solution was washed with three 20-mL portions of brine and dried over $MgSO_4$. After the solvent was removed under reduced pressure, the residue was found to contain only dibenzyl sulfide (by ^1H NMR analysis).

2. Sodium (0.05 g, 2 mmol) was added to a solution of **5** (0.5 g, 2 mmol) in 5 mL of toluene. The mixture was heated at reflux for 8 h and was then allowed to cool to room temperature. The solution was washed with three 20-mL portions of brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, giving a complex mixture from which **7** was specifically absent (GC–MS analysis).

Parallel reactions with **4** also failed to produce **7**. (The yield of **7** was less than 1% by GC–MS analysis.)

Acknowledgment. We are grateful to Professor J. K. Whitesell for samples of the nitrobenzyl thioethers **6a** and **6b** used in this study. Support of this research by the National Science Foundation and the Robert A. Welch Foundation is gratefully acknowledged. M.A.F. is also grateful for support as an Alfred P. Sloan Research Fellow and as a Camille and Henry Dreyfus Teacher–Scholar.

Registry No. **2a**, 5398-93-6; **2b**, 16222-10-9; **2c**, 2408-88-0; **2d**, 52264-85-4; **2e**, 84538-92-1; **2f**, 21875-74-1; **3a**, 79992-70-4; **3b**, 84538-93-2; **3c**, 84538-94-3; **3d**, 84538-95-4; **3e**, 84538-96-5; **3f**, 84538-97-6; **6a**, 84538-99-8; **6b**, 84539-01-5.

Activated Metallic Nickel as a Reagent for the Dehalogenative Coupling of Halobenzenes

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Activated metallic nickel powder, prepared by the reduction of nickel halides with lithium and with naphthalene as an electron carrier, is a simple and a convenient reagent for the dehalogenative coupling of iodobenzenes and bromobenzenes under mild conditions. The intermediates, ArNiX and Ar_2Ni species (Ar = C_6F_5), were isolated as the phosphine complexes.

Recently, considerable interest has centered on the use of zerovalent transition metals and their complexes as selective and mild reagents in organic synthesis.[1] However, some of the useful complexes coordinated with ligands such as phosphine or carbon monoxide are unstable and not easy to prepare or are toxic. Other studies using the metal atom vaporization technique have also been successful in employing transition metals in synthesis.[2] In many cases, however, this approach does not lend itself to being completely general.

There are few reports of oxidative addition of metallic transition metals under mild conditions;[3] two reports involving group 8 elements have appeared. Fischer and Bürger reported the preparation of π-allylpalladium complex by the reaction of palladium sponge with allyl bromide.[4] The Grignard-type addition of allyl halides to aldehydes has been carried out by reacting allylic halides with cobalt or nickel metal prepared by reduction of cobalt or nickel halides with manganese/iron alloy–thiourea.[5]

In a series of our studies on the chemistry of activated metals, we have shown that the transition-metal powders prepared by the reduction of metal halides with alkali metal in an ethereal or a hydrocarbon solvent have high reactivities in their metallic state toward organic and inorganic substrates.[6] In a previous paper, we reported preliminary results showing that activated nickel powder can induce the dehalogenative coupling of iodo- or bromobenzene.[7] We report here the application of activated metalic nickel as a reagent for the homo coupling of a variety of halobenzenes. In addition, the mechanistic considerations will be discussed on the basis of the isolation of intermediates, ArNiX and Ar_2Ni species (Ar = C_6F_5), as their phosphine complexes.

Results and Discussion

Activated nickel powder employed for the reactions was simply prepared by stirring a 1:2.3 mixture of nickel halide and lithium metal (eq 1) under argon with a catalytic

$$NiX_2 \xrightarrow[\text{glyme}]{\text{Li (2.3 equiv)}/C_{10}H_8\text{ (0.1 equiv)}} [Ni] \qquad (1)$$

$$ArX' \xrightarrow[\text{glyme (Me}_2\text{SO or DMF)}]{[Ni]} {}^1/_2ArAr \qquad (2)$$

amount of naphthalene (10 mol % based on nickel halide) at room temperature for 12 h in 1,2-dimethoxyethane (glyme). The resulting black slurry, which slowly settled after the stirring was stopped, was washed with freshly distilled glyme to remove the naphthalene and was used for the reaction with halobenzenes. As the presence of the naphthalene did not disturb the following reaction, the removal procedure is optional. The dehalogenative coupling reactions were carried out at 80 °C by using a 0.7–0.8:1 mixture of halobenzene and the nickel powder (eq 2). The course of the reaction was followed, and the yields were determined by GLC.

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Table I. Reaction of Iodobenzenes with Activated Nickel Powder

iodobenzene	NiX_2	time, h	product, %[a] coupling	product, %[a] reduction	% conversion[b]
C_6H_5I	NiI_2	2	83	15	100
$4\text{-}CH_3OC_6H_4I$	NiI_2	2	85 (68)[c]	15	100
$4\text{-}ClC_6H_4I$	NiI_2	4	75	22	100
$4\text{-}ClC_6H_4I$	$NiBr_2$	4	77	25	100
$4\text{-}ClC_6H_4I$	$NiCl_2$	5	74	23	96
$4\text{-}NCC_6H_4I$	NiI_2	2	85[c]	<1	100
C_6F_5I	NiI_2	2	100	0	100
$2\text{-}CH_3OC_6H_4I$	NiI_2	4	<1	85	56
$2\text{-}O_2NC_6H_4I$	NiI_2	6	<1	<1	<1

[a] The yields were determined by GLC based on the iodobenzene consumed unless otherwise noted. [b] Conversion = 100 × [(millimoles of the iodobenzene consumed)/(millimoles of the iodobenzene charged)]. [c] Isolated yield.

Table II. Reaction of Bromobenzenes with Activated Nickel Powder

bromobenzene	NiX_2	solvent	time, h	product, %[a] coupling	product, %[a] reduction	% conversion[b]
$4\text{-}ClC_6H_4Br$	$NiBr_2$	glyme	20	36	55	100
$4\text{-}ClC_6H_4Br$	$NiBr_2$	Me_2SO	15	41	52	95
$4\text{-}ClC_6H_4Br$	$NiBr_2$	DMF	4	<1	89	100
$4\text{-}ClC_6H_4Br$	NiI_2	glyme	20	61	32	100
$4\text{-}CH_3OC_6H_4Br$	$NiBr_2$	glyme	30	0	100	43
$4\text{-}CH_3COC_6H_4Br$	$NiBr_2$	glyme	18	57	43	75
$4\text{-}CH_3COC_6H_4Br$	NiI_2	glyme	8	46[c]	*d*	100
$4\text{-}NCC_6H_4Br$	NiI_2	glyme	21	71[c]	*d*	100
$4\text{-}NCC_6H_4Br$	$NiBr_2$	DMF	15	55	<1	100
C_6F_5Br	$NiBr_2$	glyme	8	37	32	100
C_6F_5Br	NiI_2	glyme	4	49	22	100

[a] The yields were determined by GLC based on the bromobenzene consumed unless otherwise noted. [b] Conversion = 100 × [(millimoles of the bromobenzene consumed)/(millimoles of the bromobenzene charged)]. [c] Isolated yield. [d] Not determined.

The results of the homo-coupling reaction of iodobenzenes by activated nickel powder are summarized in Table I. Metallic nickel worked well for the dehalogenative coupling of unsubstituted and 4-substituted iodobenzenes. For instance, the reaction of 4-iodomethoxybenzene reached completion in 2 h at 80 °C to afford 4,4′-dimethoxybiphenyl in 85% yield (via GLC), along with the reduction product, anisole (15%). The usual workup of the reaction mixture gave the biphenyl in 68% isolated yield. Previous workers obained 4,4′-dimethoxybiphenyl in 85% yield using copper powder; however, drastic conditions (225 °C) were required to promote the reaction.[8]

In the case of 4-iodochlorobenzene, oxidative addition occurred exclusively at the carbon–iodine bond, and the chlorine–carbon bond was unreactive toward the nickel powder. In this particular reaction, the effect of varying the halide of the nickel salt reduced was examined. There was essentially no difference in the yield of the reaction in the series $NiCl_2$, $NiBr_2$, or NiI_2. This effect was not studied in detail for the other iodobenzene reactions but most probably would have been the same.

Ortho substituents on the aryl groups seems to inhibit the coupling. For example, 2-iodomethoxybenzene failed to couple and gave exclusively anisole in moderate yield. 2-Iodonitrobenzene did not react at all under similar conditions. These facts are significantly different from those of copper-promoted reaction, in which electron-withdrawing substituents such as a nitro group in the ortho position enhance the reactivity.[9]

Table II summarizes the results of the reaction of bromobenzenes with activated nickel. Although the reactivity of bromobenzenes toward nickel was relatively lower than that of iodobenzenes, they reacted at 85 °C to give biphenyls in moderate to good yields, together with the corresponding reduction products. The reaction of 4-bromochlorobenzene with nickel powder from nickel bromide in glyme afforded chlorobenzene as the major product. Dimethyl sulfoxide and dimethylformamide were tried; these solvents did not greatly improve the yield of the coupled product. However, the yield of 4,4′-dichlorobiphenyl could be improved to 61% by using nickel powder obtained from nickel iodide. This observation suggests that the reaction was facilitated by the halogen–halogen exchange reaction which occurred between the substrate and iodide present.

Electron-donating substituents seem to lower the reactivity. For example, 4-bromomethoxybenzene failed to couple and gave only anisole in 43% yield. Substituents such as carbonyl and cyano groups were compatible with the reaction conditions employed, and the corresponding biphenyls were obtained in good yields.

As for mechanistic considerations of homogeneous zerovalent-nickel-induced biaryl synthesis, several possibilities have been discussed. Semmelhack et al.[10] suggested the coupling of aryl halides using bis(1,5-cyclooctadiene)nickel(0) in DMF occurs via Scheme I. This scheme

Scheme I (L = Solvent or COD)

$$ArX + NiL_2 \rightarrow ArNi^{II}XL_2$$

$$ArNi^{II}XL_2 + ArX \rightarrow Ar_2Ni^{IV}X_2 + 2L$$

$$Ar_2Ni^{IV}X_2 \rightarrow ArAr + NiX_2$$

involves a second oxidative addition of the initially formed

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arylnickel(II) halide complex, yielding the diarylnickel(IV) species, which yields the biaryl product by reductive elimination.

On the basis of detailed studies, Tsou and Kochi[11] concluded that the nickel(I) and arylnickel(III) species are the reactive intermediates in a radical chain process (Scheme II). However, these studies were carried out in hydrocarbon solvents, and the conclusion, as pointed out by Semmelhack et al.,[12] is not completely consistent with the product studies performed in DMF.

Scheme II

$$\mathrm{Ni^{I}X + ArX \rightarrow ArNi^{III}X_2}$$

$$\mathrm{ArNi^{III}X_2 + ArNi^{II}X \rightarrow Ni^{II}X_2 + Ar_2Ni^{III}X}$$

$$\mathrm{Ar_2Ni^{III}X \rightarrow ArAr + Ni^{I}X}$$

The following experiments were made concerning the mechanism of the coupling reaction mediated by metallic nickel. The reaction of iodopentafluorobenzene with nickel powder prepared from nickel iodide was investigated in detail. Iodopentafluorobenzene was found to react with nickel at room temperature; however, decafluorobiphenyl could not be detected in the reaction mixture. Triphenylphosphine (2 equiv) was then added to the mixture to trap the arylnickel intermediate as the phosphine complex, and a usual workup afforded bis(triphenylphosphine)bis(pentafluorophenyl)nickel(II) in 45% yield. As the diarylnickel(II) species seemed to be derived by disproportionation from an initially formed oxidative adduct, (pentafluorophenyl)nickel(II) iodide, the trapping of the arylnickel(II) iodide was tried. In the presence of 2 equiv of triethylphosphine, the reaction of iodopentafluorobenzene with nickel was carried out at room temperature, and bis(triethylphosphine)(pentafluorophenyl)nickel(II) iodide was isolated in 15% yield.

These results strongly suggest that the initial oxidative addition of aryl halide yields the arylnickel(II) halide species, which most likely is coordinated with glyme. Klabunde has shown that the arylnickel(II) halide species are not stable unless they are coordinated to some ligand.[13] The arylnickel(II) halide then disproportionates to diarylnickel(II) and nickel halide. The final step is the formation of biaryl by reductive elimination of diarylnickel(II) under the reaction conditions employed (Scheme III).

Scheme III (L = Solvent)

$$\mathrm{[Ni] + ArX + L_{\mathit{n}} \rightarrow ArNi^{II}XL_{\mathit{n}}}$$

$$\mathrm{2ArNi^{II}XL_{\mathit{n}} \rightarrow Ar_2Ni^{II}L_{\mathit{n}} + Ni^{II}X_2 + L_{\mathit{n}}}$$

$$\mathrm{Ar_2Ni^{II}L_{\mathit{n}} \rightarrow ArAr + [Ni] + L_{\mathit{n}}}$$

It is well-known that thermal decomposition of arylnickel(II) halide complexes such as bis(triphenylphosphine)phenylnickel(II) bromide[14] or bis(triethylphosphine)(4-fluorophenyl)nickel(II) chloride[15] gave the corresponding biphenyls by successive disproportionation and reductive elimination reactions.[16] Scheme III is also consistent with these facts.

In conclusion, oxidative addition of aryl halides to metallic nickel proceeded smoothly under mild conditions, and the corresponding biaryls were obtained in good yields. The present reaction is superior to the Ullmann synthesis in the scope of the reaction conditions[9] and to the coupling reaction of Grignard reagents catalyzed by transition metals.[17] Finally, because of the simple and easy procedure for the preparation of the nickel powder, it is far more convenient to work with than zerovalent nickel complexes such as tetrakis(triphenylphosphine)nickel(0) or bis(1,5-cyclooctadiene)nickel(0).[12]

Experimental Section

Measurement. Melting points were uncorrected. The infrared spectra were measured on a Perkin-Elmer 283 spectrophotometer with samples as KBr disks. The nuclear magnetic resonance spectra were obtained by the use of a Varian EM 390 spectrometer with Me_4Si as the internal standard. Analytical gas chromatography was carried out on a Hewlett-Packard 5702A with stainless steel columns (0.5 × 100–150 cm) packed with silicone SE-30 (10%), OV-17 (3%), and Apiezon L (10%) on Chromsorb P AW-DMCS (80/100 mesh).

Materials. Halobenzenes were commercially available and were used as received. 1,2-Dimethoxyethane (glyme) was distilled prior to use from sodium–potassium alloy under argon. Dimethylformamide (DMF) and dimethyl sulfoxide (Me_2SO) were distilled under argon from calcium hydride. Anhydrous nickel halides were purchased from Cerac, Inc., and were used as received.

Preparation of nickel powder and its reaction with halobenzenes were carried out in essentially the same manner under an atmosphere of argon, and a typical procedure is described below. The coupling and reduction products were identified by the comparison of their physical and spectral properties with those of commercially available authentic samples or reported values. Conversion of reactions and yields of products were determined by GLC using an appropriate internal standard calibrated against the pure sample.

Preparation of Activated Nickel Powder. A 50-mL two-necked flask was equipped with a magnetic stirrer, a rubber septum, and a condenser topped with an argon inlet. The flask was charged with nickel iodide (3.82 g, 12.22 mmol), freshly cut lithium (0.195 g, 28.1 mmol), naphthalene (0.16 g, 1.25 mmol), and glyme (30 mL), and the mixture was stirred vigorously at room temperature for 12 h. The nickel powder precipitated as a black slurry in a colorless clear solution after the stirring was stopped. The top of the glyme was removed by syringe, and freshly distilled glyme (20 mL) was added and was stirred for 5 min. This procedure was repeated two times to remove the naphthalene.

In those cases where the coupled product was easily separable from naphthalene, the removal procedure of napthalene was optional because the naphthalene did not disturb the coupling reaction at all. Glyme could be replaced with other solvents such as DMF or Me_2SO, after the evaporation of the glyme under reduced pressure.

Reaction of 4-Iodomethoxybenzene with Activated Nickel Powder. To the nickel powder (12.22 mmol) was added 4-iodomethoxybenzene (1.88 g, 8.02 mmol), and the mixture was stirred at 85 °C for 2 h. The reaction mixture changed to reddish brown, and most of the nickel powder was consumed. GLC analysis of the reaction mixture showed that 4,4′-dimethoxybiphenyl and anisole were formed in 85% and 15% yields, respectively. The reaction mixture was poured into ether (100 mL) and was filtered. The filtrate was washed with water (50 mL) and dried over anhydrous magnesium sulfate. The solution was concentrated to 10 mL, and ethanol (10 mL) was added to precipitate the product (0.69 g, 78%). Recrystallization from ether–ethanol (1:1) gave 4,4′-dimethoxybiphenyl (0.58 g, 68%) as colorless flakes: mp 176–177 °C (lit.[18] mp 176–178 °C); IR (KBr)

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1250 cm^{-1} (C–O); NMR ($CDCl_3$, Me_4Si) δ 3.83 (s, OCH_3, 6 H), 6.95 (d, J = 9 Hz, arom, 4 H), 7.50 (d, J = 9 Hz, arom, 4 H).

In the case of less soluble biphenyls in ether such as 4,4′-dicyano- or 4,4′-diacetylbiphenyl, chloroform was used for extraction. The reaction mixture was poured into chloroform (150 mL) and washed with 3% HCl solution followed by water (100 mL).

4,4′-Dicyanobiphenyl: mp 236–237 °C (sublimation) (lit.[19] mp 237–238 °C); IR (KBr) 2220 cm^{-1} ($C\equiv N$); NMR ($CDCl_3$, Me_4Si) δ 7.69 (d, J = 9 Hz, arom, 4 H), 4.82 (d, J = 9 Hz, arom, 4 H).

4,4′-Diacetylbiphenyl: mp 190–191 °C (glyme) (lit.[20] mp 192–193 °C); IR (KBr) 1675 cm^{-1} (C=O); NMR ($CDCl_3$, Me_4Si) δ 2.60 (s, CH_3CO, 6 H), 7.70 (d, J = 9 Hz, arom, 4 H), 8.05 (d, J = 9 Hz, arom, 4 H).

Trapping of Bis(pentafluorophenyl)nickel(II) Species with Triphenylphosphine. Activated nickel was prepared by stirring a mixture of nickel iodide (2.54 g, 8.14 mmol), lithium (0.130 g, 18.7 mmol), and naphthalene (0.104 g, 0.81 mmol) at room temperature for 12 h. To the nickel powder was added iodopentafluorobenzene (1.85 g, 6.29 mmol), and the mixture was stirred for 24 h at the same temperature. To the formed reddish brown reaction mixture was added triphenylphosphine (4.27 g, 16.28 mmol), and this was stirred overnight at room temperature. The glyme was removed under reduced pressure, the residue was dissolved in benzene (30 mL), and the solution was filtered under argon. The benzene solution was concentrated to 3 mL, and methanol (20 mL) was added. The yellow powder which precipitated was separated by filteration. Recrystallization from benzene–methanol gave the yellow crystalline solid bis(triphenylphosphine)bis(pentafluorophenyl)nickel(II): 1.31 g (45%); mp 203–204 °C dec (lit.[21] mp 201–204 °C dec); IR spectrum is consistent with the reported values.[21]

Trapping of (Pentafluorophenyl)nickel(II) Iodide Species with Triethylphosphine. To nickel powder in glyme (30 mL) prepared from nickel iodide (3.95 g, 12.7 mmol) in a similar manner was added triethylphosphine (2.99 g, 25.3 mmol) at room temperature. After the mixture was stirred 1 h, iodopentafluorobenzene (3.01 g, 10.3 mmol) was added and the mixture stirred at room temperature for 24 h. The reaction mixture was evaporated under reduced pressure, benzene (20 mL) was added to the residue, and the mixture was filtered under argon. The filtrate was evaporated, and the residue was recrystallized from methanol to give the brown crystalline solid bis(triethylphosphine)(pentafluorophenyl)nickel(II) iodide: 0.91 g (15%); mp 149–149.5 °C (lit.[21] mp 151–152 °C). Anal. Calcd for $C_{18}H_{30}F_5INiP_2$: C, 37.10; H, 5.19. Found: C, 36.96% H, 5.17.

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Registry No. C_6H_5I, 591-50-4; 4-$CH_3OC_6H_4I$, 696-62-8; 4-ClC_6H_4I, 637-87-6; 4-NCC_6H_4I, 3058-39-7; C_6F_5I, 827-15-6; 4-ClC_6H_4Br, 106-39-8; 4-$CH_3COC_6H_4Br$, 99-90-1; 4-NCC_6H_4Br, 623-00-7; C_6F_5Br, 344-04-7; 2-$CH_3OC_6H_4I$, 529-28-2; 2-$O_2NC_6H_4I$, 609-73-4; 4-$CH_3OC_6H_4Br$, 104-92-7; nickel, 7440-02-0; bis(triphenylphosphine)bis(pentafluorophenyl)nickel(II), 14832-18-9; bis(triethylphosphine)(pentafluorophenyl)nickel(II) iodide, 13978-69-3.

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Method for the Racemization of Optically Active Amino Acids

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A practical method for the racemization of optically active amino acids has been developed. A wide variety of optically active α-amino acids, including neutral amino acids, acidic amino acids, basic amino acids, and imino acids, could be racemized by heating in a medium of acetic acid at 80–100 °C for 1 h in the presence of 0.05 molar equiv of an aliphatic or an aromatic aldehyde. The factors influencing the racemization were investigated. Phenylglycine, (*p*-hydroxyphenyl)glycine, and serine could be racemized without complete dissolution of the optically active isomers. Thus, isolation of the racemic modification was easily achieved by simple filtration of the racemic modification suspended in the reaction mixture. The mechanism of the racemization is discussed.

In order to improve the industrial production of optically active amino acids, we have been studying optical resolution of DL-amino acids by preferential crystallization procedures. Since one enantiomer of the racemic modification has economical use, it is desirable to racemize the unwanted enantiomer obtained by optical resolution to recycle it for the resolution process.

Various methods for racemization of optically active amino acids are known. For example, optically active amino acids can be racemized (i) by heating with water in the presence of strong base or strong acid,[1] (ii) by heating with water in the absence of strong base or strong acid in a sealed vessel at 150–250 °C,[2] (iii) by heating with water in the presence of an aldehyde and a metal ion under neutral or weakly alkaline conditions,[3] (iv) by heating with water in the presence of pyridoxal or pyridoxal analogues, including the so-called resin catalyst, and metal ion,[4,5] or (v) by heating with a lower aliphatic acid such as acetic

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