceeds smoothly without an addition of PPh_3 in a nonpolar solvent such as THF. The addition of PPh_3 or the use of dipolar aprotic solvents such as DMF, HMPA, or *N*,*N*-dimethylacetamide cause problems frequently in isolating the coupled products.

In conclusion, we have shown that a variety of biaryls and bipyridines can be prepared in moderate to good yields by using the coupling of aryl halides with the nickel catalyst prepared from $NiBr_2(PPh_3)_2$ and zinc in the presence of Et_4NI in THF.

Experimental

General. ^1H and ^{13}C NMR spectra were recorded on a Varian XL-100, or JEOL JNM-PMX60Si and JNM-FX90Q instruments. Spectra were recorded in δ referenced to Me_4Si. IR spectra were observed on a Hitachi EPI-G3 spectrometer. Mass spectral analysis (MS) were performed on a JEOL JMS-O1SG-2 instrument. Melting points were determined on a Mettler FP-2 apparatus and are uncorrected. Column chromatography was carried out with use of Daisogel 1001 w, Merck Silica Gel 60, 70—230 mesh, or Neutral Alumina Act. II—III, 70—230 mesh. Analytical TLC was performed by using plates (0.25 mm) prepared from Merck Silica Gel GF-254.

Materials. $NiBr_2(PPh_3)_2$[27] was prepared from 1 equiv of $NiBr_2$ and 2 equiv of PPh_3 in refluxing 1-butanol and purified by continuous extraction with 1-butanol in a Soxlet extractor, followed by heating at 80 °C under reduced pressure. $NiCl_2(PPh_3)_2$ and $NiI_2(PPh_3)_2$ were prepared by literature methods.[27,28] Zinc powder was washed successively with dil hydrochloric acid, water, ethanol, acetone, and diethyl ether, and dried under reduced pressure. Tetraethylammonium iodide was purchased from Tokyo Kasei Kogyo Co. and dried at 100 °C under reduced pressure. All solvents were dried by conventional procedures. Reactions involving air-sensitive organometallic reagents were carried out under nitrogen or argon atmosphere.

General Procedure for Table 1. Coupling of Bromobenzene. A 50-ml, round-bottomed, two-necked flask containing a magnetic stirring bar was charged with 1 mmol of $NiX_2(PPh_3)_2$ (X=Cl, Br, or I), 981 mg (15 mmol) of zinc dust and 2.57 g (10 mmol) of Et_4NI. A rubber septum was placed over one neck of the flask and a 3-way stopcock adapter attached with an argon-filled balloon in the other. The flask was evacuated and filled with argon several times (vacuum line). Dry THF, DMF, acetonitrile, or acetone (10 ml) was added via syringe through the septum. The reaction mixture was stirred at room temperature. After the dark brown catalyst had formed (30 min), an argon-purged solution of 1.57 g (10 mmol) of bromobenzene in the same solvent (5 ml) was added via syringe to the reaction mixture. The resulting mixture was heated at 50 °C for 2 h, and then filtered. The solid mass was washed with benzene, and the filtrate and washings were evaporated in vacuo. The residue was separated by column chromatography on silica gel (50 g) using hexane as eluent to give biphenyl in yields shown in Table 1. Mp 68—69 °C (lit,[29] 71 °C).

General Procedure for Table 2. Coupling of Aryl Bromides. In a 50-ml round-bottomed, two-necked flask containing a magnetic stirrer bar and stoppered with a rubber septum were placed 372 mg (0.5 mmol) of $NiBr_2(PPh_3)_2$, 491 mg (7.5 mmol) of zinc dust and various amounts of Et_4NI. The flask was degassed with argon, and dry THF (10 ml) was added via syringe through the septum, and the reaction mixture was stirred at room temperature for 30 min. An argon-purged solution of 5 mmol of aryl bromides in THF (5 ml) was added and the resulting mixture was heated at 50 °C for 1.5—24 h. After the reaction had been completed (monitored by TLC), the mixture was filtered and washed with dichloromethane. The filtrate and washings were evaporated in vacuo, and the residue was chromatographed on silica gel (50 g) to give the corresponding biaryls in yields shown in Table 2.

Dimethyl 1,1′-Biphenyl-4,4′-dicarboxylate: Mp 215.5—216.5 °C (lit,[30] 215—217 °C).

4,4′-Dimethoxybiphenyl: Mp 175.5—176.5 °C (lit,[31] 176.5—177 °C).

Dimethyl 1,1′-Biphenyl-2,2′-dicarboxylate: Mp 72—73 °C (lit,[32] 73—74 °C).

General Procedure for Table 3. Coupling of Aryl Halides Having *p*- and/or *m*-Substituents. In a 50-ml round-bottomed, two-necked flask containing a magnetic stirrer bar and filled with argon and stoppered with a rubber septum were placed 372 mg (0.5 mmol) of $NiBr_2(PPh_3)_2$, 491 mg (7.5 mmol) of zinc dust, and 129 mg (0.5 mmol) of Et_4NI. Dry THF (10 ml) was added, and the reaction mixture was stirred at room temperature for 30 min. An argon-purged solution

of 5 mmol of aryl halides in THF (5 ml) was added and the resulting mixture was stirred at 50 °C for 4—20 h. After separation of inorganic precipitates by filtration, the precipitates were washed with benzene. The filtrate and washings were evaporated in vacuo, and the residue was chromatographed on silica gel (50 g) to give the corresponding biaryls in yields shown in Table 3.

4,4′-Dimethylbiphenyl: Mp 117—119 °C (lit,[33] 121 °C).

4,4′-Diacetylbiphenyl: Mp 189—190 °C (lit,[34] 191 °C).

4,4′-Diformylbiphenyl: Mp 145—145.5 °C (lit,[35] 145 °C).

Dimethyl 1,1′-Biphenyl-3,3′-dicarboxylate: Mp 102—103 °C (lit,[35,36] 103 °C).

4,4′-Dimethoxy-3,3′-dimethylbiphenyl: Mp 151—153 °C (lit,[37] 154.5 °C).

General Procedure for Table 4. Coupling of *o*-Substituted Aryl Halides. To the nickel catalyst prepared from 1—2.5 mmol of $NiBr_2(PPh_3)_2$, 491 mg (7.5 mmol) of zinc, and 1.29 g (5 mmol) of Et_4NI in THF (10 ml), was added a solution of 5 mmol of aryl halides in THF (5 ml), and the mixture was stirred at 50 °C for 3—46 h. After separation of inorganic precipitates by filtration, the precipitates were washed with benzene. The filtrate and washings were evaporated in vacuo, and the residue was chromatographed on silica gel (50 g) to give the corresponding 2,2′-biaryls in yields shown in Table 4.

2,2′-Dimethoxybiphenyl: Mp 154—155 °C (lit,[35] 154—155 °C).

2,2′-Dimethylbiphenyl: Bp ca. 100 °C/8 Torr (1 Torr= 133.322 Pa) (lit,[8a] 69 °C/0.5 Torr).

2,2′-Dichlorobiphenyl: Mp 52—55 °C (lit,[38] 59 °C).

General Procedure for Table 5. Coupling of 2-Halopyridines (5 and 7). To the nickel catalyst prepared from 2.23 g (3 mmol) of $NiBr_2(PPh_3)_2$, 981 mg (15 mmol) of zinc, and 1—10 mmol of Et_4NI in THF (20 ml), was added a solution of 10 mmol of 2-halopyridines (**5** or **7**) in THF (10 ml), and the mixture was stirred at 50 °C for 6—30 h. The reaction mixture was poured into 2 M aqueous ammonia (100 ml; 1 M=1 mol dm^{-3}), and ether (50 ml) and benzene (50 ml) were added. Precipitates were filtered and the organic layer was separated. The aqueous layer was extracted with ether/benzene (1:1) (50 ml×2). The combined organic layers were washed successively with water and saturated aqueous NaCl solution, dried with anhydrous $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel (50 g) using benzene/ether as eluent to give 2,2′-bipyridine (**6**) in yields shown in Table 5. Mp 67.5—69.5 °C (lit,[23a] 71—72 °C).

3,3′-Bipyridine (9). To the nickel catalyst prepared from 2.23 g (3 mmol) of $NiBr_2(PPh_3)_2$, 981 mg (15 mmol) of zinc, and 2.57 g (10 mmol) of Et_4NI in THF (20 ml), was added a solution of 1.58 g (10 mmol) of 3-bromopyridine (**8**) in THF (5 ml). After stirring at 50 °C for 6 h, the mixture was poured into 2 M aqueous ammonia (100 ml). Benzene (50 ml) and ethyl acetate (50 ml) were added, and precipitates were separated. The aqueous layer was extracted with benzene/AcOEt (1:1) (50 ml×2). The organic layer was washed successively with water and saturated aqueous NaCl solution, dried with anhydrous $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel (50 g) (benzene/AcOEt → AcOEt) to give 3,3′-bipyridine (**9**) (573 mg, 73%); bp ca 130 °C/0.1 Torr (lit,[39] 162—164 °C/8 Torr).

3,3′-Bis(methoxycarbonyl)-2,2′-bipyridine (11). To the nickel catalyst prepared from 1.12 g (1.5 mmol) of $NiBr_2(PPh_3)_2$, 490 mg (7.5 mmol) of zinc, and 1.29 g (5 mmol) of Et_4NI in THF (15 ml), was added a solution of 858 mg (5 mmol) of methyl 2-chloronicotinate (**10**) in THF (5 ml). After stirring at 50 °C for 3 h, the mixture was poured into 2 M aqueous ammonia (50 ml). To the resulting mixture was added chloroform and precipitates were filtered. The organic layer was separated and the aqueous layer was extracted with chloroform. The combined organic layers were washed successively with water and saturated aqueous NaCl solution, dried with anhydrous $MgSO_4$, and evaporated in vacuo. The residue was passed through a short alumina column (benzene/AcOEt 4:1) and then chromatographed on silica gel (50 g) using benzene/AcOEt as eluent to give **11** (360 mg, 53%); mp 150.5—151.0 °C (lit,[20a] 151 °C); ^1H NMR (100 MHz, $CDCl_3$) δ=3.68 (s, 6H), 7.46 (dd, J=5.0, 8.0 Hz, 2H), 8.39 (dd, J=2.0, 8.0, 2H), 8.81 (dd, J=2.0, 5.0 Hz, 2H).

5,5′-Bis(methoxycarbonyl)-3,3′-bipyridine (13). To the nickel catalyst prepared from 1.12 g (1.5 mmol) of $NiBr_2(PPh_3)_2$, 490 mg (7.5 mmol) of zinc, and 1.29 g (1.5 mmol) of Et_4NI in THF (15 ml), was added a solution of 1.08 g (5 mmol) of methyl 5-bromonicotinate (**12**) in THF (5 ml). After stirring at 50 °C for 20 h, the mixture was poured into 2 M aqueous ammonia (30 ml). Chloroform (100 ml) was added, and precipitates were filtered. The aqueous layer was extracted with chloroform (50 ml×2). The combined organic layers were washed with water and aqueous NaCl solution, dried with $MgSO_4$, and evaporated in vacuo. The residual solid was triturated by CH_2Cl_2 to give **13** (459 mg, 67%); mp 226—226.5 °C (from benzene); IR (KBr) 1727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=4.02 (s, 6H), 8.55 (m, 2H), 9.05 (br s, 2H), 9.29 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=52.71 (CH_3), 126.43 (C-3), 132.45 (C-5), 135.48 (C-4), 150.68 (C-2), 151.59 (C-6), 165.34 (CO); MS m/z 272 (M^+). Found: C, 61.54; H, 4.39; N, 10.18%. Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29%.

6,6′-Dimethoxy-2,2′-bipyridine (15). To the nickel catalyst prepared from 2.23 g (3 mmol) of $NiBr_2(PPh_3)_2$, 981 mg (15 mmol) of zinc, and 2.57 g (10 mmol) of Et_4NI in THF (20 ml), was added a solution of 1.44 g (10 mmol) of 2-chloro-6-methoxypyridine (**14**) in THF (5 ml). The mixture was stirred at 50 °C for 20 h. Aqueous workup and chromatography on silica gel (50 g) using hexane/benzene as eluent to give **15** (975 mg, 90%), mp 119—119.5 °C (lit,[23a] 118—119 °C).

General Procedure for the Coupling of Haloquinolines 16, 18, and 20. A solution of 5 mmol of haloquinolines **16**, **18**, or **20**, in THF (5 ml) was added to a suspension of the nickel catalyst in THF (15 ml) [prepared from 1.12 g (1.5 mmol) of $NiBr_2(PPh_3)_2$, 490 mg (7.5 mmol) of Zn, and 1.29 g (5 mmol) of Et_4NI]. The mixture was stirred at 50 °C for 20 h. Aqueous workup and chromatography on silica gel (benzene/AcOEt) to give biquinolines **17**, **19**, or **21** in 84, 61, or 77% yields, respectively.

2,2′-Biquinoline (17); mp 194—195.5 °C (lit,[40] 196 °C).

3,3′-Biquinoline (19); mp 268.5—269 °C (lit,[41] 271 °C); ^1H NMR (100 MHz, $CDCl_3$) δ=7.56—8.15 (m, 6H), 8.20 (dd, J=0.5, 8.0, 2H), 8.45 (d, J=2, 2H), 9.29 (d, J=2, 2H).

4,4′-Biquinoline (21); mp 171—172 °C (lit,[23a,42] 172—173 °C).

1,1′-Biisoquinoline (23). A solution of 1.64 g (10 mmol)

of 1-chloroisoquinoline (**22**) in THF (5 ml) was added to a suspension of the nickel catalyst in THF (20 ml) [prepared from 2.23 g (3 mmol) of $NiBr_2(PPh_3)_2$, 981 mg (15 mmol) of Zn, and 2.57 g (10 mmol) of Et_4NI]. The mixture was stirred at 50 °C for 18 h. Aqueous workup and chromatography on silica gel (benzene/AcOEt) to give 1,1′-biisoquinoline (**21**) (473 mg, 37%); mp 162.5—164 °C (lit,[40,43] 164—165 °C).

4,4′-Biisoquinoline (25). A solution of 2.08 g (10 mmol) of 4-bromoisoquinoline (**24**) in THF (5 ml) was added to a suspension of the nickel catalyst [prepared from 2.23 g (3 mmol) of $NiBr_2(PPh_3)_2$, 981 mg (15 mmol) of Zn, and 2.57 g (10 mmol) of Et_4NI]. The mixture was stirred at 50 °C for 20 h. Aqueous workup and chromatography on silica gel (benzene → AcOEt) to afford **25** (763 mg, 60%); mp 147—148 °C (lit,[44] 149 °C).

The authors wish to thank Professor Kenkichi Sonogashira for his helpful discussions. The authors also wish to thank Mr. Tomoaki Okada for measuring properties of **9** and **21**.

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