experiments described herein greatly increase the usefulness of the bicyclo[3.3.1]nonane system as a synthetic precursor to polycyclic natural products.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Dichloromethane was distilled from phosphorus pentoxide. Infrared spectra were determined on a Beckman IR-4250 spectrometer. Nuclear magnetic resonance spectra were determined on a Varian EM 360 60-MHz instrument and on a Nicolet 300-MHz instrument. Carbon-13 NMR spectra were determined on a JEOL FX-90Q Fourier transform instrument. High-resolution mass spectra were determined on a Kratos mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc.

1-Allyl-4-carbomethoxy-7-methylbicyclo[3.3.1]nonan-3-one (2). To a flask containing potassium hydride (1.73 mmol) was added a mixture of compound 1 (0.144 g, 0.75 mmol) and 2.5 mL of dimethyl carbonate at room temperature under nitrogen. The mixture was stirred at room temperature overnight. It was then poured into cold aqueous ammonium chloride solution and extracted with methylene chloride. The organic layer was dried and concentrated. The crude product was chromatographed with 10:1 hexanes-ethyl acetate to yield 0.152 g of product (81% yield): ^{1}H NMR ($CDCl_3$) δ 0.84 (d, J = 6.3 Hz, 3 H), 0.9–2.9 (m, 13 H), 3.75 (s, 3 H), 5.1 (m, 2 H), 5.8 (m, 1 H); IR ($CDCl_3$) 3060, 1740, 1700, 1430, 1285, 1100, 980 cm^{-1}.

Büchi Ring Contraction. General Procedure. To a 1 M solution of keto ester (1 equiv) in methanol at −15 °C under nitrogen was added a 1 M solution of *tert*-butyl hypochlorite (1.1 equiv) in methanol. The mixture was then cooled in the refrigerator overnight and then stirred at rrom temperature for 4 h. The mixture was then concentrated to afford a crude product, which was taken on to the next step without purification. To a 0.2 M solution of the crude product (1 equiv) in xylene were added glass beads and sodium carbonate (1 equiv). The mixture was then heated to reflux for 12 h. The mixture was cooled, filtered through Celite, and then concentrated. The crude product was chromatographed on silica gel. The overall yields for **3** and **5** were 72% and 81%, respectively.

1-Allyl-3-carbomethoxy-7-methylbicyclo[3.2.1]oct-2-ene (3): ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 6 Hz, 3 H), 1.1–3.0 (m, 10 H), 3.72 (s, 3 H), 5.05 (m, 2 H), 5.8 (m, 1 H), 6.6 (s, 1 H); ^{13}C NMR ($CDCl_3$) 21.65, 26.47, 33.04, 39.02, 40.19, 42.47, 48.77, 49.55, 51.24, 117.25, 134.55, 137.47, 147.81, 165.31 ppm; IR ($CDCl_3$) 3070, 2950, 1710, 1640, 1610, 1455, 1260, 1225, 1195, 1080, 910, 780 cm^{-1}; HRMS, m/e for $C_{14}H_{20}O_2$ requires 220.14633, measured 220.1469.

1-Hydroxy-3-carbomethoxybicyclo[3.2.1]oct-2-ene (5): ^{1}H NMR ($CDCl_3$) δ 1.1–3.2 (m, 9 H), 3.72 (s, 3 H), 6.60 (s, 1 H); IR (film) 3440, 3060, 2960, 1740, 1710, 1610, 1445, 1140, 880, 735 cm^{-1}; mass spectrum; m/e 55, 67, 81, 95, 108, 123, 140, 153, 167, 182.

3-(Hydroxymethyl)bicyclo[3.2.1]octan-1-ol (6). To 35 mL of liquid ammonia was added a solution of **5** (0.235 g, 1.29 mmol) and *tert*-butyl alcohol (0.478 g, 6.45 mmol) in 3 mL of THF. To the resulting solution was added lithium (0.070 g, 10 mmol) in pieces. The solution was stirred at −33 °C for 2 h and quenched with ammonium chloride, and then the ammonia was allowed to evaporate. The crude mixture was neutralized with 3 N HCl and extracted with CH_2Cl_2. The organic layer was dried and concentrated. The crude product was chromatographed with ethyl acetate to afford 0.082 g of product (41% yield): ^{1}H NMR ($CDCl_3$) δ 1.00–2.80 (m, 12 H), 3.70 (d, J = 8 Hz, 2 H). IR ($CDCl_3$) 3400, 2960, 1440, 1330, 1260, 1090, 1020, 810, 720 cm^{-1}.

Sulfide Oxidation and Elimination. The sulfide was oxidized with sodium periodate in methanol at room temperature. The crude sulfoxide (0.283 g, 0.74 mmol) was heated at 180 °C for 24 h in a two-phase reaction of carbon tetrachloride (5 mL) and water (1 mL) containing 0.148 g of calcium carbonate. The reaction was conducted in a sealed tube. The crude product was purified by flash chromatography using 5:1 hexanes–ether to afford a 58% yield: 300-MHz ^{1}H NMR ($CDCl_3$) δ 0.95–2.90 (m, 20 H), 5.32–5.45 (m, 1 H), 5.61–5.68 (m, 1 H); IR (film) 2930, 1680–1700 (br), 1440, 1095, 900 cm^{-1}; mass spectrum, m/e 258.

Ozonolysis and Cyclization To Produce Aldehyde 9. To a solution of the alkene (0.060 g, 0.23 mmol) in 2 mL of methylene chloride at −78 °C was passed ozone until a pale blue color appeared. The solution was purged with nitrogen, and then 2 mL of dimethyl sulfide was added at −78 °C. The reaction was allowed to warm to room temperature and was then concentrated. The crude dialdehyde was unstable and was taken on to the next step without purification. To a solution of the crude dialdehyde (0.038 g, 0.13 mmol) in 1 mL of dry benzene were added two drops of piperidine and three drops of acetic acid. The solution was heated at 70 °C overnight, cooled, and concentrated. The crude product was purified by silica gel chromatography to afford a 46% overall yield of **9**: ^{1}H NMR ($CDCl_3$) δ 0.95–3.02 (m, 16 H), 3.20–3.45 (m, 2 H), 6.58 (s, 1 H), 9.56 (s, 1 H); ^{13}C NMR ($CDCl_3$) 25.22, 25.39, 25.64, 33.92, 37.72, 43.71, 46.50, 48.38, 50.91 53.59, 56.62, 61.76, 150.86, 151.09, 188.11, 206.23, 209.19; mass spectrum, m/e 91, 107, 120, 162, 230, 272; HRMS; m/e for $C_{17}H_{20}O_3$ found 272.1422, calcd 272.14125.

Acknowledgment. We thank the National Institutes of Health for generous financial support.

Registry No. (±)-**1**, 96791-72-9; **2**, 102537-76-8; (±)-**3**, 102537-77-9; **4**, 102537-78-0; (±)-**5**, 102537-79-1; **6**, 102537-80-4; (±)-**7**, 102537-81-5; (±)-**7** (alkene), 102537-82-6; (±)-**7** (sulfoxide), 102537-84-8; (±)-**8**, 102537-85-9; (±)-**9**, 102537-83-7.

Coupling of Aryl Chlorides by Nickel and Reducing Metals

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Received November 1, 1985

An efficient synthesis of biaryls (diarenes) from aryl chlorides has been developed and investigated. The coupling reagent is a catalytic mixture of anhydrous nickel salt and triphenylphosphine in the presence of a reducing metal (Zn, Mg, or Mn). The reaction occurs rapidly under mild conditions, tolerates a variety of functional groups, employs air-stable starting materials, and can be run conveniently in ordinary laboratory glassware. Excess reducing metal drives the coupling process and allows even aryl chlorides to be coupled to high yields, a distinguishing advantage over previous coupling processes which employed stoichiometric zero-valent nickel reagents. The reaction is pseudo-zero-order in aryl chloride and is promoted by 2,2′-bipyridine and by halide salts (F < Cl < Br < I). A number of reaction variables have been examined and their effects on the kinetics and yields are discussed. Reduction and aryl transfer from triphenylphosphine, the major side reactions, can be minimized in most cases. A coupling mechanism consistent with the observed kinetics and reaction parameters is proposed in which the key step is reduction of an arylnickel species by zinc to an arylnickel(I) complex.

Aryl–aryl carbon bonds are formed by many methods which require metals.[1] Examples are direct oxidative dehydrodimerization by Pd,[2] V,[3] Cu,[4] and Tl[5] and reductive coupling with loss of a substituent group, as in the

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classical[6] and modified[7] Ullmann reactions. A number of recent methods are the Kharasch-type cross-coupling reactions of an aromatic Grignard reagent with an aryl halide by nickel(II), palladium(II), or other reagents.[8,9]

Direct coupling of aryl bromides and iodides by zerovalent nickel reagents has been accomplished in high yield under mild conditions. However, Semmelhack's original method[10] has several limitations: (a) stoichiometric amounts of expensive Ni(0) reagents are necessary; (b) the air-sensitive reagents require careful handling; and (c) aryl chlorides give poor yields.

Several research groups have recognized these limitations and have sought alternative methods, improvements, or modifications.[11-23] Kende and co-workers[11] introduced the preparation of active nickel(0) reagent in situ from bis(triphenylphosphine)nickel(II) dichloride, triphenylphosphine, and zinc dust in *N,N*-dimethylformamide. Kumada and co-workers[13] demonstrated that Kende's procedure could be made catalytic in nickel by using a stoichiometric amount of zinc. A similar catalytic system with nickel(0) triethylphosphine complexes was reported recently[15] but aryl chlorides gave low yields.

Independent from the research of Kende,[11] Kumada,[13] and others,[12,14-23] we discovered a method for coupling aryl halides in which the nickel catalyst is generated in situ from simple nickel salts and excess reducing metal.[24] Our investigation has revealed that excess reducing metal plays a crucial role, which allows biaryls to be formed rapidly in excellent yields from aryl *chlorides* under mild conditions. Side reactions, such as reduction, are usually minimal. Molar scale reactions have been demonstrated by using ordinary laboratory glassware under a nitrogen atmosphere.

Table I. Coupling of Chlorobenzene with Zinc and Nickel Compounds[a]

reagent	time (h)	yield (%)	
		benzene	biphenyl
$NiCl_2$	2	1	99
$NiBr_2$	2	1	99
$NiI_2 \cdot 6H_2O$	2	42	58
$Ni(OOCCH_3)_2 \cdot 4H_2O$	17	34	66
$Ni(acac)_2 \cdot 2H_2O$	17	18	82
$Ni(NO_3)_2 \cdot 6H_2O$	24	0	0[b]
NiO	24	0	0[b]
NiF_2	24	0	0[b]

[a] Conducted with 1 mmole of Ni compound, 7.6 mmol of TPP, 31 mmol of Zn, and 20 mmol of chlorobenzene in 10 mL of DMAc at 80 °C; yields by GC analysis. [b] Only unreacted chlorobenzene detected; catalyst solutions did not turn red-brown.

Table II. Coupling of Chlorobenzene with Nickel Chloride and Various Metals[a]

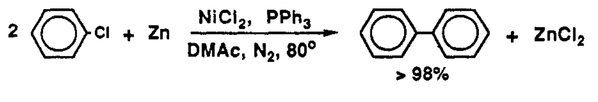
metal	time (h)	yield (%)	
		benzene	biphenyl
Fe	24	0	0
Zn	2	1	99
Mn	24	0	>99
Al	5	76	22
Mg	2	4	96
Na	24	6	5
Ca	6	77	22 (65[b])

[a] At 65–80 °C in DMAc (see Experimental Section) yields by GC analysis. [b] Calcium oxide layer removed and 2,2′-bipyridine added (see Experimental Section).

We believe this method is superior to any current procedure for coupling aryl halides, especially aryl chlorides.[12,14,22] We shall discuss the scope, limitations, side reactions, and kinetic behavior of this reaction. We also propose a mechanism which accounts for the effects of reaction variables, particularly the necessity for a reducing metal, on the coupling of aryl chlorides.

Results and Discussion

The pioneering research of Semmelhack and co-workers demonstrated good yields of biphenyl from bromo- or iodobenzene but only 14% yield from chlorobenzene at 50 °C after 29 h.[10a] Under our conditions, chlorobenzene is coupled quantitatively in a few minutes by using a catalytic amount of nickel, triphenylphosphine, and excess zinc in a dry, dipolar aprotic solvent at 60–80 °C. Considering that both systems nominally rely on active nickel(0) species, why then are aryl chlorides coupled so efficiently under our conditions?



We have shown that the reducing metal is necessary for coupling aryl chlorides. When stoichiometric zero-valent

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nickel–triphenylphosphine complex (obtained commercially or prepared by reducing nickel chloride with zinc in the presence of triphenylphosphine followed by careful filtration to remove excess zinc) was used to couple chlorobenzene, the yield of biphenyl was only 40% after 24 h at 70–80 °C. When these inactive solutions were transferred to a flask containing zinc, all of the remaining chlorobenzene was quickly converted to biphenyl. Zinc drives the coupling of chlorobenzene, which differentiates our reaction from those using only zero-valent nickel reagents.

Scope and Limitations. A number of nickel salts can be used to generate the catalyst (Table I). Nickel chloride and bromide were most effective. The hydrated nickel salts led to substantial reduction.

Although many metals have reduction potentials lower than that of nickel, only zinc, magnesium, and manganese gave high yields of coupled products from chlorobenzene (Table II). Calcium and aluminum effected complete reaction, but the major product was benzene. Rieke has demonstrated that reactive metal powders, formed by reduction of nickel salts by alkali metal, oxidatively add aryl halides[25,26] to produce biaryls.[21] We found that solutions of NiCl$_2$ reduced by sodium were blood-red, indicative of low valent nickel complexes, but observed little reaction with chlorobenzene and primarily reduction to benzene.

Triarylphosphines were the best ligands. Trialkylphosphines gave much slower reactions and lower yields. Bidentate arylphosphines such as bis(1,2-diphenylphosphino)ethane were ineffective.

The limitations for the aryl halides (Table III) were similar to those described by Semmelhack and co-workers.[10] Nitro groups completely inhibited the reaction, perhaps by the formation of nitrosonickel(0) complexes.[27] Acidic substituents, such as phenolic hydroxyl and carboxylic acids, caused reduction to arene. In fact, deliberate addition of water or other protic sources converts the process to a mild, selective method for reducing aromatic carbon–halogen bonds.[28] Reduction can be prevented by removing the proton source. For example, *p*-chlorophenyl acetate can be coupled in excellent yields (example 5, Table III) and converted to 4,4′-biphenol. Aryl chlorides with electron-withdrawing or weakly electron-donating substituents gave high yields of biaryl (Table III).

Substrates with strong electron-donating substituents, such as methoxy or amino, produced some monosubstituted biaryl byproducts. This side reaction (see below) was suppressed by 2,2′-bipyridine (example 8, Table III).

Aryl bromides and iodides also gave high yields of diarenes, although somewhat more reduction to arene was found. The overall reaction times were slower than those for aryl chlorides under comparable conditions (see Figure 4 and Experimental Section). The bromides and iodides are generally less available, expensive, and offer no particular synthetic advantage for coupling under our conditions.

We have demonstrated reactions on the scale of 1 mol of aryl chloride employing common laboratory equipment (see Experimental Section). No special handling is required because all the reagents are air-stable. An inert atmosphere must be used and the aprotic solvent should be dried thoroughly to suppress reduction.

Table III. Coupling of Various Aryl Chlorides[a]

example	aryl chloride	products	yield (%)[b]
1	*p*-chloronitrobenzene	none	0
2	chlorobenzene	biphenyl	99
		benzene	1
3	*p*-chlorophenol	4,4′-biphenol	25
		phenol	62
4	*p*-chlorophenyl acetate	4,4′-diacetoxybiphenyl	66
		phenylacetate	11
		4-acetoxybiphenyl	3
5	*p*-chlorophenyl acetate[c]	4,4′-diacetoxybiphenyl	90 (75)
		phenylacetate	5
6	*p*-chloroaniline	4,4′-diaminobiphenyl	31
		biphenyl	31
		4-aminobiphenyl	26
7	*p*-chloroanisole	4,4′-dimethoxybiphenyl	69
		anisole	12
		4-methoxybiphenyl	19
8	*p*-chloroanisole[c]	4,4′-dimethoxybiphenyl	96
		anisole	3
9	*p*-chlorotoluene	4,4′-dimethylbiphenyl	90
		toluene	3
10	*p*-chlorobenzaldehyde	4,4′-diformylbiphenyl	94 (62)
11	*p*-chloroacetophenone	4,4′-diacetylbiphenyl	100
12	*p*-chlorobenzonitrile	4,4′-dicyanobiphenyl	98
13	2-chlorothiophene	2,2′-bithenyl	98
14	2-chloropyridine	2,2′-bipyridine	(70)[d]

[a] The general small-scale procedure was used unless otherwise noted (see Experimental Section). [b] Determined by GC; values in parentheses are isolated yields from 0.5–1 molar scale reactions (in example 5, product isolated as 4,4′-biphenol). [c] Bipyridine ligand added (1 mol/mol Ni). [d] GC yield not obtained because product is chelated by Zn^{2+}.

Side Reactions. Reduction. Acidic (protic) substituents or contaminates such as water caused substantial reduction. This also occurs when Ni(0) reagents are used in the absence of active metals.[10,40] Either the Ni(0) complex reacts with the active hydrogen compounds to produce nickel hydrides which produce reduction products or the arylnickel intermediates react with the protic sources to yield arene.[28] In any event, reduction was minimized when the active hydrogen source was removed. Calcium and aluminum gave primarily reduction products in spite of these precautions. These metals probably interact directly with the solvent; alternate solvents were not examined.

Monosubstituted Biphenyls. Strong electron-donating groups tend to favor another side reaction—formation of monosubstituted biphenyls. Nickel can insert into aromatic C–O and C–S bonds;[29,30] palladium can cleave aromatic C–N bonds.[31] Under our conditions, insertion and then subsequent reaction with solvent or trace water could account for the loss of the heteratom. However, the ratio of mono- to disubstituted biphenyl remained fairly constant during the reaction. Furthermore, after all of the aryl chloride was consumed, there was no change in the product distribution. The monosubstituted products

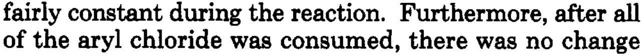

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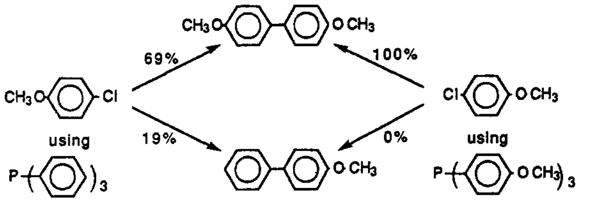
Table IV. Effect of Ligands and Temperature on the Formation of 4-Methoxybiphenyl from *p*-Chloroanisole[a]

example	TPP[b]	bipyridine[b]	T (°C)	4-methoxybiphenyl (%)[c]
1	7.6		60	4
2	7.6		70	13.5
3	15.2		70	10.7
4	7.6		80	19
5	7.6	1.0	70	1.8
6	7.6	1.5	70	0.75
7	7.6	2.0	80	0.45

[a] Reactions with 1 mmol of $NiCl_2$, 30 mmol of Zn, 20 mmol of *p*-chloroanisole in 15 mL of dry DMAc. [b] Equivalents relative to $NiCl_2$. [c] Yield by GC analysis with internal standard.

did not result from a secondary reaction, i.e., cleavage, of the disubstituted products.

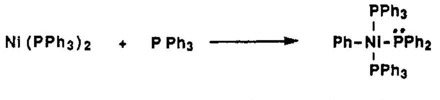
Our results indicate that the monosubstituted products originate from the triphenylphosphine ligand. A 19% yield of 4-methoxybiphenyl was formed from *p*-chloroanisole when triphenylphosphine ligand was used. When tris(*p*-methoxyphenyl)phosphine was used instead, 4-methoxybiphenyl was not detected. However, a trace amount of 4-methoxybiphenyl was detected when chlorobenzene was coupled using this ligand.



Transfers of aryl groups from triarylphosphines to metals have been reported for nickel,[32,33] palladium,[34] cobalt,[35] and rhodium,[36] including conditions similar to Kende's.[11,37] This side reaction in our process was enhanced by higher reaction temperatures but was suppressed by higher triphenylphosphine concentrations (Table IV). This is consistent with the effective degree of coordinative unsaturation of the metal catalyst, which is known to be influenced by temperature and ligand concentration. Triphenylphosphine is so bulky that even at room temperature the nickel(0) compound exists in solution almost entirely as the tris complex.[38] Higher temperatures would favor formation of the highly coordinatively unsaturated bis complex. Oxidative addition

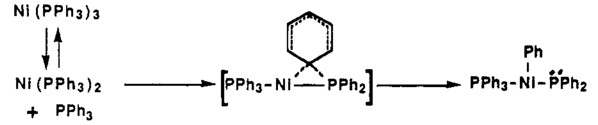
$$Ni(PPh_3)_3 \rightleftharpoons Ni(PPh_3)_2 + PPh_3$$

of triphenylphosphine can then occur, as suggested by Fahey[33] and Blum.[36] This phenyl–nickel species can produce the observed byproduct by cross-coupling with an aryl chloride.

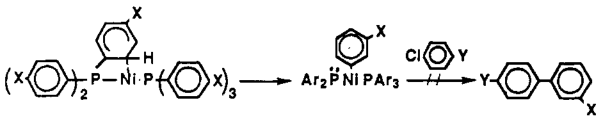


$$Ni(PPh_3)_2 + PPh_3 \longrightarrow Ph\text{-}\underset{PPh_3}{\overset{PPh_3}{Ni}}\text{-}\ddot{P}Ph_2$$

An alternative mechanism is direct phenyl transfer from coordinated phosphine ligand to the coordinatively unsaturated metal, a process proposed by Otsuka[32] and Matsuda.[34]



Phenyl migration must involve ipso substitution of nickel for phosphorus on the phenyl group. We have ruled out migration via ortho-metalation because 4-substituted phosphines did not form the isomeric 3′-substituted products.



Bidentate ligands, which dissociate less readily than triphenylphosphine, should suppress formation of the highly coordinately unsaturated complex and, consequently, should also suppress aryl transfer. Indeed, 2,2′-bipyridine suppressed the formation of 4-methoxybiphenyl from *p*-chloroanisole very effectively (Table IV). Even a small amount of bipyridine along with the triphenylphosphine was effective (see examples 4 and 5, Table III), but large amounts of bipyridine adversely affected the reaction rate.[39]

Kinetics. Previous coupling methods[10,11,13] required reaction times of several hours. We have observed complete reaction within minutes under certain conditions. In the absence of added salts, the coupling of chlorobenzene at 80 °C was complete in 90 min (Figure 1, curve a). The reaction was autocatalytic, which could be due to zinc or chloride ions, e.g., $ZnCl_2$. Control experiments clearly demonstrated that the autocatalytic behavior was due to formation of chloride ion; the metal cationic species play no role in the acceleration.

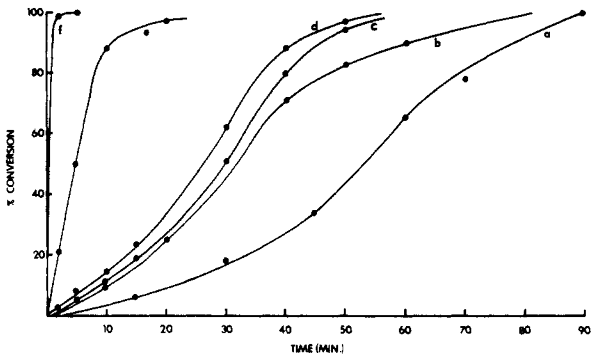


Figure 1. Effect of added salts on the conversion of chlorobenzene [2M] to biphenyl in DMAc at 80 °C: (a) no salt, (b) NaF, (c) Na_2SO_4, (d) NaCl, (e) NaBr, (f) NaI.

Halides and other anions increased the reaction rate in the order $F^- < SO_4^{2-} < Cl^- \ll Br^- < I^-$ (Figure 1). With sodium iodide present, chlorobenzene was completely coupled within 2 min! On the other hand, iodide ion did not improve the coupling efficiency by zero-valent nickel reagents in the *absence* of zinc. This indicates that the mechanism operating in the presence of excess zinc is different from coupling with only zero-valent nickel. Our evidence does not support halide exchange, e.g., to ArI, followed by rapid coupling; aryl iodides generally gave poorer biaryl yields (see below). Our results do not parallel

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(32) Nakamura, A.; Otsuka, S. *Tetrahedron Lett.* **1974**, 463.

(33) Fahey, D. R.; Mahan, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 4499.

(34) Kikukawa, K.; Takagi, M.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1493.

(35) Michman, M.; et al. *J. Organomet. Chem.* w1979, *182*, 547; *J. Organomet. Chem.* **1979**, *182*, 555.

(36) Lewin, M.; Aizenshtat, Z.; Blum, J. *J. Organomet. Chem.* **1980**, *184*, 255.

(37) Mitchell, R. H.; Chaudhary, M.; Dingle, T. W.; Williams, R. V. *J. Am. Chem. Soc.* **1984**, *106*, 7776.

(38) Tolman, C. A.; Seidel, W. C.; Gerlach, D. H. *J. Am. Chem. Soc.* **1972**, *94*, 2669.

(39) This is probably due to strong chelation of Ni^0 by bipyridine to form a coordinatively saturated species. Presumably, coordinative unsaturation is a driving force for oxidative addition.

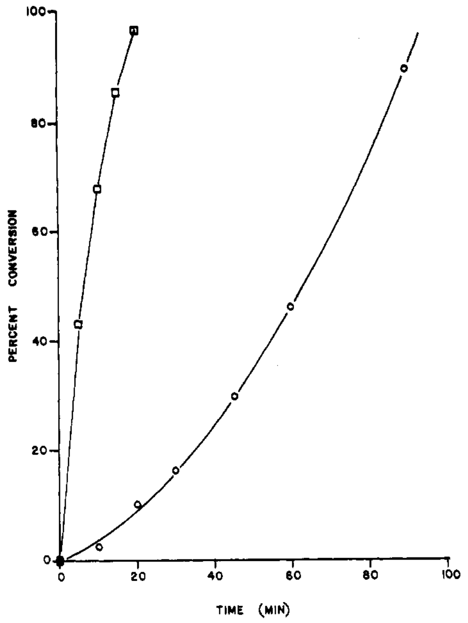

Figure 2. Effect of ligands on the conversion of chlorobenzene by zinc and nickel catalyst: 3.8/1 molar ratio TPP/2,2′-bipyridine (squares); TPP only (circles).

Table V. Effect of Initial Concentrations on the Coupling Rate of Chlorobenzene in DMAc at 70 °C

$NiCl_2$ [M]	ClC_6H_5 [M]	NaBr [M]	observed rate (M/s)^a
0.025	2	1	3.78
0.05	2	1	7.20
0.10	2	1	13.8
0.10	1	1	13.2
0.10	1	0.25	3.24

^{a} Rate of disappearance of chlorobenzene.

those for nickel-catalyzed carbonylation of aromatic halides,[40] in which autocatalytic behavior due to chloride and bromide ions was observed, but iodides were deactivating.

Kinetic analyses were based on reactions in which the autocatalytic effect was suppressed by added sodium bromide. Kinetic plots linear between 0% and 80% conversion were obtained (see Figure 1, curve e) which implies pseudo-zero-order aryl halide dependence throughout most of the reaction. The reaction rate was first order in nickel and bromide ion (Table V). The temperature dependence of the observed rate constant gave the relationship $k = 2.38 \times 10^5\, e^{-10700/RT}$ ($\Delta H^{\ddagger} = 10$ kcal/m and $\Delta S^{\ddagger} = -36$ eu).

Phosphine ligand concentration had a limited effect on the reaction rate. The rate increased when the triphenylphosphine to nickel ratio was increased from 3 to 6 but leveled off rapidly at higher ratios. Rate inhibition at high phosphine to nickel ratios was not observed. This is consistent with the activation parameters which suggest that the rate-determining step is associative and not dissociative.

The reaction rate increased dramatically when 1 equiv (to nickel) of bipyridine was added (Figure 2). Excess zinc also influenced the reaction rate (Figure 3). We will return to these results in the discussion of the reaction mechanism.

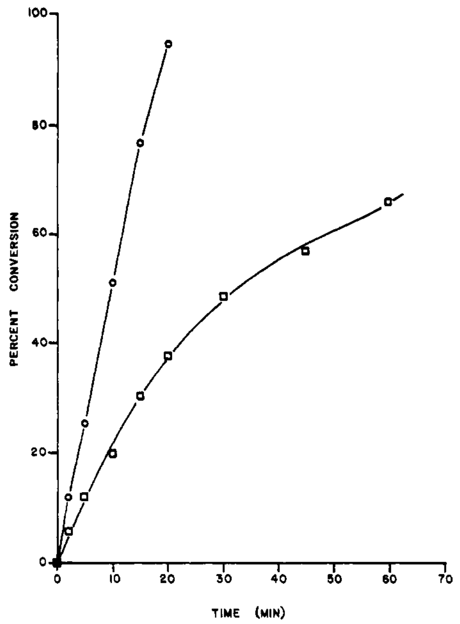

Figure 3. Effect of zinc on the conversion of chlorobenzene: 1.5 equiv of zinc (squares) and 6.2 equiv (circles).

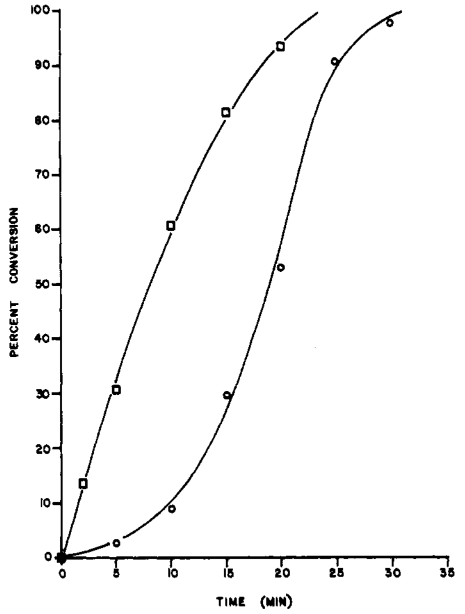

Figure 4. Comparison of the coupling of 2 M chlorobenzene in the presence of 1 M NaBr (squares) to the coupling of 2 M bromobenzene (circles).

A consequence of the pseudo-zero-order dependence on aryl halide is that chlorobenzene should react as fast as bromobenzene. The conversion of chlorobenzene (2 M) to biphenyl in the presence of 1 M NaBr is compared in Figure 4 to that of bromobenzene (2 M). Considering the autocatalytic behavior of the latter reaction due to bromide ion, the comparison must be made at 50% conversion, i.e., 1 M bromide ion in each system. The rate (slope) of the bromobenzene reaction approximately equaled that of chlorobenzene under these conditions. The coupling of iodobenzene was also autocatalytic but was slower than bromobenzene. This might be due to side reactions leading to phosphonium salts with iodobenzene.[41] These results contrast with the behavior of stoichiometric zero-valent nickel reagents, where aryl halides react in the order iodide > bromide ≫ chloride.

Halogen exchange, observed under other conditions,[42,43] was not evident under our reaction conditions. Bromo- or iodobenzene was not detected when chlorobenzene was

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[40] Cassar, L.; Foa, M. *J. Organomet. Chem.* **1973**, *51*, 381.

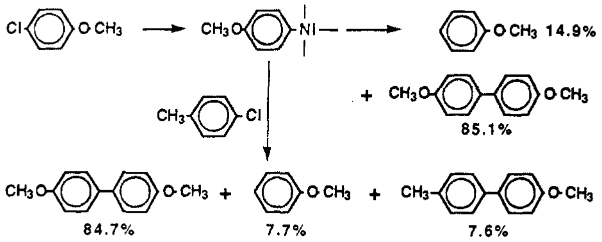
[41] Cassar, L.; Foa, M. *J. Organomet. Chem.* **1974**, *74*, 75.

[42] Tsou, T. T.; Kochi, J. K. *J. Org. Chem.* **1980**, *45*, 1930.

[43] Takagi, K.; Hayama, N.; Okamoto, T. *Chem. Lett.* **1978**, 191.

coupled in the presence of bromide or iodide ion even though the overall conversion rates of the aryl bromides and iodides were slower than that of chlorobenzene. Furthermore, in our hands, the procedures[44,45] reported to couple aryl iodides with potassium iodide and zinc powder[22,44,45] were ineffective with aryl chlorides.

Cross-Coupling. Our coupling procedure is inadequate for the synthesis of unsymmetrical biaryls.[8] Simultaneous coupling of two aryl chlorides gave a mixture of biaryl products. We did, however, make an interesting observation: most aryl chlorides gave residual arylnickel species which remained after all of the aryl chloride had been consumed. The following scheme summarizes the results of staged, cross-coupling experiments in which *p*-chloroanisole was coupled followed after 1 h by the addition of *p*-chlorotoluene. Prior to the addition of *p*-chlorotoluene, analysis showed no detectable *p*-chloroanisole. After *p*-chlorotoluene was added, the amount of anisole decreased after 1 h and the cross-coupled product 4-methoxy-4′-methylbiphenyl (MMB) was observed.

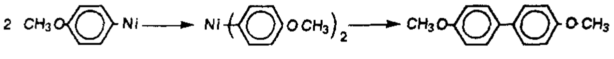


A control experiment verified that no cross-coupled product (MMB) was produced when *p*-chlorotoluene was coupled in the presence of anisole. We believe the appearance of the cross-coupled product is strong evidence for residual aryl nickel species which are long-lived in the *absence* of aryl chloride.

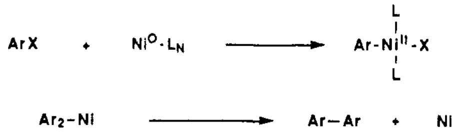
The initial gas chromatographic analysis, after all of the *p*-chloroanisole had been consumed, gave the proper mass balance (with internal standard) because the residual arylnickel species decomposed to anisole on the injection port (or upon exposure to air and the acetone quench before analysis). When *p*-chlorotoluene was added to this "completed" reaction, it quickly reacted with the residual, unconverted arylnickel to form the cross-coupled product (the remainder of the *p*-chlorotoluene reacted to form 4,4′-dimethylbiphenyl and some toluene).

We infer that the 15% anisole observed at the end of *p*-chloroanisole coupling arose from reduction (7.7%) and the balance from the residual anisylnickel species (7.6%), i.e., about 50% of the available nickel was in the latter form.

It is significant that only cross-coupling of the residual arylnickel occurred; that is, the dimethoxybiphenyl yield did not increase after the addition of *p*-chlorotoluene. However, in the absence of additional aryl chloride, the dimethoxybiphenyl yield increased very slowly from 85.1% to 87.6% while the anisole yield decreased from 14.9% to 12.4% over 3 h. The residual arylnickel species evidently react very slowly in the absence of aryl chloride to form coupled product, probably by a metathesis to a diaryl nickel species.



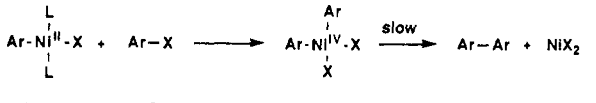
Mechanism. Several mechanisms have been proposed for similar coupling reactions and this topic has excited some debate. Two points are generally agreed upon. First, the initial process is oxidative addition of aryl halide to nickel(0) to form an arylnickel(II) intermediate[46-51] (at least with aryl chlorides and bromides). Second, biaryl formation occurs by reductive elimination from a diarylnickel intermediate. The intervening steps from the arylnickel(II) to the diarylnickel species and the oxidation state of the latter are controversial.



$$ArX + Ni^{0}\cdot L_N \longrightarrow Ar\text{-}\overset{L}{\underset{L}{Ni^{II}}}\text{-}X$$

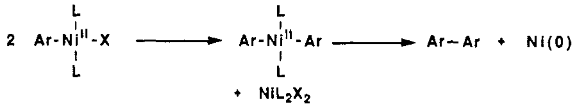
$$Ar_2\text{-}Ni \longrightarrow Ar\text{-}Ar + Ni$$

Semmelhack proposed that an arylnickel(II) intermediate reacts with aryl halide to form diarylnickel(IV) which undergoes reductive elimination as the slow step. This conclusion was based on the observation that formation of biphenyl was slower than the disappearance of iodobenzene when reacted with Ni(COD)$_2$.[10]



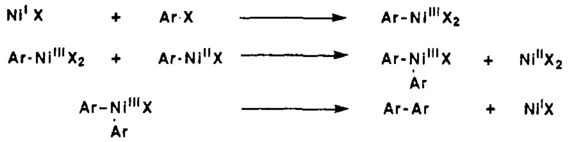
$$Ar\text{-}\overset{L}{\underset{L}{Ni^{II}}}\text{-}X + Ar\text{-}X \longrightarrow Ar\text{-}\overset{Ar}{\underset{X}{Ni^{IV}}}\text{-}X \xrightarrow{slow} Ar\text{-}Ar + NiX_2$$

Analogous to mechanisms proposed for cross-coupling with Grignard reagents,[8a] a diarylnickel(II) complex might be formed by metathesis of arylnickel(II).[21,32,49] The diarylnickel(II) complex could then undergo reductive elimination to yield biaryl.



$$2\ Ar\text{-}\overset{L}{\underset{L}{Ni^{II}}}\text{-}X \longrightarrow \underset{+\ NiL_2X_2}{Ar\text{-}\overset{L}{\underset{L}{Ni^{II}}}\text{-}Ar} \longrightarrow Ar\text{-}Ar + Ni(0)$$

Instead of intermediates with formal oxidation states of +2 and +4, +1 and +3 nickel intermediates have been proposed by Tsou and Kochi,[52] in which a nickel(I) species oxidatively adds aryl halide to form an arylnickel(III) intermediate. This undergoes metathesis with arylnickel(II) to yield a diarylnickel(III) intermediate, which then undergoes rapid reductive elimination to form biaryl and regenerate nickel(I).



$$Ni^{I}X + ArX \longrightarrow Ar\text{-}Ni^{III}X_2$$

$$Ar\text{-}Ni^{III}X_2 + Ar\text{-}Ni^{II}X \longrightarrow Ar\text{-}\underset{Ar}{Ni^{III}}X + Ni^{II}X_2$$

$$Ar\text{-}\underset{Ar}{Ni^{III}}X \longrightarrow Ar\text{-}Ar + Ni^{I}X$$

Their arylnickel(II) complexes gave high yields of homocoupled products in polar solvents without consuming aryl halide. In nonpolar solvents biaryls were formed in low yield in the absence of aryl halide but quantitatively in the presence of aryl halide. The presence of aryl halide was important in nonpolar solvents but not important in polar solvents, which implies a change in mechanism. In our process, the presence of aryl halide appears to be important in polar solvents.

The ligand on the metal may also be important. Otsuka and co-workers[53] obtained biphenyl quantitatively from a phenyltriphenylphosphine–nickel(II) complex in toluene.

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(44) Takagi, K.; Hayama, N.; Inokawa, S. *Chem. Lett.* **1979**, 917.

(45) Takagi, K.; Hayama, N.; Inokawa, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3691.

(46) Foa, M.; Cassar, L. *J. Chem. Soc., Dalton Trans.* **1975**, 2572.

(47) Hidai, M.; Kashiwagi, T.; Ikeuchi, T.; Uchida, Y. *J. Organomet. Chem.* **1971**, *30*, 279.

(48) Fahey, D. R. *J. Am. Chem. Soc.* **1970**, *92*, 402. Fahey, D. R.; Mahan, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 2501.

(49) Parshall, G. W. *J. Am. Chem. Soc.* **1974**, *96*, 2360.

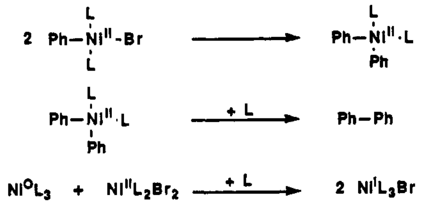
(50) Corain, B.; Favero, G. *J. Chem. Soc., Dalton Trans.* **1975**, 283.

(51) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 6319.

(52) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 7547.

(53) Otsuka, S.; Nakamura, A.; Yoshida, T.; Naruto, M.; Atoka, K. *J. Am. Chem. Soc.* **1973**, *95*, 3180.

When excess triphenylphosphine was present, a univalent nickel compound ($NiX[PPh_3]_3$) was isolated. Although this might imply a mechanism involving nickel(I) and nickel(III) species, a conventional mechanism can also explain these results: where the last step is a synproportionation.[54]



$$2\ \mathrm{Ph{-}\overset{L}{\underset{L}{Ni^{II}}}{-}Br} \longrightarrow \mathrm{Ph{-}\overset{L}{\underset{Ph}{Ni^{II}}}{\cdot}L} + \mathrm{Ni^{II}L_2Br_2}$$

$$\mathrm{Ph{-}\overset{L}{\underset{Ph}{Ni^{II}}}{\cdot}L} \xrightarrow{+L} \mathrm{Ph{-}Ph} + \mathrm{Ni^{0}L_3}$$

$$\mathrm{Ni^{0}L_3} + \mathrm{Ni^{II}L_2Br_2} \xrightarrow{+L} 2\ \mathrm{Ni^{I}L_3Br}$$

Morvillo and Turco demonstrated that phenylnickel(II) complexes decompose thermally in toluene in the absence of aryl halide to produce biphenyl in high yields after 12 h. They also obtained high yields from chlorobenzene and their nickel(0) complex after 24 h.[55] A bimolecular process was suggested.

$$2\ \mathrm{Ni(X)(Ph)L_N} \longrightarrow \mathrm{Ph{-}Ph} + 2\ \mathrm{Ni(X){-}L_N}$$

The reducing environment of the electrochemical synthesis[19] of biaryls using a nickel catalyst most closely simulates our conditions. One of the proposed mechanisms[20] is summarized as follows: The last step produces an

$$\mathrm{ArNiL_2X} + e^- \xrightarrow{+L} \mathrm{ArNiL_3} + X^-$$

$$2\ \mathrm{ArNiL_3} \xrightarrow{\bullet\ 2L} \mathrm{Ar{-}Ar} + 2\ \mathrm{Ni^{0}{\cdot}L_4}$$

$$\mathrm{ArNiL_3} + e^- \longrightarrow [\mathrm{ArNiL_3}]^-$$

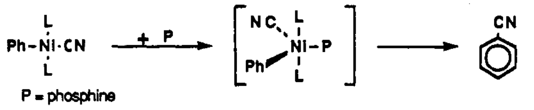
$$[\mathrm{ArNiL_3}]^- + \mathrm{ArNiL_2X} \xrightarrow{+3L} \mathrm{Ar{-}Ar} + 2\ \mathrm{Ni^{0}{\cdot}L_4} + X^-$$

$$[\mathrm{ArNiL_3}]^- + \mathrm{ArX} \longrightarrow \mathrm{Ar_2NiL_2} + X^- + L$$

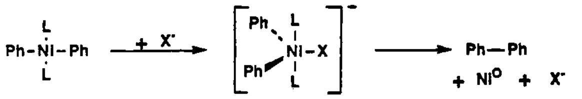
electrochemically inactive complex.

Considering the diverse conditions and observations reported, it is unlikely that one mechanism is operating under all reaction conditions. Key factors are the solvent, the ligands present, the type of aryl halide (I, Br, or Cl), substituents on the aryl halide, and whether or not excess aryl halide or ligand is present. Under our reaction conditions, nickel is used catalytically with excess zinc, which creates a reducing environment and also the potential for heterogeneous or surface reactions. Our reaction should be closer mechanistically to the electrochemical reactions than the others we have mentioned.

Our data does not support oxidative addition as rate limiting because the dependence on aryl chloride is pseudo-zero-order in the presence of Br^- and autocatalytic in the absence of added halide. However, rate-limiting reductive elimination seemed possible. The activation parameters of the coupling reaction are similar to those for the reductive elimination of benzonitrile from cyanophenyl complexes of nickel(II) ($\Delta H^{\ddagger} = 8.1$/kcal/mol, $\Delta S^{\ddagger} = -38$ eu), which was postulated to involve a five-coordinate complex in the rate-determining step.[56] If reductive



elimination were to occur from a diarylnickel(II) intermediate, it would be slow because of the *trans*-square-planar geometry.[57] This square-planar complex could, however, react with halide ion to form a pentacoordinate anionic complex which would facilitate reductive elimination due to the proximity of the phenyl groups. This



sequence could explain the rate enhancement by halide and the first-order dependence on added bromide. The rate enhancement by 2,2′-bipyridine (Figure 2) could also be explained, because this bidentate ligand would force the diarylnickel(II) complex into a cis aryl geometry. (The ineffectiveness of phosphorous bidentate ligands is consistent with other observations.[47,57,58])

However, one experimental observation was not consistent with reductive elimination as the rate-determining step: the reaction rate was dependent on the amount of zinc (Figure 3). This result implied that intermolecular electron transfer could be rate determining.

Examination of the reduction of nickel(II) to nickel(0) by zinc dust in *N*,*N*-dimethylacetamide (DMAc) in the absence of aryl chloride showed that the nickel salts are reduced in the order $NiI_2 > NiBr_2 > NiCl_2$. Halide salts accelerated the reduction of $NiCl_2$ to active catalyst in the sequence $I^- > Br^- > Cl^- >$ no salt, which was identical with the halide enhancement of the coupling reaction rate (Figure 1). Similar effects have been observed for the electroreduction of Ni(II).[58,59] In addition, 2,2′-bipyridine dramatically increased the reduction rate of $NiCl_2$ by zinc dust, also consistent with its effect on the coupling rate (Figure 2).

The role of halide in the reduction of nickel by zinc may involve bridging between nickel and zinc, as suggested by Kumada,[13] or may be a consequence of increased electrical conductivity of the medium.[60] The role of bipyridine in reduction may involve a bridge-inner-sphere electron transfer process.[61] Regardless of the exact role of halide and bipyridine, the similarity of their effect on the rate of reduction of Ni(II) to Ni(0) and on the rate of coupling of aryl chlorides suggests that the rate-determining step in both cases could be electron transfer. This would also explain the dependence of the coupling reaction rate on zinc.

Under our reaction conditions, two steps can be rate determining, depending upon the amount of aryl halide present. During the first ~80% conversion of chlorobenzene in the presence of bromide ion, the coupling rate is independent of the aryl chloride concentration. The rate then decreases dramatically as the concentration of aryl chloride approaches the catalyst concentration. We also showed that after all aryl chloride was consumed, residual aryl–nickel species remained which only slowly produced biaryl (see above). As a working model, we propose the mechanism shown in Scheme I.

The first step involves reduction of nickel(II) salt to zero-valent nickel by zinc. The second step is oxidative addition, which is known to be very fast,[46] to form an arylnickel(II) intermediate. These complexes can undergo reaction to yield biaryl, but that process is too slow with

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(54) Nilges, M. J.; Barefield, E. K.; Belford, R. L.; Davis, P. H. *J. Am. Chem. Soc.* **1977**, *99*, 755.

(55) Morvillo, A.; Turco, A. *J. Organomet. Chem.* **1981**, *208*, 103.

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(60) The solubilities f various salts in solvents such as DMF are $I^- > Br^- > Cl^-$. For example, see: Kittila, R. S., *Dimethylformamide Chemical Uses*; E. I. du Pont de Nemours & Co.: 1967; p 226.

(61) Magno, F.; Bontempelli, G.; Corain, B. *J. Chem. Soc., Dalton Trans.* **1979**, 1330.

Scheme I

$$Ni^{II}Cl_2 + 3\,L + Zn \longrightarrow Ni^{0}L_3 + ZnCl_2 \qquad (1)$$

$$Ni^{0}L_3 + ArCl \xrightarrow{-\,L} ArNi^{II}ClL_2 \qquad (2)$$

$$ArNi^{II}ClL_2 + 1/2\ Zn \xrightarrow{+\,L} ArNi^{I}L_3 + 1/2\ ZnCl_2 \qquad (3)$$

$$ArNi^{I}L_3 + ArCl \xrightarrow{-\,L} (Ar)_2Ni^{III}ClL_2 \qquad (4)$$

$$(Ar)_2Ni^{III}ClL_2 \xrightarrow{+\,L} Ar\text{-}Ar + Ni^{I}ClL_3 \qquad (5)$$

$$Ni^{I}ClL_3 + 1/2\ Zn \longrightarrow Ni^{0}L_3 + 1/2\ ZnCl_2 \qquad (6)$$

$$Ni^{I}ClL_3 + ArCl \xrightarrow{-\,2L} ArNi^{III}Cl_2L \qquad (7)$$

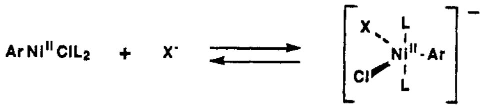
$$ArNi^{III}Cl_2L + Zn \xrightarrow{+\,2L} ArNi^{I}L_3 + ZnCl_2 \qquad (8)$$

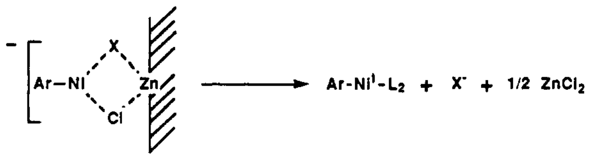
aryl chlorides to account for the rapid reactions we observe. Analogous to Bontempelli's electrochemical mechanism,[20] we propose that under the reducing conditions of excess zinc, the arylnickel(II) complex is reduced to an arylnickel(I) complex[62] (eq. 3). This complex oxidatively adds aryl chloride[63] to form a diarylnickel(III) complex (eq 4) which is known to undergo rapid reductive elimination[52,57,64-66] (eq 5). The direct reaction of aryl chloride with arylnickel (eq 4) is implicated by our cross-coupling results, in which the residual arylnickel species underwent exclusive cross-coupling rather than homocoupling (see above). The nickel(I) produced in step 5 may be reduced to nickel(0) (eq 6) which reenters the reaction cycle at step 2. Alternatively, it may react with aryl chloride by oxidative addition (eq 7) to yield an arylnickel(III) intermediate which under the highly reducing conditions is reduced to arylnickel(I) and continues the cycle in step 4.

The key intermediate in our proposed mechanism is an arylnickel(I) species (eq 3, 4, and 8). It has been demonstrated[52] that nickel(I) species are responsible for rapid coupling of aryl halides. Tsou and Kochi[51] reported that nickel(I) species are readily generated by the reaction of nicke(0) reagents with aryl iodides or bromides but are not generated from nickel(0) with aryl chlorides. Although we cannot rigorously exclude a metathesis step between arylnickel(II) and arylnickel(III) as proposed by Tsou and Kochi,[52] our results are consistent with formation of arylnickel(I) in the presence of reducing metals. Rather than simply acting as an agent for regenerating nickel(0), zinc is crucially involved in the formation of the active intermediate (eq 3 and/or 8), which is inaccessible from aryl chlorides without zinc. *The presence of zinc (or Mg or Mn) allows aryl chlorides to be coupled efficiently by nickel.*

In the presence of excess aryl chloride the reaction is pseudo-zero-order in aryl chloride and a reduction step (eq 3, 6, or 8) must be rate determining. This is consistent with the first-order dependence on nickel concentration and with the effect of excess zinc on the reaction rate. The parallel effects of added halide ion and bipyridine on both the rate of formation of the Ni(0) reagent (in the absence of aryl halide) and on the overall coupling reaction rate also imply that reduction is a reasonable rate-limiting step. Electrochemical data has shown that the reduction of arylnickel(II) occurs at a more negative potential than that of nickel(I).[18,20,59] We speculate that step 3 is the most difficult reduction and is rate limiting.

One hypothesis to explain the role of halide and the activation parameters in the presence of halide is the formation of a five-coordinate intermediate in step 3 (or 6 or 8). The nickelate intermediate could form a bridged Zn complex on the zinc surface which would facilitate electron transfer. The effects of halides would correlate with their ability to act as bridging ligands. The measured activation parameters are consistent with this associative bond-forming process. The first-order dependence on bromide can be explained by rapid formation of such five-coordinate intermediates or by rapid exchange of bromide for chloride in $ArNi^{II}ClL_2$, $Ni^{I}Cl_3$, or $ArNi^{III}Cl_2L$. There is some evidence that halide ligand exchange is more facile for Ni(I) than for Ni(0) complexes.[67]





At high conversions of aryl chloride, its concentration approaches that of nickel. Step 4 or 7 must then become rate determining because the rate becomes highly dependent on aryl chloride concentration (Figure 1). This implies that the rate constants for oxidative addition to arylnickel(I) and for reduction are probably within an order of magnitude of each other.

A different, slower mechanism must be responsible for biaryl formation in the absence of aryl chloride. This probably involves bimolecular metathesis of arylnickel(I) species,[68] because nickel(III) or nickel(II) species are unlikely to be long-lived in the highly reducing medium.

$$2\ ArNi^{I}L_3 \xrightarrow{-L} \underset{+\ Ni^{0}\text{-}L_3}{Ar_2\text{-}Ni^{II}L_2} \xrightarrow{+L} Ar\text{-}Ar + Ni^{0}\text{-}L_3$$

As with other reactions of aryl halides with Ni(0) reagents, the coupling reaction is sensitive to substituent effects. With electron donating groups, such as methoxy, the reaction rate was more sensitive to aryl chloride concentration and side reactions were observed. These observations are accommodated by our mechanism. Because electron-donating groups retard oxidative addition,[46] step 6 could become rate determining for *p*-chloroanisole. Oxidative addition to the arylnickel(I) species would be relatively slow and side reactions would become competitive. Electron-donating groups should stabilize intermediate I and species II leading to the phenylarylnickel intermediate (III), which explains why this side reaction

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[62] For evidence that nickel(I) complexes are viable under our conditions, see: Schiavon, G.; Bontempelli, G.; DeNobili, M.; Corain, B. *Inorg. Chim. Acta* **1980**, *42*, 211. Bontempelli, G.; Magno, F.; Schiavon, G.; Corain, B. *Inorg. Chem.* **1981**, *20*, 2579.

[63] For precedents for oxidative addition of organic halides to Ni(I), see: Gosden, C.; Healy, K. P.; Pletcher, D. *J. Chem. Soc., Dalton Trans.* **1978**, 972.

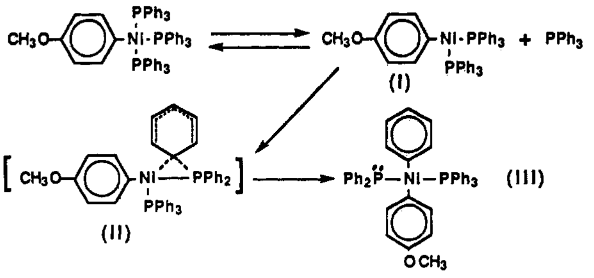
[64] Almemark, M.; Akermark, B. *J. Chem. Soc., Chem. Commun.* **1978**, 66.

[65] Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 1634.

[66] Smith, G.; Kochi, J. K. *J. Organomet. Chem.* **1980**, *198*, 199.

[67] Bontempelli, G.; Magno, F.; Denobili, M.; Schiavon, G. *J. Chem. Soc., Dalton Trans.* **1980**, 2288.

[68] Barefield, E. K.; Krost, D. A.; Edwards, D. S.; Vanderveer, D. G.; Trytko, R. L.; Orear, S. P.; Williamson, A. N. *J. Am. Chem. Soc.* **1981**, *103*, 6219.



is observed only for these aryl chlorides.

Our mechanism does not explain the failure of powerful reducing metals, e.g., Na, to effect the reaction. The high reduction potential of the alkali metals may cause overreduction. For example, reduction of arylnickel complexes to anionic nickel(0) complexes could lead to catalytically inactive species, as suggested for electrochemical systems.[19,20] Alternatively, the coupling reaction may require a metal capable of simultaneously providing two electrons or a metal that can form the proposed bridged complexes.

Summary and Conclusions

We have discovered independently that aryl chlorides are coupled rapidly to biaryl compounds in very high yields under mild conditions by a catalytic nickel reagent (generated in situ) and excess reducing metal. The reaction uses air-stable reagents and is run conveniently in ordinary laboratory equipment under an inert atmosphere. Many aryl chlorides are coupled to greater than 90% yield under appropriate conditions. Bromide and iodide ions and 2,2′-bipyridine accelerate the reaction.

A variety of functional groups, other than nitro or protic groups, are tolerated. Electron-withdrawing substituents generally give higher yields of diarene. With electron-releasing groups, side reactions may occur, but these are minimized by the addition of 2,2′-bipyridine.

Mechanistic studies suggest that a reduction process involving nickel and zinc metal is rate limiting in the presence of excess aryl chloride. Cross-coupling experiments have implicated arylnickel species which react preferentially with aryl chloride to yield diarylnickel intermediates which, in turn, rapidly undergo reductive elimination. We propose a mechanism which involves an arylnickel(I) intermediate and which also accounts for the necessity for reducing metal when coupling aryl chlorides. The basicity and reduction potential of the reducing metal has a profound influence on the efficiency of biaryl formation. In polar solvents such as dimethylacetamide only three metals (Zn, Mg, and Mn) produce biaryls in high yield.

Although a full mechanistic understanding of this complex reaction awaits further study, we believe the mechanism proposed in Scheme I accommodates our experimental data better than any mechanism previously proposed. Further research may provide refinements of this mechanistic model, but we suspect that the crucial role of the metal in the reduction of an arylnickel species will remain a central feature for the coupling of aryl chlorides.

Our results demonstrate that aryl–aryl carbon bonds can be formed from aryl chlorides quickly and efficiently. We believe that, within the limitations discussed, this coupling method is superior to any biaryl synthesis now known.

Experimental Section

General Procedure. All reagents were purchased from commercial sources (Aldrich or Alfa), were anhydrous, and were used without further purifications except as noted.

The catalyst is prepared by reacting a nickel salt, such as anhydrous $NiCl_2$, with three or more equivalents of triphenylphosphine (TPP), and zinc in a dry, aprotic solvent under nitrogen at 40–50 °C. For maximum reaction rates, 1–3 equiv of NaBr may also be added to the catalyst mixture. The reaction mixture color changes from green to aqua and finally to the characteristic blood-red color of $Ni(PPh_3)_3$.[11] A nitrogen-purged solution of the aryl chloride is added, which causes the reaction mixture to turn green. The mixture is heated to 50–80 °C. When the reaction is complete the characteristic red-brown color returns—a built-in indicator. For larger-scale runs the aryl chloride is added gradually, because the coupling reaction is exothermic, especially with heteroaromatic halides. The Ni(0) catalyst need not be preformed; the reaction works if the aryl halide is included with the nickel salt–triphenylphosphine–zinc mixture before the solvent is added. The reaction is conveniently run with a few mole percent nickel and at least 50% stoichiometric excess of the reducing metal, such as zinc. Powdered (−325 mesh) zinc is purified by stirring it with acetic acid, filtering, washing thoroughly with ethyl ether, and drying under vacuum. The best solvents are dipolar aprotic solvents such as DMF (*N,N*-dimethylformamide) or DMAc (*N,N*-dimethylacetamide). These solvents are conveniently dried by multiple treatment with molecular sieves. The reaction rate drops sharply as the solvent polarity decreases. In some cases other ligands or salts were added to the reaction, as discussed herein.

General Procedure for Small-Scale Reactions. A 50-mL, round-bottomed, two-necked flask was charged with 0.13 g (1 mmol) of $NiCl_2$, 2.0 g (7.6 mmol) of triphenylphosphine, and 2.0 g (30.6 mmol) of zinc dust. A rubber serum cap was placed over one neck of the flask and a stopcock adapter in the other. The flask was evacuated and filled with nitrogen several times (vacuum line). Dry DMAc or DMF (15 mL) was added via syringe through the serum cap. The reaction flask was then placed in an oil bath at 50–80 °C and stirred magnetically. After the red-brown catalyst had formed, a nitrogen-purged solution of aryl chloride (usually 20 mmol) in the dry aprotic solvent (or neat liquid) was added via syringe to the reaction mixture. The reaction was conducted at 50–80 °C until GC analysis indicated completion.

GC Analysis. Reaction products were identified by comparison of their retention times to authentic commercial samples. Analyses were conducted on a HP 5830 gas chromatograph using a flame ionization detector and a $^1/_8$ in. × 6 ft stainless steel OV-17 column. When materials were not commercially available, the products were identified by GC/MS.

Kinetic Data. Kinetic analysis of the coupling of chlorobenzene was made by removing 0.1-mL aliquots of the reaction mixture by syringe, quenching with acetone, and shaking in the presence of air to yield light green solutions. When the solvent peak interfered with the analysis, the sample was partitioned between aqueous acid and ether. The ether samples were then analyzed by GC as described above (programmed at 40 °C for 2 min and then increased to 300 °C at 20°/min) using toluene as an internal standard.

Observed rate constants (in the presence of bromide) were determined from the slope of the initial linear portion of the plots of percent conversion of chlorobenzene vs. time. For the activation parameter data, the reactions were run with 0.13 g (1 mmol) of $NiCl_2$, 2.0 g (7.6 mmol) of TPP, 4.0 g (61.2 mmol) of Zn, 2.0 g (19.4 mmol) of NaBr, and 4.4 g (4 mL, 39.3 mmol) of chlorobenzene in 20 mL of DMAc. The oil bath temperature was controlled by a Thermowatch to within ±1 °C and data was collected at 60, 70, 75, 80, and 85 °C. The Arrhenius plot of log k vs. $1/T$ gave a straight line (correlation coefficient 0.983).

Procedure for Figure 2. One flask was charged with 0.13 g (1 mmol) of $NiCl_2$, 3.0 g (45.8 mmol) of Zn, 1.0 g (3.8 mmol) of TPP, and 0.15 g (1 mmol) of 2,2′-bipyridine and another with 0.13 g of $NiCl_2$, 3.0 g of Zn, and 1.5 g (5.7 mmol) of TPP. Each flask was purged and 15 mL of dry DMAc was added. After the catalyst had formed, 2.2 g (2 mL, 19.7 mmol) of dry chlorobenzene was added and both reactions were heated at 70 °C.

Procedure for Figure 3. One flask was charged with 0.13 g (1 mmol) of $NiCl_2$, 0.50 g (7.66 mmol) of Zn, 0.50 g (4.86 mmole of NaBr, and 1.0 g (3.81 mmol) of TPP and another with 0.13 g of $NiCl_2$, 2.0 g (30.6 mmol) of Zn, 0.50 g of NaBr, and 1.0 g of TPP. Each flask was purged and 15 mL of dry DMAc was added. After the catalyst had formed, 2.0 mL of a 1:1 mixture of chlorobenzene and toluene (9.8 mmol of chlorobenzene) was added to each flask and both were heated to 70 °C.

Procedure for Figure 4. Two flasks were charged with 0.13 g (1 mmol) of $NiCl_2$, 2.0 g (7.6 mmol) of TPP, and 2.0 g (30.6 mmol) of Zn. In addition, 1.0 g (9.7 mmol) of NaBr was placed in the first flask. The flasks were purged and 10 mL of DMAc was added. After the mixtures turned red-brown, 2.2 g (2 mL, 19.7 mmol) of chlorobenzene was added to the first flask and 3.1 g (2.1 mL, 19.9 mmol) of bromobenzene was added to the second flask. The two mixtures were reacted at 70 °C.

A similar comparison was made between chlorobenzene and iodobenzene. Chlorobenzene (2 mL, 19.7 mmol) was reacted with $NiCl_2$, TPP, Zn, and NaI (1.5 g, 10 mmol) in 20 mL of DMAc at 70 °C, conversion of chlorobenzene was 84% after 5 min and complete within 10 min. Iodobenzene (2.2 mL, 19.7 mmol) was reacted under similar conditions without added NaI; conversion of iodobenzene was 5, 38, 82, and 93% after 10, 20, 30, and 35 min, respectively, and complete after 40 min. We have also noted that although the yields of biphenyl were very high, e.g., >90%, somewhat more benzene (2–5%) was produced from iodobenzene than from chlorobenzene.

Procedure for Table II. Mg. A flask was charged with 0.13 g (1 mmol) of NiCl, 1.0 g (6.7 mmol) of NaI, 2.0 g (7.63 mmol) of TPP, and 2.0 g (82.3 mmol) of magnesium (20 mesh). The flask was purged with nitrogen and 10 mL of DMAc was added. The solution initially turned red-brown, but it eventually became deep green. Chlorobenzene (2.2 g, 2 mL, 19.7 mmol) was added and the reaction was heated to 70 °C.

Al [0.13 g of $NiCl_2$, 2.0 g of TPP, 2.0 g (74 mmol) of Al powder (−325 mesh), and 10 mL of dry DMAc]. After the red-brown catalyst had formed, 2.2 g of chlorobenzene was added and the reaction heated at 65 °C.

Fe [0.13 g of $NiCl_2$, 2.0 g of TPP, 1.5 g (10 mmol) of NaI, 2.0 g (35.8 mmol) of iron powder (−200 mesh), and 10 mL of DMAc]. The reaction mixture turned deep red almost immediately after the solvent was added. Chlorobenzene (2.2 g) was added and the mixture heated at 60 °C. GC analysis revealed no reaction after 2–18 h at 80 °C.

Mn [0.13 g of $NiCl_2$, 4.0 g (15.2 mmol) of TPP, 1.0 g of NaI, 2.0 g (36.4 mmol) of manganese powder (−325 mesh), and 20 mL of DMAc]. The purged reaction flask was placed in an 80 °C oil bath. After the reaction mixture became pink, 2.2 g of chlorobenzene was added. After a short period a mustard-colored precipitate formed. While this precipitate was present little reaction occurred. Only after the precipitate disappeared did coupling begin.

Ca [0.13 g of $NiCl_2$, 2.0 g of TPP, 2.0 g (49.9 mmol) of calcium turnings, and 10 mL of DMAc]. Chlorobenzene (2.2 g) was added and reacted at 65 °C. When the oxide layer was scraped off of the calcium and 0.10 g (0.6 mmol) of bipyridine was also added, the yield of biphenyl was increased to 65%.

Na [0.13 g of $NiCl_2$, 2.0 g of TPP, 1.0 g of NaBr, 0.5 g (21.7 mmol) of Na, and 10 mL of DMAc]. The initially green reaction mixture slowly turned red-brown and after $^1/_2$ h 2.2 g of chlorobenzene was added. The reaction was conducted at 80 °C; the reaction mixture remained red-brown throughout the reaction (24 h).

Cross-Coupling Experiments. For each reaction 0.13 g (1 mmol) of $NiCl_2$, 0.16 g (1 mmol) of 2,2′-bipyridine, 1.0 g (3.8 mmol) of TPP, 2.0 g (30.6 mmol) of Zn, and 15 mL of dry DMAc were used. After the catalyst was formed, 2.0 mL of a 1:1 (on a molar basis) mixture of *p*-chloroanisole (8.1 mmol) and *p*-xylene was added and reacted at 70 °C. After 1 h, GC analysis (*p*-xylene internal standard) showed all *p*-chloroanisole consumed and the appropriate mass balance. *p*-Chlorotoluene (8.4 mmol, 1 mL) was added to the reaction mixture and the mixture reanalyzed after 1 h.

Additional experiments were conducted in which the addition of *p*-chlorotoluene was added after 2 h and in which the coupling of *p*-chloroanisole was followed by several GC analyses over 3 h.

Qualitative Analysis of the Reduction of Nickel Halide Salts and of $NiCl_2$ in the Presence of Halide. Four flasks were charged with 1.0 g (3.8 mmol) of TPP and 0.10 g (1.5 mmol) of Zn. The first flask also received 0.10 g (1 mmol) of NiF_2, the second 0.13 g (1 mmol) of $NiCl_2$, the third 0.22 g (1 mmol) of $NiBr_2$, and the fourth 0.32 g (1 mmol) of NiI_2. The flasks were purged with Ar and placed in a 60 °C oil bath. Ten milliliters of DMAc was added. The times required to form the red-brown zero-valent nickel catalyst were, respectively: never, 5 min, 2 min, and 40 s. To assess the effect of halide salts, four reactions were run with 0.13 g (1 mmol) of $NiCl_2$, 0.5 g (7.6 mmol) of Zn, and 1.0 g of TPP in 10 mL of DMAc. The first flask received no additive, the second received 0.6 g (10.3 mmol) of NaCl, the third 1.0 g (9.7 mmol) of NaBr, and the fourth 1.5 g (10 mmol) of NaI. The times required to generate the red-brown color at 65 °C were, respectively: 14 min, 8 min, 1.5 min, and 35 s.

Attempts To Couple Chlorobenzene Using Bidentate Phosphorus Ligands and Trialkylphosphines. In three flasks were placed 0.13 g (1 mmol) of $NiCl_2$ and 2.0 g (30.6 mmol) of zinc. One flask received 2.0 g of 1,2-bis(diphenylphosphino)ethane, another 2.0 g of 1,3-bis(diphenylphosphino)propane, and the third 2.0 g of 1,4-bis(diphenylphosphino)butane. Ten milliliters of DMAc was added to each nitrogen-purged flask. Even after 1 h at 70 °C all the solutions were green. Chlorobenzene (2.2 g, 2 mL, 19.7 mmol) was added to each and the flasks were heated at 70 °C for 2 h. There was no detectable reaction, even when the reactions were repeated with less phosphine and added halide salts.

Two flasks were charged with 0.13 g (1 mmol) of $NiCl_2$, 1.0 g (6.7 mmol) of NaI, and 2.0 g (30.6 mmol) of Zn. Triethylphosphine (0.8 g, 6.8 mmol) was added via syringe to one flask and triisopropylphosphine (1 mL, 5 mmol) was added to the other. DMAc (15 mL) and 2.2 g of chlorobenzene were added and the reactions were heated at 70 °C. GC analysis revealed that the reactions had stopped after 16 h. The conversions of chlorobenzene to biphenyl were 77% and 30%, respectively.

Coupling of Chlorobenzene with $Ni(PPh_3)_4$. In a nitrogen drybox 10 g (9 mmol) of tetrakis(triphenylphosphine)nickel (Strem Chemicals) was added to a 50-mL flask. The flask was sealed with a serum cap and removed from the drybox. Thirty milliliters of dry, purged DMAc was added via syringe to the flask, and the mixture was stirred magnetically at 70 °C for 10 min, and then 0.9 mL (8.8 mmol) of chlorobenzene was added via syringe. Only half of the theoretical amount of chlorobenzene (based on Ni) was used, but GC analyses showed that 37% was still unreacted even after 24 h.

Coupling of Chlorobenzene in the Absence of Excess Zinc. A catalyst solution was prepared from 0.13 g (1 mmol) of $NiCl_2$, 0.5 g (7.6 mmol) of Zn, 1.0 g (3.8 mmol) of TPP, and 10 mL of dry DMAc. The solution was filtered under nitrogen through a medium fritted glass disk into a second flask (also under nitrogen). Ten milliliters of fresh DMAc was used to rinse the first flask and filter. The filtered wash was combined with the filtrate in the second flask. A 1:1 (v/v) degassed solution (1.2 mL) of chlorobenzene (6 mmol) and toluene was added to the filtered catalyst solution. This mixture was reacted at 70 °C and samples were removed periodically for GC analysis. Less than 40% of the expected (stoichiometric) amount of chlorobenzene reacted. When this reaction mixture was transferred to another nitrogen-purged flask containing excess zinc, rapid quantitative conversion to biphenyl was observed.

Large-Scale Experiments. 4,4′-Biphenyl Dialdehyde. A 2-L, four-necked, dried round-bottomed flask equipped with a 500-mL addition funnel, mechanical stirrer, thermometer, and stopcock adapter was charged with 131 g (2.00 m) of Zn, 15.0 g (0.146 m) of NaBr, 131 g (0.50 mol) of TPP, and 6.5 g (0.050 mol) of $NiCl_2$. The reaction flask was evacuated and filled with nitrogen several times. Nitrogen was then swept through the system by opening the stopcock to the addition funnel for 15 min. Nitrogen-purged, dry DMF (600 mL) was added through the addition funnel and the mixture was heated by an electric mantle. The solution quickly became red-brown. A solution of 145 g (1.0 m) of *p*-chlorobenzaldehyde (97% pure, Aldrich) in 100 mL of dry DMF was placed in the addition funnel. When the catalyst mixture reached 60 °C the heating mantle was removed and slow addition of the *p*-chlorobenzaldehyde solution was begun. Although the exotherm was gradual at first (50% reactant added in 20 min), the second half of the reactant was added over a 40-min period and still the reaction temperature exceeded 90 °C. The heating mantle was not replaced until the reaction temperature cooled to 70 °C after the addition of *p*-chlorobenzaldehyde was complete. The reaction was then maintained at 70 °C for 3 h. The solution was blood-red again, indicating complete reaction.

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The reaction mixture was filtered to remove excess Zn and the filtrate diluted with 2000 mL of CHCl$_3$. This solution was extracted 4 times with 500 mL of distilled water and once with 200 mL of saturated NaCl solution. The organic phase was dried over Na$_2$SO$_4$ for 1 h, filtered to remove excess Zn, and flash evaporated. The residual solid was extracted with 1 L of 1:1 heptane–toluene. This mixture was filtered and the solid was dried to give 65 g (isolated yield 62%) of pure (>99%) dialdehyde.[69]

4,4′-Biphenol. A 500-mL, three-necked flask equipped with a 250-mL addition funnel, mechanical stirrer, and stopcock adapter was charged with 49 g (0.75 mol) of Zn, 35 g (0.13 mol) of TPP, 3.9 g (0.025 mol) of 2,2′-bipyridine, and 3.25 g (0.025 mol) of NiCl$_2$. After the flask was evacuated and filled with nitrogen several times, 250 mL of dry nitrogen-purged DMAc was added and the flask was placed in a 65 °C oil bath. After the dark-brown catalyst had formed, 85.3 g (0.50 mol) of neat *p*-chlorophenylacetate was slowly added via the addition funnel. The reaction was heated at 70 °C for 4 h and then filtered. A solution of NaOH (100 g/L water) was added to the filtrate and the mixture was stirred overnight at room temperature. Diethyl ether (500 mL) was added, the mixture was vigorously mixed for $^1/_2$ h and filtered, and the filtrate was separated in a separatory funnel. The aqueous layer was acidified with concentrated HCl to pH ~1. The resulting precipitate was collected by filtration, washed with hot water, and dried to yield 35 g (75% isolated yield) of 4,4′-biphenol.

Acknowledgment. We are indebted to B. V. Watkins and F. N. Ferrara for their excellent technical assistance and to Dr. M. J. Youssefi for providing mass spectral data. We also thank Drs. G. T. Kwiatkowski, L. M. Maresca, J. W. Lynn, R. K. Barnes, and J. E. McKeon for their encouragement and support and Professors R. G. Bergman (University of California, Berkeley) and M. F. Semmelhack (Princeton University) for helpful suggestions and stimulating discussions.

Registry No. Ni(PPh$_3$)$_3$, 25136-46-3; Zn, 7440-66-6; chlorobenzene, 108-90-7; *p*-chlorophenol, 106-48-9; *p*-chlorophenyl acetate, 876-27-7; *p*-chloroaniline, 106-47-8; *p*-chloroanisole, 623-12-1; *p*-chlorotoluene, 106-43-4; *p*-chlorobenzaldehyde, 104-88-1; *p*-chloroacetophenone, 99-91-2; *p*-chlorobenzonitrile, 623-03-0; 2-chlorothiophene, 96-43-5; 2-chloropyridine, 109-09-1; biphenyl, 92-52-4; 4,4′-biphenol, 92-88-6; phenol, 108-95-2; 4,4′-diacetoxybiphenyl, 32604-29-8; phenyl acetate, 122-79-2; 4-acetoxybiphenyl, 148-86-7; 4,4′-diaminobiphenyl, 92-87-5; 4-aminobiphenyl, 92-67-1; 4,4′-dimethoxybiphenyl, 2132-80-1; anisole, 100-66-3; 4-methoxybiphenyl, 613-37-6; iodobenzene, 591-50-4; 4,4′-dimethylbiphenyl, 613-33-2; 4,4′-diformylbiphenyl, 66-98-8; 4,4″diacetylbiphenyl, 787-69-9; 4,4′-dicyanobiphenyl, 1591-30-6; 2,2′-bithienyl, 492-97-7; 2,2′-bipyridine, 366-18-7.

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[69] Isolated yields are generally lower than those indicated by GC analysis because of the difficulty of separating excess triphenylphosphine from the reaction. We have found subsequently a convenient laboratory procedure which avoids this problem. After the excess zinc and solvent are removed, the crude reaction product is stirred in xylene with excess methyl iodide to form the insoluble Wittig salt which is removed by filtration. Pure product can be isolated after the solvent and methyl iodide are evaporated.

An Approach to Pseudomonic Acids from Acetylenic Precursors: Synthesis of 2-(Hydroxymethyl)-3-butyn-1-ol

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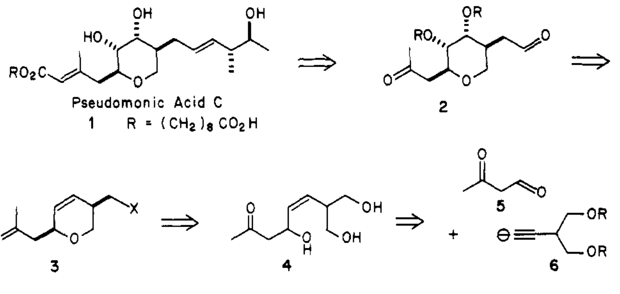
Received October 22, 1985

The acetonide of 2-(hydroxymethyl)-3-butyn-1-ol (**17**) was prepared from bis(hydroxymethyl)malonate (**11**) or from 1,3-dihydroxypropanone (**22**). Alternative routes to **17** involving the intermediacy of highly unstable alkynal **21** or the corresponding acetate were unsuccessful. Condensation of the anion of **17** with aldehyde **30** followed by semihydrogenation and deprotection afforded keto triol **33**, which cyclized stereoselectively to dihydropyran **34**. Osmylation and functional group manipulation afforded **40** and **42**, precursors to pseudomonic acid C (**1**).

The pseudomonic acids, a group of structurally related antibiotics produced by *Pseudomonas fluorescens*, possess potent antibiotic activity.[1] The pseudomonic acids display no cross resistance with other antibiotics due to their novel mechanism of action, interference with bacterial protein synthesis by inhibition of isoleucyl-tRNA synthetase. Recently considerable effort has been directed toward total synthesis of the pseudomonic acids.[2]

Scheme I



Our retrosynthetic analysis of pseudomonic acid C (**1**) is depicted in Scheme I. We envisaged that the unsaturated side chains could be elaborated from a protected derivative of keto aldehyde **2** and that the cis vicinal diol could be introduced by stereoselective osmylation of the double bond in 5,6-dihydro-2*H*-pyran **3**. Previous syntheses of pseudomonic acids have also employed derivatives of **3**.[2] Retrosynthetically, the aldehyde side chain in **2** can be degraded by one carbon in order to introduce a simplifying element of symmetry into **3**. We anticipated that dihydropyran **3** might be formed with a high degree

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