paratus. The conversion of α-keto acids was determined by UV and also checked by GLC after methylation with diazomethane.

Photodecarboxylation of 1a in D_2O–MeCN. A mixture of **1a** (0.15 g, 1 mmol), D_2O (2 mL), and MeCN (8 mL) in a Pyrex tube was irradiated for 2 h with a 300-W medium-pressure Hg lamp. After dilution with water, the benzaldehyde produced was extracted twice with 10 mL of CH_2Cl_2, washed two times with water, and dried over Na_2SO_4; GLC analysis showed the formation of benzaldehyde in 95% yield. The NMR spectra showed that the purity of the resulting PhCDO was 99%, which was also ascertained by GC–MS spectra.

Reaction of Aryl and Vinyl Halides with Zerovalent Nickel–Preparative Aspects and the Synthesis of Alnusone

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Abstract: Zerovalent nickel complexes such as bis(1,5-cyclooctadiene)nickel and tetrakis(triphenylphosphine)nickel react rapidly with aryl and vinyl halides to produce the symmetrical coupling products, a low-temperature analogue of the Ullman reaction. The reaction proceeds through oxidative addition of the organic halide to Ni(0), and the reactivity of the Ni(II) intermediates has been examined. Arylnickel halide complexes decompose rapidly to biaryls in DMF. The coupling of simple vinyl halides proceeds with isomerization of the double bond but 3-haloacrylates give efficient coupling with retention of geometry. Cyclizations to form ortho-bridged biaryls are efficient in simple cases (6-, 7-, 8-, 9-, 10-, and 14-membered rings) but fail with an ortho-disubstituted case. The 13-membered meta-bridged cyclic biphenyl, alnusone, is prepared efficiently with the crucial aryl halide coupling to form the ring proceeding in 50% yield. A side reaction promoted by the presence of protons and with certain ortho-substituted aryl halides is reduction of the aryl halide to the arene. This process can be enhanced by deliberate addition of acid during reaction with Ni(0) and a series of aryl halides underwent successful reduction.

Nickel is relatively unique among the transition metals in that a variety of complexes is easily prepared containing nickel in the zerovalent state.[1-3] Like most complexes of low-valent metals from group 8 of the periodic table, the NiL_n species generally

$$NiL_n + R\text{–}X \longrightarrow R\text{–}\underset{\displaystyle L}{\overset{\displaystyle L}{Ni}}\text{–}X$$

undergo oxidative addition of organic halides (R–X) under mild conditions.[4] This reaction represents direct formation of a σ-bonded organometal species, in a process reminiscent of the formation of a Grignard reagent. An important difference is the much lower polarization of the carbon–nickel bond and the potential compatibility of the reaction with common polar functional groups such as alcohols, carbonyl groups, etc.

Of particular interest is the ease with which aryl and vinyl halides enter into oxidative addition with Ni(0), Pd(0), and Pt(0).[5] These halides, which are quite unreactive in classical polar reactions, often add to the zerovalent metals as readily as methyl and primary alkyl halides. While the mechanism of oxidative addition continues to be an active area of study[6,7] and different metals react by different mechanisms,[4] it is likely that there is a strong electron-transfer component in the particularly fast reaction of Ni(0) with aryl halides.[7] We reported in preliminary form the coupling of aryl[8,9] and vinyl halides[10] promoted by zerovalent nickel and postulated initial formation of aryl- and vinylnickel(II) intermediates. We are prompted to present details of this work including previously unpublished aspects in light of the recent development of a convenient in situ preparation of zerovalent nickel[11,12] and a study of two important steps in the aryl–aryl coupling method.[7,13]

The principle of metal-promoted coupling of aryl halides continues to see development, most generally in the Ullman reaction where copper powder serves as the zerovalent metal.[14-17] No comparably general method exists for coupling of vinyl halides, although certain β-haloacrylates under Ullman-type coupling.[18]

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(1) For general discussions, see: (a) P. W. Jolly and G. Wilke, "The Organic Chemistry of Nickel", Vols. I and II, Academic Press, New York, 1974; (b) L. Malatesta and S. Cenini, "Zerovalent Compounds of Metals", Academic Press, New York, 1974.

(2) (a) B. Bogdanovic, M. Kroner, and G. Wilke, *Justus Liebigs Ann. Chem.* **669**, 1 (1966); (b) M. F. Semmelhack, *Org. React. (N.Y.)*, **19**, 178 (1972); (c) R. A. Schunn, *Inorg. Synth.*, **15**, 5 (1974); (d) F. Guerrieri and G. Salerno, *J. Organomet. Chem.*, **114**, 339 (1976).

(3) R. A. Schunn, *Inorg. Synth.* **13**, 124 (1973).

(4) For a summary of oxidative-addition with d^{10} metals, see: J. K. Stille and R. Love, *Acc. Chem. Res.*, **10**, 434 (1977).

(5) For a general discussion, see: (a) G. W. Parshall, *J. Am. Chem. Soc.*, **96**, 2360 (1974). For examples with Pd(0), see: (b) P. Fitton and J. E. McKeon, *J. Chem. Soc. D*, 4 (1968); (c) P. Fitton, M. P. Johnson, and J. E. McKeon, *Ibid.*, 6 (1968). The oxidative addition of aryl halides and alkenyl halides with Pd(0) complexes is the basis of a powerful method of vinyl substitution for hydrogen: R. Heck, *Acc. Chem. Res.*, **12**, 146 (1979). For examples with Pt(0), see: (d) S. Sergi, V. Marsala, P. Pietropaolo, and F. Faraone, *J. Organomet. Chem.*, **23**, 281 (1970); (e) J. Ibers, J. Rajaram, and R. Pearson, *J. Am. Chem. Soc.*, **96**, 2103 (1974). For early examples of well-characterized aryl–Ni and vinyl–Ni complexes from oxidative addition of Ni(0), see: (f) M. Nidsi, T. Kashiwagi, T. Ikenchi, and Y. Uchida, *J. Organomet. Chem.*, **30**, 279 (1971); (g) L. Cassar and A. Giarrusso, *Gazz. Chim. Ital.*, **103**, 793 (1973); (h) D. R. Fahey and J. E. Mahan, *J. Am. Chem. Soc.*, **99**, 2501 (1977). Oxidative addition of aryl and alkenyl halides to Pd(0) and Ni(0) complexes is the basis of catalyzed coupling of organomagnesium halides (and Li, Al, Hg, Zr, An, and B analogues) with aryl and alkenyl units. For recent examples and leading references, see: (i) T. Hayashi, M. Konishi, and M. Kumada, *J. Organomet. Chem.*, **186**, C1 (1980). For a discussion of the mechanism, see: (j) D. G. Morrell and J. K. Kochi, *J. Am. Chem. Soc.*, **97**, 7262 (1975).

(6) For general discussions, see: J. K. Kochi, "Organometallic Mechanisms and Catalysis", Academic Press, New York, 1979.

(7) For a specific study of oxidative addition of aryl halides with Ni(0), see: T. T. Tsou and J. K. Kochi, *J. Am. Chem. Soc.*, **101**, 6319 (1979).

(8) M. F. Semmelhack, P. M. Helquist, and L. D. Jones, *J. Am. Chem. Soc.*, **93**, 5909 (1971).

(9) M. F. Semmelhack and L. S. Ryono, *J. Am. Chem. Soc.*, **97**, 3873 (1975).

(10) M. F. Semmelhack, P. M. Helquist, and J. D. Gorzynski, *J. Am. Chem. Soc.*, **94**, 9234 (1972).

(11) A. S. Kende, L. S. Liebeskind, and D. M. Braitsch, *Tetrahedron Lett.*, 3375 (1975).

(12) M. Zembayashi, K. Tamao, J.-i. Yoshida, and M. Kumada, *Tetrahedron Lett.*, 4089 (1975).

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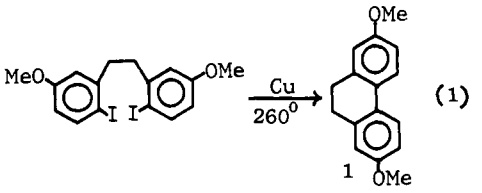
Isolated examples of Pd(0) and Pt(0) derivatives entering into oxidative addition with aryl halides and giving subsequent aryl–aryl coupling have been reported[19] but have not been developed into general synthesis methods. Many other examples of transition-metal-promoted coupling of aryl units are known[20] where the aryl group is first activated as the arylmagnesium halide. However, the need to begin with the highly reactive aryl species severely limits the usefulness of such coupling procedures.

Intramolecular examples of Ullman-type coupling are few.[15c,21] A successful case (67% yield of **1**), which also exemplifies the high reaction temperature of the classical Ullman method, is presented in eq 1.[21a] Closely related examples proceed in much lower



(1)

yield.[21b,c] At the same time, there is a growing class of natural products which are related in containing a biphenyl unit as part of a ring, including the alkaloids related to protostephanine,[22] the stegnane ligands,[23] and the meta-bridged alnusanes (e.g., **2**, **3**).[24]

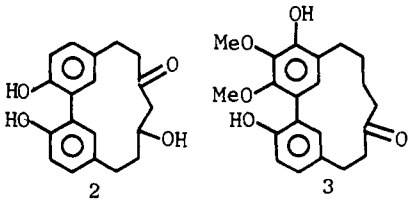
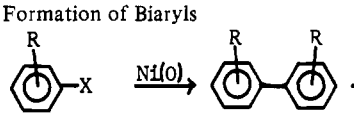
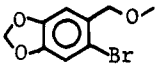
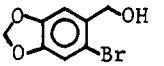


Table I. Formation of Biaryls



no.	aryl halide	temp, °C/ time,[a] h	% yield of biaryl
1	PhBr	55/26	82[b]
2	PhI	40/21	71[c]
3	PhCl	50/29	14[c] (55)[d]
4	4-iodotoluene	40/20	63[e]
5	2-bromotoluene	34/131	41[e] (26)[d]
6	4-bromoacetophenone	45/36	93[e]
7	4-bromochalcone	50/9, 51/22 65/3	62[e]
8	4-bromobenzaldehyde	35/20	79[e]
9	ethyl 4-bromobenzoate	40/19	81[e]
10	methyl 2-bromobenzoate	41/11, 54/8	81[e] (17)[d]
11	4-bromoanisole	40/23	83[e]
12	4-bromobenzonitrile	36/11	81[e]
13	4-bromoacetonitrile	33/26	79[e]
14	4-bromoaniline	34–45/94	54[b] (30)[e]
15	2-bromothiophene	42/22	30[e]
		40/24 53–60/10	67[e]
17		34/24	0 (51)[d] (31)[f]
18	2-bromo-*m*-xylene	54/95	0 (high)[d]
19	4-bromobenzoic acid	40/17, 60/5	0[g]
20	4-bromophenol	40/27	0 (80)[d]
21	4-bromoacetanilide	50/11, 60/10	0 (47)[f]
22	sodium 4-bromobenzoate	45/7, 65/3.5	0 (95)[d]
23	sodium 4-bromophenoxide	37/10, 60/12	3[e] (60)[d]
24	2-bromonitrobenzene	36/24	0 (58)[d]
25	4-bromonitrotoluene	40/17	0 (60)[d]

[a] For the experimental procedure, see Experimental Section. [b] Determined by ^{1}H NMR. [c] Determined by quantitative GLPC. [d] Percent recovery of unreacted aryl halide. [e] Yield based on isolated, recrystallized biaryl. [f] Yield for reduction product, substitution of hydrogen for halide in the starting aryl halide. [g] A mixture of benzoic acid and 4-bromobenzoic acid was obtained but not completely separated.

A recent synthesis of myricanone (**3**) employed zerovalent nickel for the crucial phenyl–phenyl coupling.[25] Recently, one of us reported independently the use of zerovalent nickel to form the biphenyl unit in a model for protostephanine.[22a]

In this article we report the nickel-prompted coupling of aryl halides to form biaryls, the coupling of vinyl halides to form 1,3-dienes, and intramolecular examples of each of these including the first synthesis of alnusone.[9] In addition, observations relevant to the mechanism of the reaction are discussed, especially the side reaction which leads to hydrogenolysis of the aryl halide. In general, bis(1,5-cyclooctadiene)nickel [Ni(COD)$_2$] is chosen as the source of zerovalent nickel although tetrakis(triphenylphosphine)nickel is used to advantage in intramolecular coupling.

Results and Discussion

A. Intermolecular Coupling of Aryl Halides. The reaction of Ni(COD)$_2$ with aryl halides is a general method for preparation of biaryls. The conditions are mild and are compatible with most common functional groups. An aryl halide is added to a suspension of 0.5 mol equiv of Ni(COD)$_2$ in dimethylformamide (DMF) under nitrogen or argon and the mixture is stirred at 40–50 °C for 12–20 h. The resulting green mixture is partitioned between water and ether, and the biaryl is isolated by standard techniques. Additional simplification is now available by using in situ gen-

(13) T. T. Tsou and J. K. Kochi, *J. Am. Chem. Soc.*, **101**, 7547 (1979).
(14) F. Ullmann and J. Bielecki, *Chem. Ber.*, **34**, 2174 (1901).
(15) Recent Reviews: (a) J. F. Normant, *Synthesis*, 63 (1972); (b) M. Goshaev, O. S. Ostroshchenko, and A. S. Sadykok, *Russ. Chem. Rev. (Engl. Transl.)*, 1046 (1972); (c) P. E. Fanta, *Synthesis*, 9 (1974); (d) A. E. Jukes *Adv. Organomet. Chem.*, **12**, 215 (1974).
(16) (a) T. Cohen and I. Cristea, *J. Am. Chem. Soc.*, **98**, 748 (1976); (b) J. Cornforth, A. F. Sierkowski, and T. W. Wallace, *J. Chem. Soc., Chem. Commun.*, 294 (1979); (c) R. D. Ricke and L. D. Rhyne, *J. Org. Chem.*, **44**, 3445 (1979).
(17) For examples and leading references, see: F. E. Ziegler, I. Chliver, K. W. Fowler, S. J. Kanfer, S. J. Kuo, and N. D. Senha, *J. Am. Chem. Soc.*, **102**, 790 (1980).
(18) T. Cohen, I. Cristea, *J. Org. Chem.*, **40**, 3649 (1975).
(19) (a) R. R. S. Clark, R. O. C. Norman, and C. B. Thomas, *J. Chem. Soc., Perkin Trans. 7*, 121 (1975); (b) P. S. Braterman, R. J. Cross, and G. B. Young, *J. Chem. Soc., Dalton Trans.* 1306 (1976).
(20) (a) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-metallic Substances", Constable and Co., Ltd., London, 1954, Chapter 5. (b) A. McKillop, L. F. Elson and E. C. Taylor, *J. Am. Chem. Soc.*, **90**, 2423 (1968); (c) R. Pallaud and J. L. Zenou, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **266**, 35 (1968); (d) G. Adda and R. Pallaud, *Ibid.*, **266**, 35 (1968); *Chem. Abstr.*, **69**, 18720 (1968); (e) J. P. Morizur, *Bull. Soc. Chim. Fr.*, 1331 (1964); (f) W. B. Smith, *J. Org. Chem.*, **26**, 4206 (1961); (g) J. P. Morzur and R. Pallaud, *C. R. Hebd. Seances Acad. Sci.*, **252**, 3076 (1961); (h) R. Pallaud and J. M. Pleau, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **267**, 507 (1968); *Chem. Abstr.*, **70**, 37860 (1969); (i) B. Sarry and W. Hanke, *Z. Anorg. Allg. Chem.*, **296**, 229 (1958).
(21) M. Rieger and F. H. Westheimer, *J. Am. Chem. Soc.*, **72**, 28 (1950); (b) P. E. Fanta, *Chem. Rev.*, **38**, 139 (1946); (c) P. E. Fanta, *Ibid.*, **64**, 613 (1964).
(22) (a) Cf. M. Shamma, "The Isoquinoline Alkaloids", Academic Press, New York, 1972, pp 418 ff. (b) P. M. Helquist, A. Marfat, and S. Brandt, *Tetrahedron Lett.*, 2193 (1979).
(23) (a) S. M. Kupchan et al., *J. Am. Chem. Soc.*, **95**, 1335 (1973)f (nb) A. S. Kende and L. S. Liebeskind, *Ibid.*, **98**, 267 (1976); (c) L. R. Hughes and R. A. Raphael, *Tetrahedron Lett.*, 1543 (1976).
(24) (a) M. Nomura and T. Tokoroyama, *J. Chem. Soc., Chem. Commun.*, 65 (1974); (b) M. J. Begley, R. V. M. Campbell, L. Chrombie, B. Tuck, and D. A. Whiting, *J. Chem. Soc. C*, 3634 (1971); (c) M. Yasue, *Mokuzai Gakukaishi*, **11**, 146, 152 (1965); (d) R. V. M. Campbell, L. Chrombie, and D. A. Whiting, *J. Chem. Soc. D*, 1206 (1970); (e) M. Nomura, T. Tokoroyama, and T. Kubota, *J. Chem. Soc., Chem. Commun.*, 316 (1975); (f) T. Anthonson, G. B. Lorentzen, and K. E. Malterud, *Acta Chem. Scand., Ser. B*, **B29**, 529 (1975); (g) K. E. Malterud, T. Anthonsen, and J. Hjortas, *Tetrahedron Lett.*, 2335 (1978).
(25) D. A. Whiting and A. F. Wood, *Tetrahedron Lett.*, 2335 (1978).

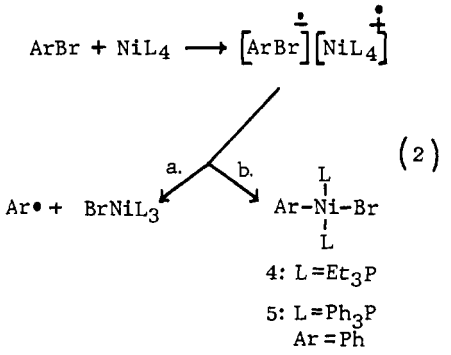
eration of the zerovalent nickel through reduction of Ni(II) salts by zinc,[11,12] but this technique was not employed in our exploratory work.

The entries of Table I indicate the high efficiency and functional group compatibility of the procedure. Notable is the efficient coupling of aryl halides bearing ketone, aldehyde, ester, and nitrile groups. In contrast to the classical Ullman procedure,[15] bromoaniline reacts smoothly to form benzidine (entry 14). The unsuccessful substrates are listed in entries 17–25. As exhibited by entries 5 and 18, steric hindrance due to ortho substituents severely impedes the oxidative addition step. With 2-bromotoluene and 2-bromo-*m*-xylene, a substantial amount of unreacted aryl halide is recovered after the usual reaction time. At higher temperatures, the nickel reagent rapidly decomposes to produce a nickel metal mirror without increasing the extent of conversion of the aryl halides. A special case is 6-bromopiperonyl methyl ether which is coupled in good yield, perhaps due to a favorable coordinating effect of the ortho substituent (entry 16).

Proton donors inhibit the reaction, also a feature of the Ullmann reaction.[15] When the usual reaction conditions are employed with an aryl halide bearing an alcohol, phenol, or carboxylic acid function, the primary process is replacement of the halide by hydrogen (entries 19–21). These results suggest a mild technique for reducing aryl halides, and some development of this reaction is presented below. Conversion of the acidic groups to sodium salts appears to strongly retard the interaction with nickel(0), and the halide is recovered efficiently (entries 22, 23). At the same time, powerful electron-withdrawing substituents also inhibit the coupling reaction (entries 24, 25). The reactivity of the aryl halide is approximately in the order I > Br > Cl, paralleling the reactivity pattern in rates of oxidative-addition.[4] Phenol *p*-toluenesulfonate esters are completely unreactive.

The effects of various solvents and added ligands are summarized in Table II by using iodobenzene as the test case. In toluene and tetrahydrofuran (THF), no coupling is observed and the $Ni(COD)_2$ decomposes to a nickel mirror more rapidly than in DMF. However, the addition of a few mole equivalent of DMF or triphenylphosphine is sufficient to promote efficient biaryl formation.

B. Mechanistic Considerations in Aryl–Aryl Coupling. Mechanistic alternatives for nickel-promoted coupling of aryl halides have been summarized by Kochi and Tsou.[13] Two likely steps in the process, oxidative addition of the aryl halide to give arylnickel halide (e.g., **4**) and reaction of **4** with aryl halides, have been studied carefully by the same authors.[7,13] These studies were carried out in hydrocarbon solvents and led to conclusions which are not completely consistent with the product studies we have carried out in DMF. Their studies suggest a strong electron-transfer component in the initial oxidative addition which leads to substantial hydrogenolysis via the aryl radical (a in eq 2). With



(2)

aryl iodides, the radical side reaction can become the major pathway (up to 83% with *p*-iodoanisole in THF).[7] The results in Table I demonstrate that with $Ni(COD)_2$ in DMF, conversion of aryl halide to arene via aryl radicals is generally insignificant, as most of the aryl halide is accounted for as biaryl (e.g., *p*-iodoanisole gives the coupling product in 83% yield).

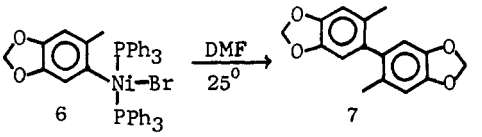
The study of reaction of **4** with aryl halides[13] concluded that transfer of an aryl unit to the triethylphosphine ligand (to give a phosphonium salt) is an important process and that the aryl-bis(triethylphosphine)nickel bromide complexes are stable in solution until aryl halide is added to initiate coupling. We find that in DMF with $Ni(PPh_3)_4$ or a mixture of $Ni(COD)_2$ with 2–4 mol equiv of *n*-butylphosphine, reaction of aryl halides proceeds efficiently to give biaryls, precluding significant formation of phosphonium salts (Tables I and II).

Table II. Effect of Added Ligands, Solvents on the Conversion of Iodobenzene to Biphenyl

no.	solvent	added ligand	ratio of ligand/ $Ni(COD)_2$	temp, °C/ time, h	yield of biphenyl[a]
1	DMF			40/21	71 (0)[b]
2	DMF	Ph_3P	4	37/21	48 (0)[b]
3	THF			36/22	2 (high)[b]
4	THF	DMF	4	36/20	68 (16)[b]
5	THF	Ph_3P	4	37/21	42 (0)[b]
6	toluene			37/22	0 (high)[b]
7	toluene	DMF	20	36/22	44 (1)[b]
8	toluene	Ph_3P	4	42/21	54 (0)[b]
9	HMPA[c]			40/21	0
10	pyridine			45/21	1 (36)[b]

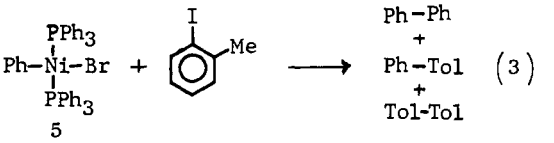
[a] A mixture of $Ni(COD)_2$ and iodobenzene in a mole ratio of 2.5:1 was allowed to react in the solvent/ligand combination specified. The yield of biphenyl was determined by quantitative GLPC. [b] Unreacted aryl halide detected by GLPC. [c] HMPA is hexamethylphosphoric triamide. Bromobenzene was used in place of iodobenzene.

We have also considered the reactivity of arylnickel halide complexes, with the goal of developing a process for selective cross-coupling of two different aryl halides. Using the triphenylphosphine ligand and DMF as solvent, our conclusions again differ from Kochi and Tsou.[13] We find that bis(triphenylphosphine)phenylnickel bromide (**5**)[5f] begins to decompose even at 25 °C in DMF, and biphenyl is obtained in 99% yield after 12 h at 50 °C. Similar results were reported for decomposition of **5** in toluene at 80 °C.[26] Reaction of **5** with iodobenzene in DMF proceeds only a little faster than the self-reaction of **5**, and after 12 h at 50 °C, biphenyl is obtained in 69% yield. Similarly, the complex (**6**) from 5-iodo-4-methyl-1,2-methylenedioxybenzene decomposes at 25 °C in DMF to give the biaryl (**7**) in 70% yield.



6 7

Attempted cross-coupling leads to extensive scrambling of the aryl units (symmetrical coupling), also observed by Kochi and Tsou.[13] For example, complex **5** and *o*-iodotoluene give essentially an equimolar mixture of the three possible biaryls (eq 3). In a series



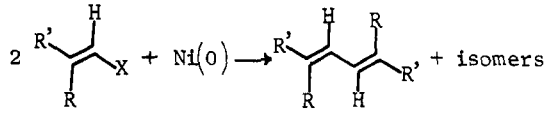
5 (3)

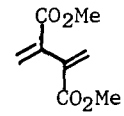
of similar experiments involving various aryl halides, solvents, and arylnickel complexes, we have not been able to achieve better than 50% selectivity for the cross-coupling product. All attempts to produce unsymmetrical biaryls by mixing two different aryl halides with Ni(0) failed to give useful selectivity.

The evidence for Ni(I) and Ni(III) intermediates[13] in the reaction of aryl halides with Ni(0) is useful in guiding future analysis of this reaction. However, the system they chose to study differs in several significant ways compared to the optimum conditions for preparative formation of biaryls. It is not clear as yet whether

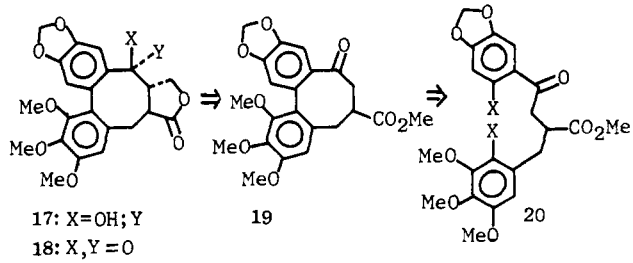
(26) S. Otsuka, A. Nakamura, T. Yoshida, N. Naruto, and K. Ataka, *J. Am. Chem. Soc.*, **95**, 3180 (1973).

Table III. Coupling of Alkenyl Halides with Ni(0)



alkenyl halide	solvent, ligand	time, h/temp, °C	products (% of total 1,3-diene)	yield of total diene (% conversion)
X = Br, R = Ph, R′ = H	DMF none	10/25, 2/35	trans,trans (100%)	70 (100)
X = Br, R = H, R′ = CH_3	DMF, none	14/25, 5/35	t,t[a] (0); c,t[b] (50); c,c[c] (50)	52 (100)
X = Br, R = H, R′ = CH_3	ether, Ph_3P	12/25	t,t (19); c,t (81); c,c (0)	66 (100)
X = Br, R = CH_3, R′ = H	ether, $(n\text{-}Bu)_3P$	5/25	t,t (94); c,t (6); c,c (0)	58 (90)
X = Br, R = CH_3, R′ = H	ether, Ph_3P	12/25	t,t (84); c,t (18); c,c (0)	70 (100)
X = Br, R = CH_3, R′ = H	DMF, none	22/25	t,t (72); c,t (28); c,c (0)	48 (100)
X = H, R = Br, R′ = CO_2Me	ether, none	4.5/25		12 (85)
X = H, R = Br, R′ = CO_2Me	ether, Ph_3P	4.5/25	same	89 (100)
X = H, R = Cl, R′ = CO_2Me	ether, Ph_3P	4.5/25	same	67 (75)
X = H, R = Cl, R′ = CO_2Me	ether, Ph_3P	9.0/25	same	69 (100)
X = Br, R = H, R′ = CO_2Me	ether, Ph_3P	15/25	c,c (100)	99 (100)
X = Br, R = CO_2Me, R′ = H	ether, $(n\text{-}Bu)_3P$	5.0/25	t,t (100)	91 (100)
X = Br, R = CO_2CH_2Ph, R′ = H	DMF, none	18/25	t,t (100)	90 (100)

[a] t,t = trans,trans. [b] c,t = cis,trans. [c] c,c = cis,cis.



17: X=OH; Y
18: X,Y=O

19

20

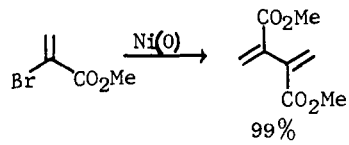
Figure 1. Strategy for steganone.

the mechanistic information obtained with PEt_3 complexes in toluene is relevant in all respects to the reaction with 1,5-cyclooctadiene and PPh_3 complexes in DMF.

C. Coupling of Alkenyl Halides. Alkenyl bromides and iodides react with $Ni(COD)_2$ under mild conditions to produce symmetrical 1,3-dienes. The reaction is performed by adding the alkenyl halide to a suspension of $Ni(COD)_2$ in DMF at −78 °C under argon. After 5–20 h at 25–35 °C, the reaction mixture is partitioned between ether and water, and the diene is separated from the 1,5-cyclooctadiene. For the reaction to proceed efficiently, donor ligands appear to be required. DMF can play this role, but in other solvents such as acetonitrile, ether, and pentane, the reaction proceeds slowly or not at all. Ether containing 2 mol equiv of triphenylphosphine [based on $Ni(COD)_2$] gives rates and efficiency similar to DMF.

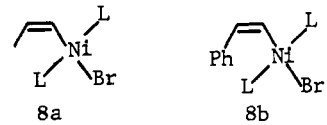
The entires in Table III lead to the conclusion that coupling of simple alkenyl halides occurs with only moderate efficiency. Increased reaction time gives progressively lower yields, suggesting that the 1,3-diene products are reacting further. Oligomerization of 1,3-dienes with zerovalent nickel is well established and is likely to be competitive with the coupling reaction.[27] In addition, simple alkenyl halides give mixtures of 1,3-diene geometrical isomers with a tendency toward formation of the trans,trans products from both cis and trans alkenyl halides.

More efficient and stereospecific are the coupling reactions of α- and β-haloarylates (Table III, entries 7–13). Even chloroacrylates react at 25 °C, in good yield (>70%, isolated), and the isomeric β-bromoacrylates couple with 100% retention of geometry. The mildness of the procedure is particularly evident with methyl α-bromoacrylate (eq 4). Both starting material and product are induced to polymerize by heat, light, radical initiators, and base.[28]



(4)

Parallel with the pathway for coupling of aryl halides, a reasonable mechanism for alkenyl halide coupling would involve initial oxidative addition to give an alkenylnickel(II) halide such as **8a**



8a 8b

from *cis*-2-bromopropene. This intermediate is analogous to those in copper- and silver-promoted coupling of alkenyllithium compounds.[29] However, the mixture of isomers observed in the coupling of simple alkenyl halides is surprising in light of the high stereospecificity observed using copper and silver.[29] The isomerization could occur during formation of **8a** or during subsequent steps leading to the coupled product. We have made no effort to isolate the intermediate (i.e., **8a**) from oxidative addition of *cis*-propenyl bromide in order to inspect the configuration of the double bond at this stage; in the only closely related example, *cis*-β-bromostyrene reacted with Ni(0) to give **8b** with complete retention of configuration.[5g] In an experiment designed to generate **8a** by an alternate route and to examine the configurations of the resulting dienes, *cis*-propenyllithium[29] was mixed with bis(triphenylphosphine)nickel dibromide[30] in ether at 0 °C. After 4.0 h at 25 °C, decomposition to 2,4-hexadienes was complete, with the distribution (cis,cis):(cis,trans):(trans,trans) of 68:25:6, corresponding to 81% retention of geometry of the double bonds. The direct coupling of *cis*-propenyl bromide under the same conditions gives much larger amounts of isomerized product (Table III, entry 2), suggesting that substantial isomerization occurs during for-

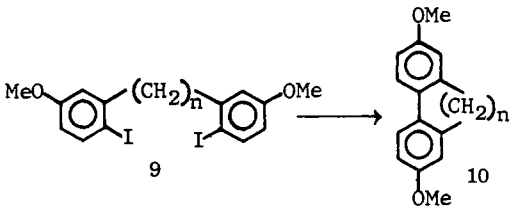
(27) G. Wilke, *Angew. Chem., Int. Ed. Engl.*, **5**, 151 (1966).

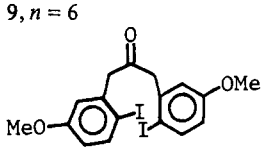
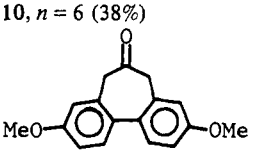
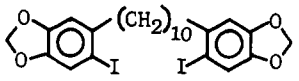
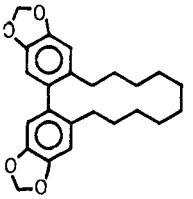
(28) C. S. Marvel, J. Dec, H. G. Cooke, Jr., and J. C. Cowan, *Angew Chem., Int. Ed. Engl.*, **62**, 3495 (1940).

(29) G. M. Whitesides, C. P. Casey, and J. K. Krieger, *J. Am. Chem. Soc.*, **93**, 1379 (1971).

(30) K. Yamamoto, *Bull. Chem. Soc. Jpn.*, **27**, 501 (1954).

Table IV. Formation of Cyclic Biaryls



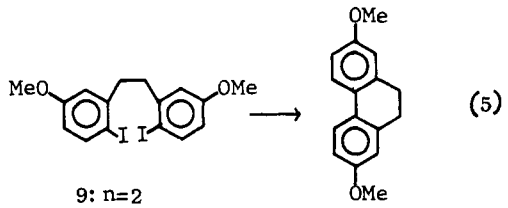
	substrate	conditions[a]	product (% yield)[b]
1	9, $n = 2$	55 °C/40 h	10, $n = 2$ (81%)
2	9, $n = 3$	60 °C/40 h	10, $n = 3$ (83%) (74%)[c]
3	9, $n = 4$	48 °C/40 h	10, $n = 4$ (76%)
4	9, $n = 5$	35 °C/58 h	10, $n = 5$ (85%)
5	9, $n = 6$	60 °C/14 h	10, $n = 6$ (38%)
6		30 °C/9 h	 (85%)
7		55 °C/18 h	 (58%)

[a] The diiodide (1 mol) was added to tetrakis(triphenylphosphine)nickel (1.4 mol) in DMF. [b] The yields are based on chromatographically pure or recrystallized material. [c] Yield from the Ullmann reaction, Cu metal at 240 °C/3 h. [d] A mixture of $Ni(COD)_2$ and tri-*n*-butylphosphine (1:2 mol ratio) in ether was used in place of tetrakis(triphenylphosphine)nickel(0) in DMF.

mation of **8a** by oxidative addition. The stereospecific coupling of β-bromoacrylates demonstrates that the oxidative addition proceeds with complete retention of configuration with these substrates.

D. Intramolecular Coupling of Aryl Halides and an Alkenyl Halide. Formation of symmetrical products limits the synthesis utility of the intermolecular coupling of aryl and alkenyl halides. The potential for practical applications is much higher in formation of rings. This virtue was an important aspect of the nickel-promoted coupling of allylic halides, where macrocyclic rings were formed efficiently.[31]

A prototype substrate is the diiodide **9** ($n = 2$), where the methoxyl groups are present to facilitate selective iodination with silver trifluoroacetate/iodine.[32] The Ullmann reaction proceeds in 70% yield in this case.[21a] Many attempts were made to carry out this cyclization (eq 5) with $Ni(COD)_2$ in DMF, ether, and

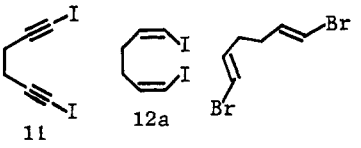


(5)

THF, with and without added tri-*n*-butylphosphine (2 mol equiv). The results were uniformly bad: complete conversion of the diiodide **9** ($n = 2$) and formation of a complex mixture of products from which the dihydrophenanthrene **10** ($n = 2$) was obtained in yields of 0–15%. However, tetrakis(triphenylphosphine)nickel(0) gave excellent results. With this reagent and diiodide **9** ($n = 2$) in DMF at 55 °C, the cyclization was complete in 20 h and **10** ($n = 2$) was isolated in 81% yield after chromatographic purification.

Table IV presents the results with a series of diiodides which were chosen to test for ring size limitations in the cyclization process. Simple 6-, 7-, 8-, and 9-membered rings are formed in good yield without resorting to high dilution techniques, while the 10-membered ring example (entry 5) was less efficient. However, the 14-membered ring was obtained in 85% yield by using ca 0.1 M concentration of reactants. These model reactions suggest applications in the synthesis of natural cyclic biphenyls, and efforts in this direction are reported below.

A single example of intramolecular alkenyl–alkenyl coupling has been studied. Addition of diborane to the diiodide **11** followed



by protonation produced the dialkenyl iodide **12a**.[33] Reaction with $Ni(COD)_2$ in DMF at 38 °C produced 1,3-cyclohexadiene in 64% yield (quantitative GLPC). We noted in an independent experiment that $Ni(COD)_2$ induces the efficient disproportionation of 1,3-cyclohexadiene to cyclohexene and benzene at 35 °C in DMF, but neither of these products was detected during cyclization of **12a**. The corresponding trans,trans isomer (**12b**, conveniently prepared as the dibromide[34]) reacted with $Ni(COD)_2$ in DMF at 40 °C but gave only high molecular weight products.

Other attempts at simple cyclization reactions were less successful. The readily available 2-bromocyclohept-2-en-1-ol[35] was converted to the series of unsymmetrical vinyl halides **13–15** but all attempts to induce cyclization failed. A probable side reaction in these systems is oxidative addition of the allylic carboxylate

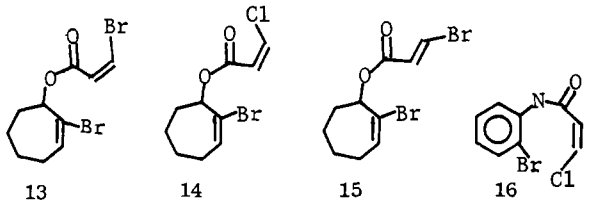
(31) (a) E. J. Corey and H. A. Kirst, *J. Am. Chem. Soc.*, **94**, 667 (1972). (b) E. J. Corey and E. Wat, *ibid.*, **89**, 2757 (1967); (c) E. J. Corey and E. Hamanaka, *ibid.*, **89**, 2758 (1967).

(32) D. E. Janssen and C. V. Wilson, "Organic Syntheses", Coll. Vol. IV, Wiley: New York, 1963, p 547.

(33) G. Zweifel and H. Arzoumanian, *J. Am. Chem. Soc.*, **89**, 5086 (1967).

(34) G. Zweifel and C. C. Whitney, *J. Am. Chem. Soc.* **89**, 2753 (1967).

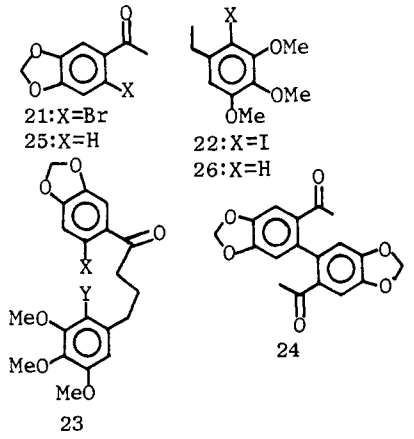
(35) W. Von, E. Doering, and A. Kentaro Hoffmann, *J. Am. Chem. Soc.*, **76**, 6162 (1954).



13 14 15 16

to the $Ni(COD)_2$, but no diagnostic products were detected. Attempted aryl–aryl coupling with amide **16** also failed to produce monomeric products.

E. Approach to the Synthesis of Cyclic Biaryls from Nature. Synthesis of Alnusone. Soon after the elucidation of structure for the antileukemic lignans steganol (**17**) and steganone (**18**),[23] we turned our attention to a synthesis strategy involving intramolecular coupling of aryl halides (Figure 1). The strategy is simplified by the observation that the ketoester **19** can serve as a precursor of **18**.[23b] The central question is whether the highly hindered and acyl-substituted haloaryl rings in **20** will couple efficiently intramolecularly. For initial testing, we prepared the aryl bromide **21**, the aryl iodide **22**, and the dihalide **23**. Under

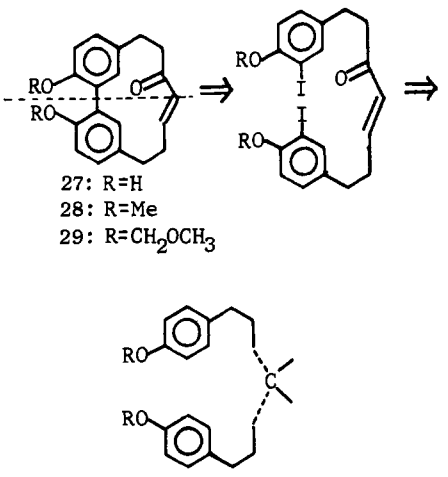


21: X=Br
25: X=H
22: X=I
26: X=H
24
23

the usual conditions, with $Ni(COD)_2$ in DMF, **21** forms the biaryl **24** in 60% yield, but it is accompanied by the reduction product **25** (39%). More dramatically, the hindered iodide **22** reacts with $Ni(COD)_2$ to produce none of the biaryl and only the reduction product **26**. The reduction process was particularly efficient (100% yield), using $Ni(COD)_2$ in THF with 4 mol equiv of tri-*n*-butylphosphine. In trials with a variety of Ni(0) reagents, solvents, and added ligands, no significant formation of biaryl from **22** was observed.

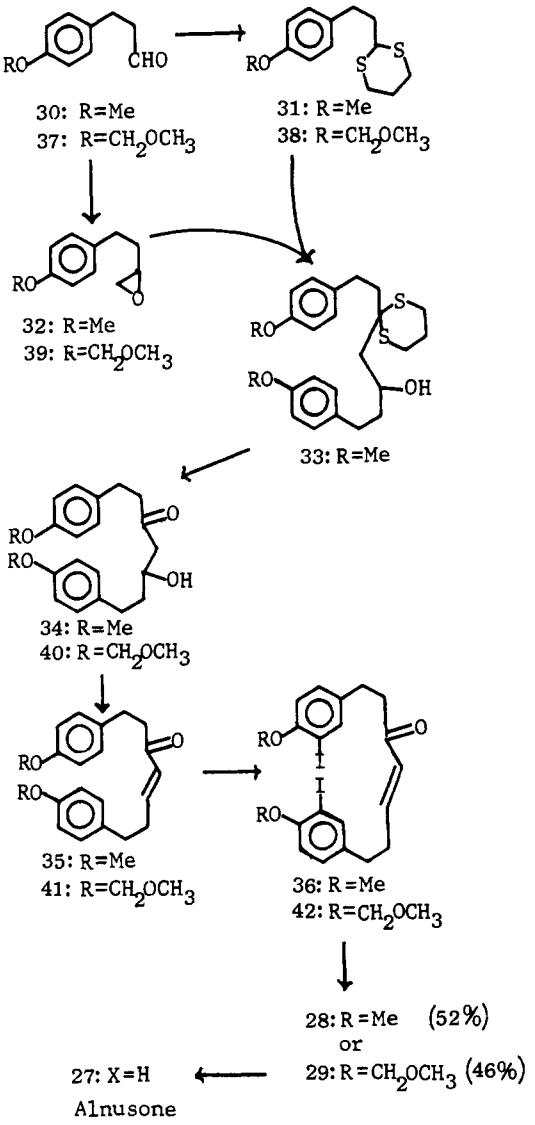
In the same way, the cyclization precursor **23** (X = Br, Y = I), when treated with tetrakis(triphenylphosphine)nickel in DMF, produces a complex mixture of products including as the major product (35% yield) the partially reduced compound **23** (X = Br, Y = H). With $Ni(COD)_2$ in ether and 2 mol equiv of tri-*n*-butylphosphine, both singly (**23**, X = Br, Y = H) and fully reduced (**23**, X and Y = H) products are obtained in 39% and 24% yields, respectively. In THF, the yield of **23** (X = Br, Y = H) is 93%. The formation of reduction products is clearly not due to protonolysis of a long-lived σ-arylnickel intermediate during the isolation procedure; using D_2O/D_2SO_4 for the acid solution during isolation led to no incorporation of deuterium into the reduction products. When THF-d_8 is used as solvent, the hindered iodide **22** is converted to reduction product **26**, leaving 35–45% deuterium at position C-2, on the basis of ^1H NMR integration. At least in this solvent, hydrogen atom transfer from the THF is significant. At the same time, reaction of **22** and $Ni(COD)_2$ in the presence of 6 mol equiv of CH_3CO_2D (>98%) in THF produces **26** with 17% deuterium present on the aromatic ring, presumably at C-2. Additional examples of protonolysis are presented below.

These experiments suggest that ortho substituted aryl halides are prone to reduction during the usual coupling procedure. A simple mechanism would involve hydrogen atom transfer to a σ-arylnickel intermediate. The problem is particularly severe with two ortho substituents; we know of no successful coupling of aryl halides of this type.[36]



27: R=H
28: R=Me
29: R=CH_2OCH_3

Figure 2. Strategy for alnusone.



30: R=Me
37: R=CH_2OCH_3
31: R=Me
38: R=CH_2OCH_3
32: R=Me
39: R=CH_2OCH_3
33: R=Me
34: R=Me
40: R=CH_2OCH_3
35: R=Me
41: R=CH_2OCH_3
36: R=Me
42: R=CH_2OCH_3
28: R=Me (52%)
or
29: R=CH_2OCH_3 (46%)
27: X=H
Alnusone

Figure 3. Synthesis of alnusone.

Alnusone (**27**) along with its close relatives alnusonol and alnusoxide appear in the wood of *Alnus japonica* Steud.[24a] The

(36) However, a highly hindered (bis-ortho-substituted) aryl bromide has been observed to couple with a π-allylnickel halide complex, a process which presumably involved a σ-arylnickel bromide intermediate: K. Sato, S. Inoue, and R. Yamaguchi, *J. Org. Chem.*, 37, 1889 (1972).

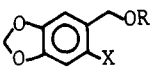
common structural feature is a 13-membered ring including a meta,meta-bridged biphenyl. The pseudosymmetry of the alnusanes suggests a simple strategy for synthesis where the intramolecular coupling of aryl halide units is the key step, and two identical phenylpropane units can be knitted together with a one-carbon unit (Figure 2).

The synthesis was optimized with the phenol units protected as methyl ethers (to give **28**), and this procedure will be described in some detail. It was found that **28** could not be converted to **27** efficiently; the synthesis procedure was repeated with the more easily removed protecting group methoxymethyl, and the product (**29**) was readily converted to alnusone. The synthesis is outlined in Figure 3. Commercially available 3-(4-methoxyphenyl)-propionic acid is converted to aldehyde **30** by reduction to the alcohol followed by oxidation with chromium trioxide–pyridine complex[37] (83% yield). Reaction with propanedithiol produces the alkyl dithiane **31** (94%). Aldehyde **30** was converted to epoxide **32** by using dimethylsulfonium methylide (80%).[38] Then the dithianyl anion[39] from **31** is allowed to react with the epoxide in order to join the two pieces, as the alcohol, **33**, which is hydrolyzed without purification to give the hydroxy ketone **34** in 99% yield overall from **31** and **32**. Acetylation and treatment with 1,5-diazabicyclononene in chloroform at 25 °C produces the α,β-unsaturated ketone **35** (87% after recrystallization). The ^{1}H NMR spectrum of **35** is consistent with the *E* configuration of the double bond (vinyl hydrogens show a coupling constant of 15 Hz). Complete iodination to give **36** requires 3 mol equiv of iodine and silver trifluoroacetate, and the yield after chromatography is 75%.

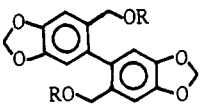
Treatment of **36** with tetrakis(triphenylphosphine)nickel(0) in DMF at 50 °C for 40 h produces alnusone dimethyl ether (**28**) in 52% yield after preparative layer chromatography. The product was identified by comparison (mass, IR, ^{1}H NMR spectral data, and TLC R_f) with a sample of **28** prepared from natural alnusone[40] with potassium carbonate and methyl iodide in methyl alcohol. A variety of conditions was studied in an attempt to demethylate **28**, but no efficient process was found; the results are summarized in the Experimental Section. Instead, the synthesis sequence was repeated by using the methoxymethyl protecting group. In this series, key intermediates **37**–**42** were isolated in yields similar to the methyl series and were fully characterized. The cyclized product, **29**, was obtained in 46% yield as colorless crystals, mp 167–169 °C, and was converted to alnusone (**27**) in 72% yield by using aqueous acetic acid/sulfuric acid. The product was shown to be identical with the sample isolated from natural sources.[40]

F. Conversion of Aryl Halides to Arenes with Zerovalent Nickel. Two distinct mechanisms for carbon–halogen bond reduction are suggested by our work and earlier efforts. As mentioned earlier, the work of Kochi and Tsou[7] specifies conditions under which aryl halides are converted to aryl radicals by Ni(0), and the radical abstracts a hydrogen atom to produce the arene. We find that acidic functional groups in the aryl halide substrate lead to substantial reduction to arene during reaction with Ni(0), suggesting a protonolysis pathway.

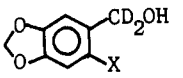
Under the usual conditions for preparative biaryl coupling [DMF; $Ni(COD)_2$ or $Ni(PPh_3)_4$], in the absence of acidic functional groups, reduction is significant only with ortho-substituted aryl halides. An interesting case is 6-bromopiperonyl alcohol (**43**) which contains both an acidic hydrogen and an *o*-alkyl unit. Reaction with $Ni(COD)_2$ in DMF as usual gives the biaryl (**44**) in 10–15% yield and piperonyl alcohol (**45**) in 59% yield. The corresponding methyl ether (**46**) produces biaryl (**47**, 77–80%) and reduction product (**48**, 10%). Using alcohol **49** with 60% deuterium labeling of the –OH unit (**48**) affords piperonyl alcohol (**50**) where the hydrogen at C-6 is labeled with deuterium (32%, by ^{1}H NMR integration), verifying that the hydroxyl group is



43: R=H, X=Br
45: R=H, X=H
46: R=CH_3, X=Br
48: R=CH_3, X=H
49: R=D, X=Br
50: R=H, X=H,D



44: R=H
47: R=Me



51: X=Br
52: X=H,D

a major source of the hydrogen involved in the reduction. Similarly, the methyl ether was prepared with >95% deuterium at the benzylic carbon (**51**). The reduction product (**52**) obtained from **51** [$Ni(COD)_2$, DMF] contains deuterium at C-6, but only 24%, indicating that the benzylic C-H can serve as a source of hydrogen (presumably H·), but is not the major source.

Deliberate addition of a proton source during reaction with Ni(0) leads to an increase in the amount of reduction product. Since this process could serve as a technique for selective reduction of carbon–halogen bonds, especially useful for introduction of deuterium or tritium from labeled water, we have tested a few key examples.[41] The results are presented in Table V. The partitioning between aryl–aryl coupling and protonation is sensitive to the strength of the acid used; addition of 2 mol equiv of water or ethyl alcohol to DMF did not decrease the yield of biaryl (>95%), but acetic acid (4.0 mol equiv) leads to acetophenone (85% yield). At the same time, higher proton concentration leads to rapid formation of Ni(II), apparently through reduction of protons to hydrogen. With acetic acid/DMF in 1:1 volume ratio (entry 5), only 7% reduction (50% recovered *p*-bromoacetophenone) is observed after 18 h at 40 °C. Trifluoroacetic acid is also useful if used in small molar excess (relative to the aryl halide), but with 20 mol equiv of trifluoroacetic acid in DMF, most of the halide is recovered unreacted after the usual period. In less polar solvents such as toluene, the direct oxidation of Ni(0) by acetic acid is relatively faster, making these solvents less useful for halide reduction. However, addition of 4 mol equiv of triphenylphosphine to the acetic acid/toluene/Ni(0) mixture promotes reduction, so that *p*-bromoacetophenone is converted to acetophenone in 92% yield after 14 h at 76 °C (entry 8).

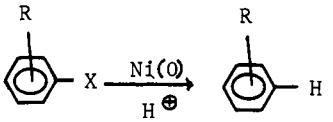
Because hydrogen atom transfer can be significant, this method of reduction of aryl halides is not useful for efficient introduction of deuterium. A mixture of D_2O and acetic anhydride (DOAc) with *p*-bromoacetophenone and $Ni(COD)_2$ in DMF as usual gives acetophenone with the para position bearing 16% H and 84% D (80% yield).

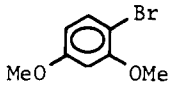
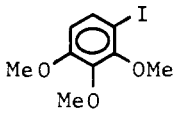
Conclusions

The coupling of aryl and alkenyl halides with zerovalent nickel complexes is a general reaction which proceeds under mild conditions and is compatible with common polar functional groups. Simple alkenyl halides tend to give the more stable (trans,trans) 1,3-diene in a process which appears to involve equilibration of geometry during oxidative addition, but 3-haloacrylate derivatives are coupled without significant isomerization of the double bond. Applications in intramolecular coupling, to form cyclic biaryls, are efficient except for highly hindered aryl halides. The natural cyclic biaryl, alnusone, was prepared in good yield by using nickel-promoted coupling as the key step. Reduction of the aryl halide to arene with Ni(0) is important with highly hindered aryl halides or those with acidic functional groups. Both hydrogen atom transfer and proton transfer are suggested to operate, depending on the reaction conditions.

(37) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).
(38) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 3782 (1962).
(39) D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **8**, 639 (1969).
(40) We are grateful to Professor T. Tokoroyama (Faculty of Science, Osaka City University, Osaka, Japan) for a generous sample of natural alnusone.
(41) An efficient palladium-catalyzed process for reduction of aryl halides to arenes has been described: (a) P. Helquist, *Tetrahedron Lett.*, 1913 (1978); (b) A. Zask and P. Helquist, *J. Org. Chem.*, **43**, 1619 (1978).

Table V. Reduction of Aryl Halides with Ni(0)/Acid



no.	halide	Ni(0) reagent	added ligand	acid	solvent (conditions)	% yield
1	*p*-$BrC_6H_4COCH_3$	$Ni(COD)_2$ (1:1)[a]		CH_3CO_2H (4)[a]	DMF (20 h/40 °C)	85
2	*p*-$BrC_6H_4COCH_3$	$Ni(COD)_2$ (1.9)[a]		CF_3CO_2H (10)[a]	DMF (12 h/35 °C)	85%
3	*p*-$BrC_6H_4COCH_3$	$Ni(COD)_2$ (2.0)[a]		CF_3CO_2H (2)[a]	toluene/DMF (5:1, 3 h/45 °C)	85
4	*p*-$BrC_6H_4COCH_3$	$Ni(COD)_2$ (2.0)[a]		CF_3CO_2H (20)[a]	DMF (13 h/40 °C)	24 (64)[b]
5	*p*-$BrC_6H_4COCH_3$	$Ni(COD)_2$ (1.1)[a]		CH_3CO_2H (1000)[a]	DMF (18 h/40 °C)	7 (50%)[b]
6	*p*-$BrC_6H_4COCH_3$	$Ni(COD)_2$ (1.2)[a]	PPh_3 (4)[a]	CF_3CO_2H (3)[a]	DMF (12 h/40 °C)	69
7	*p*-$BrC_6H_4COCH_3$	$Ni(PPh_3)_4$ (1.2)[a]		CH_3CO_2H (4.0)[a]	DMF (19 h/40 °C)	77
8	*p*-$BrC_6H_4COCH_3$	$Ni(COD)_2$ (1.8)[a]	PPh_3 (4)	CH_3CO_2H (5)	toluene (14 h/76 °C)	92
9	*p*-BrC_6H_4CHO	$Ni(COD)_2$ (1.1)[a]		CH_3CO_2H (4)	DMF (20 h/40 °C)	64
10	*m*-$BrC_6H_4COCH_3$	$Ni(COD)_2$ (1.1)[a]		CH_3CO_2H (4)[a]	DMF (20 h/40 °C)	57
11	*o*-IC_6H_4Ph	$Ni(COD)_2$ (2.0)[a]	PPh_3 (4)[a]	CF_3CO_2H (6.6)[a]	toluene (65 h/48 °C	44
12	*p*-BrC_6H_4Ph	$Ni(COD)_2$ (1.1)[a]	PPh_3 (4.5)[a]	CF_3CO_2H (6.3)[a]	toluene (24 h/68 °C)	66
13		$Ni(COD)_2$ (1.1)[a]	PPh_3 (4.4)[a]	CF_3CO_2H (7.6)[a]	toluene (2 h/70 °C)	53%
14		$Ni(COD)_2$ (1.1)[a]	PPh_3 (4.4)[a]	CF_3CO_2H (6.3)[a]	DMF (9 h/55 °C)	49%
15	*p*-BrC_6H_4COPh	$Ni(COD)_2$ (1.2)[a]	PPh_3 (4)[a]	CH_3CO_2H (5.0)[a]	toluene	66%

[a] Mole ratio with respect to aryl halide used. [b] Recovery of starting aryl halide.

Experimental Section

Standard chromatographic and spectroscopic techniques were used (see supplementary material).

Abbreviations: $Ni(COD)_2$, bis(1,5-cyclooctadiene)nickel(0); DEGS, diethyleneglycol succinate; DMF, *N,N*-dimethylformamide; HMPA, hexamethylphosphorus triamide; THF, tetrahydrofuran. The phrase "under argon" means that the system or vessel was alternately evacuated (usually with the vacuum lead of a double manifold) and then filled with argon, repeating the cycle three or more times.

Handling Air-Sensitive Compounds. Operations with air-sensitive compounds were generally performed under argon by using double-manifold techniques and Schlenk glassware.[42] For transferring $Ni(COD)_2$, the following procedure was used. The reaction vessel (e.g., a 100-mL Schlenk flask) was alternately evacuated (<0.01 torr) and filled with argon two times by use of the double manifold. The flask was weighed and then joined to a Schlenk flask containing $Ni(COD)_2$, with argon flowing from each flask. The assembled glassware was evacuated, and a portion of the solid $Ni(COD)_2$ was poured into the reaction vessel. After being filled with argon, the two flasks were disconnected from each other and alternately evacuated and filled with argon three times.

General Procedure for Reactions of Aryl Halides with $Ni(COD)_2$. The reaction vessel, generally a 100-mL Schlenk flask, was placed under argon, and a weighed amount of $Ni(COD)_2$ was added. The vessel was cooled in a dry ice–alcohol bath and DMF [5 mL/mmol of $Ni(COD)_2$] was added, followed by a solution of the aryl halide [ca. 1.8 mol/mol of $Ni(COD)_2$] in DMF or by a neat sample of the aryl halide. The suspension of yellow solid in colorless liquid was warmed to 40–60 °C over a few minutes and stirred at that temperature for ca. 20 h; during this time, the yellow solid dissolved and the solution turned green. When the reaction was judged to be complete, the mixture was cooled to 25 °C and filtered through Celite (washing with petroleum ether), and the filtrate was partitioned between water and petroleum ether. The organic layer was washed successively with three portions of water, dried, and concentrated by rotary evaporation. The residue was purified by preparative TLC, short-path distillation, and/or recrystallization.

As indicated in Table I, in some cases the yields were determined by quantitative ^1H NMR or, more often, by quantitative GLPC. Full characterization of the biaryls is given in the supplementary material.

Procedures Relating to Table II. The effect of added ligands and different solvents was studied under conditions essentially the same as the general procedure, above. Analysis for unreacted iodobenzene or bromobenzene and biphenyl was carried out by GLPC on a 6-ft × 0.25-in. column packed with 6% DEGS at 151 °C with naphthalene as internal standard. The limit of the analysis was approximately ±3%.

Decomposition of Bis(triphenylphosphine)phenylnickel Bromide (5) in DMF. A sample of *trans*-bis(triphenylphosphine)phenylnickel bromide[5f] (**5**, 0.170 g, 0.22 mmol) was suspended in 4 mL of DMF at 25 °C under argon. After 1 h at 25 °C, the yellow-orange suspension was warmed to 50 °C and allowed to stir at this temperature for 12 h, during which time the mixture became homogeneous. The mixture was cooled to 25 °C, a solution of 6 N hydrochloric acid was added, and the mixture was partitioned between ether and water. In the ether solution biphenyl was detected by quantitative GLPC (6-ft × 0.25-in. column, 5% DEGS, at 150 °C); 99% yield.

Reaction of Bis(triphenylphosphine)phenylnickel Bromide (5) with Iodobenzene. To a suspension of **5** (192 mg, 0.25 mmol) in DMF (4.0 mL) at 25 °C under argon was added iodobenzene (58 mg, 0.28 mmol). The yellow-orange suspension was stirred at 25 °C for 1 h and then at 50 °C for 20 h. The mixture was cooled to 25 °C and treated exactly as in the procedure immediately above. Biphenyl was detected; 0.17 mmol, 69%.

Reaction of Bis(triphenylphosphine)phenylnickel Bromide (5) with *p*-Iodotoluene. To a solution *trans*-bis(triphenylphosphine)phenylnickel bromide[5f] (320 mg, 0.41 mmol) at −78 °C in 6.0 mL of THF under argon was added *p*-iodotoluene (545 mg, 2.46 mmol) neat via syringe. The mixture was warmed quickly to 25 °C and allowed to stir at 25 °C for 18 h. Then 10 mL of cold 6 N hydrochloric acid was added, and the mixture was partitioned between ether and water. In the ether solution was detected by quantitative GLPC analysis (6-ft × 0.25-in. column, 5% DEGS at 95 °C) biphenyl (0.14 mmol), *p*-methylbiphenyl (0.13 mmol), and 4,4′-dimethylbiphenyl (0.15 mmol). The components were identified by comparison of retention times with commercial samples.

Preparation of Bis(triphenylphosphine)(2-methyl-4,5-methylenedioxyphenyl)nickel Iodide (6). According to a general procedure,[5f] tetrakis(triphenylphosphine)nickel (1.73 g, 1.57 mmol) was suspended in 30 mL of toluene at −78 °C under argon, and 6-iodo-3,4-methylenedioxytoluene[43] (460 mg, 1.75 mmol) was added as a solid (Schenk transfer tube). The mixture was allowed to warm to 25 °C during which time a solid separated. After 5 h at 25 °C, the solid was isolated by filtration and washed several times with hexane and ether (1.2 g, 92% yield, mp 135 °C dec). The complex was relatively unstable in $CDCl_3$ and CCl_4 and had low solubility in toluene and ether. A sample was dissolved in concentrated nitric acid, evaporated to dryness with a flame, taken up in water, and titrated for nickel by using standard procedures (EDTA, Murexide indicator). Calcd: Ni, 6.94. Found: Ni, 6.56.

Decomposition of Bis(triphenylphosphine)(2-methyl-4,5-methylenedioxyphenyl)nickel Iodide (6) to Give Biaryl 7. The complex (169 mg, 0.20 mmol) from the procedure immediately above was added as a solid to

(42) D. F. Shriver, "The Manipulation of Air-Sensitive Compounds", McGraw-Hill, New York, 1969.

(43) For the preparation of this compound, see supplementary material.

DMF (4 mL) at 25 °C under argon. After 12 h, a portion of cold 6 N hydrochloric acid solution was added, and the organic products were obtained as described in the general procedure for Ni(0) coupling reactions. Preparative layer chromatography (CH_2Cl_2, silica gel) provided a mixture of 3,4-methylenedioxytoluene and the biaryl (**1**, 0.190 g). Quantitative ^1H NMR analysis using anisole as internal standard indicated the presence of the biaryl (characteristic peak for $-CH_3$ at δ 1.80), 181 mg, 67% yield. Further purification by preparative layer chromatography and crystallization produced a colorless solid: mp 72–73 °C; ^1H NMR ($CDCl_3$): δ 7.04 (s, 2 H), 6.65 (s, 2 H), 5.90 (s, 4 H), 1.80 (s, 6 H); mass spectral mol wt 270.

General Procedure for Coupling of Alkenyl Halides with Ni(0). To a suspension of $Ni(COD)_2$ (1.5 mmol) in solvent (15–20 mL) at 25 °C under argon was added the alkenyl halide (neat, via syringe rapidly, 2.5 mmol). After being stirred at 25 °C for 5–15 h (and in some cases at higher temperature for additional time), the mixture at 25 °C was diluted with ether, washed several times with water, dried, and concentrated in vacuo (for nonvolatile diene products).

Volatile products (the isomeric 2,4-hexadienes), were distilled from the reaction mixture at 0.001 torr into a trap cooled at −196 °C. The clear colorless distillates were analyzed by GLPC (10-ft × 0.25-in., 15% UCON LB550-X, at 50 °C) with benzene as internal standard.

Coupling of β-Bromostyrene.[44] The crude product from the General Procedure was a colorless solid, mp 125–140 °C. Analysis by GLPC (triphenylmethane as internal standard) indicated the presence of 1,4-diphenyl-1,3-butadiene. Recrystallization provided a sample of mp 149.5–151 °C (lit.[45] mp 153 °C) with an ^1H NMR spectrum identical with a published spectrum.[46]

Coupling of Methyl 2-Bromoacrylate.[28] The crude product from the general procedure was analyzed by quantitative ^1H NMR spectroscopy (dibenzyl ether as internal standard) by using the absorptions at δ 6.18 and 5.82 in the spectrum of the product. Preparative GLPC (10-ft × 0.375-in. column, 20% FFAP at 208 °C) afforded a pure sample: ^1H NMR ($CDCl_3$) δ 6.18 (d, J = 1.4 Hz, 2 H), 5.83 (d, J = 1.4 Hz, 2 H), 3.68 (s, 6 H). Hydrolysis of the crude product in 0.5 N aqueous sodium hydroxide at 25 °C for 17 h gave a colorless solid which was recrystallized from ethyl acetate: mp 192–192.5 °C. For 2,3-dicarboxy-1,3-butadiene: lit.[47] mp 182–185 °C. ^1H NMR (acetone-d_6) δ 6.25 (d, J = 1.5 Hz, 2 H), 5.90 (d, J = 1.5 Hz, 2 H), 5.5–6.3 (br m, exchangeable H). The IR spectrum was identical with a published spectrum.[47]

Coupling of 3-Haloacrylates. The crude product from the general procedure was analyzed by quantitative ^1H NMR; dimethyl *cis,cis*-muconate shows signals at δ 7.85 (m, 2 H), 5.97 (m, 2 H), and 3.67 (s, 6 H). While dimethyl *trans,trans*-muconate shows ^1H NMR ($CDCl_3$) signals at δ 7.83 (m, 2 H), 6.23 (m, 2 H), and 3.81 (s, 6 H). From preparative scale experiments, the products were isolated. Dimethyl *cis,cis*-muconate was sublimed (25 °C 0.001 torr), mp 54–67 °C (lit.[48] mp 73 °C), and showed ^1H NMR spectral data superimposable with those of a published spectrum.[49] Dimethyl *trans,trans*-muconate was recrystallized from methyl alcohol; mp 157–158 °C (lit.[49a] mp 158.5 °C). Dibenzyl *trans,trans*-muconate was recrystallized from methyl alcohol: mp 109–110 °C; ^1H NMR ($CDCl_3$) δ 7.35 (m, 12 H), 6.20 (m, 2 H), 5.20 (s, 4 H); IR ($CHCl_3$) 1711 cm^{-1}.

Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.37; H, 5.78.

Characterization of the Isomeric 2,4-Hexadienes. The analytical techniques of Whitesides[29] were followed, including the purification of the *cis*- and *trans*-1-bromopropene. See the in the supplementary material procedure for details.

Reaction of *cis*-1-Propenyllithium with Bis(triphenylphosphine)nickel(II) Dibromide in Ether. Bis(triphenylphosphine)nickel dibromide (0.742 g, 1.00 mmol) was placed in a 50-mL three-neck flask equipped a stopcock and two rubber septa under argon at −78 °C. A solution of *cis*-1-propenyllithium[29] (3.88 mL, ca 1.0 mmol) was added all at once with a syringe. The mixture was stirred at 0 °C for 50 min and at 25 °C for 4 h. Flash distillation at 25 °C (9 torr) into a trap cooled at −196 °C gave 3.97 g of colorless distillate which was analyzed by quantitative GLPC. Detected were *trans,trans*-, *trans,cis*-, and *cis,cis*-2,4-hexadiene in a ratio of 1.0:4.1:11.3, respectively, and a combined yield of 62%.

General Procedure for Cyclizations in Table IV. To a suspension of tetrakis(triphenylphosphine)nickel(0) (0.3 mmol) in DMF (14 mL) at −78 °C under argon was added in one portion the α,ω-bis(iodoaryl)alkane (0.25 mmol). The reaction mixture was warmed at the temperature and for the period specified in Table IV. The homogeneous gold-brown starting mixture gradually became green and a black solid appeared. The mixture was cooled to 25 °C, poured into 50 mL of ether, and washed sequentially with 20 mL of 1 M aqueous hydrochloric acid and 40 mL of saturated aqueous salt solution, and the ether solution was dried. Concentration by rotary evaporation afforded a yellow, low melting point solid. Preliminary purification by column or preparative layer chromatography (25% dichloromethane in cyclohexane, silica gel) followed by recrystallization provided the analytical sample.

Characterization of the Products in Table IV. Compound 10, n = 2: R_f = 0.2, (3:1 hexane:dichloromethane); mp 111–112 °C (lit.[50] mp 180–109 °C); ^1H NMR ($CDCl_3$) δ 2.85 (s, 4 H), 3.8 (s, 6 H), 6.75–7.0 (m, 4 H), 7.6 (dd, J = 8 Hz, J = 2 Hz, 2 H); IR ($CHCl_3$) 1600 (m), 1490 (s), 1470 (m), 1280 (m), 1255 (m) cm^{-1}; mass spectral mol wt 240, calcd, 240.

Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.94, H, 6.63.

Compound 10, n = 3: R_f = 0.3 (3:1 hexane:dichloromethane); mp 99.5–101 °C; ^1H NMR ($CDCl_3$) δ 1.9–2.65 (m, 6 H), 0.78 (s, 6 H), 6.6–6.9 (m, 4 H), 7.2 (dd, J = 7 and 3 Hz, 2 H); IR ($CHCl_3$) 1600 (m), 1500 (s), 1255 (s), 1215 (s) cm^{-1}; mass spectral mol wt 254, calcd 254.

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.07; H, 7.11.

Compound 10, n = 4: R_f = 0.2 (3:1 hexane:dichloromethane); mp 139.5–141 °C; ^1H NMR ($CDCl_3$) δ 1.2–3.0 (m, 8 H), 3.82 (s, 6 H), 6.66–6.90 (m, 4 H), 7.02–7.25 (br d, 2 H); IR ($CHCl_3$) 1600 (s), 1500 (s), 1270 (s), 1230 (s) cm^{-1}; mass spectral mol wt 268, calcd 268.

Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.6; H, 7.5. Found: C, 80.51; H, 7.38.

Compound 10, n = 5: R_f = 0.7 (1:1 dichloromethane:cyclohexane); mp 99.5–101 °C; ^1H NMR ($CDCl_3$) δ 1.25–2.85 (m, 10 H), 3.82 (s, 6 H), 6.6–6.9 (m, 4 H), 6.95–7.3 (m, 2 H); IR ($CHCl_3$) 1600 (w), 1525 (w), 1500 (w), 1430 (w), 1220 (w), 1050 (w), 970 (s) cm^{-1}, mass spectral mol wt, 282; calcd 282.

Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.08; H, 7.85. Found C, 79.93; H, 7.88.

Compound 10, n = 6: R_f = 0.2 (3:1 cyclohexane:dichloromethane); mp 98–100 °C; ^1H NMR ($CDCl_3$) δ 1.0–1.8 (m, 8 H), 2.55 (t, J = 6 Hz, 4 H), 3.72 (s, 6 H), 6.6–7.3 (m, 6 H); IR ($CHCl_3$) 1600 (m), 1525 (w), 1500 (m), 1430 (w), 1270 (m), 1220 (s) cm^{-1}; mass spectral mol wt 296, calcd for $C_{20}H_{24}O_2$ 296.

Cyclization of 1,10-Bis(2-iodo-4,5-methylenedioxyphenyl)decane with Ni(0) (Table IV, Entry 7). According to the general procedure, above, the bis(aryl iodide) was converted to a crude product which was purified by preparative layer chromatography (1:1 cyclohexane:dichloromethane on silica gel, R_f = 0.6). The colorless solid had a melting pint of 112–113.5 °C: ^1H NMR ($CDCl_3$) δ 1.1–1.8 (m, 16 H), 2.3–2.8 (two overlapping t, J = 7 Hz, 4 H), 5.82 (s, 2 H), 5.97 (s, 2 H), 6.42 (s, 1 H), 6.58 (two overlapping s, 2 H), 6.72 (s, 1 H); IR ($CHCl_3$) 1510 (s), 1490 (s), 1230 (s), 1045 (s), 980 (s), 870 (w) cm^{-1}; mass spectral mol wt 380, calcd 380.

Anal. Calcd for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42. Found: C, 75.71; H, 7.44.

Cyclization of 1,3-Bis(2-iodo-5-methoxyphenyl)-2-propanone with Tri-*n*-butylphosphine and Ni(COD)$_2$ (Table IV Entry 6). To a suspension of $Ni(COD)_2$ (0.39 g, 1.41 mmol) in 30 mL of ether at −78 °C under argon was added tri-*n*-butylphosphine (0.53 g, 2.63 mmol) in one portion via syringe and then solid 1,3-bis(2-iodo-5-methoxyphenyl)-2-propanone (0.656 g, 1.26 mmol). The mixture was stirred at −20 to 0 °C for 1.5 h, at 0 °C for 6 h, and at 25–30 °C for 9 h. The resulting green mixture was partitioned between ether and 1 M aqueous hydrochloric acid. After the usual extraction procedures, drying, and concentrating, an oily yellow solid was obtained; 0.492 g. From preparative layer chromatography (1% ethyl alcohol in dichloromethane, silica gel), the band at R_f = 0.35 was isolated; 0.19 g (86%) of a colorless solid; recrystallization from methyl alcohol gave the analytical sample: mp 129–130 °C; ^1H NMR ($CDCl_3$) δ 3.55 (s, 4 H), 3.9 (s, 6 H), 6.7–7.1 (m, 4 H), 7.5 (d, J = 8 Hz, 2 H); IR($CHCl_3$) 1725 (s, C=O), 1625 (s), 1500 (s), 1250 (s), 1210 (m), 1170 (m), 1060 (m) cm^{-1}; mass spectral mole wt 268, calcd 268.

Anal. Calcd for $C_{17}H_{18}O_3$: C, 76.1; H, 6.01. Found: C, 76.03; H, 5.89.

(44) The β-bromostyrene was obtained from Aldrich Chemical Co. and was >98% the trans isomer.

(45) J. H. Pinkard, B. Wille, and L. Zechmeister, *J. Am. Chem. Soc.*, **70**, 1938 (1948).

(46) "Sadtler NMR Spectra", Sadtler Research Laboratories, Inc., Philadelphia, 1971, No. 5140.

(47) W. J. Bailey, R. L. Hudson, and E. T. Yates, *J. Org. Chem.*, **28**, 828 (1963).

(48) J. A. Elvidge, R. P. Linstead, P. Sims, and B. A. Orkin, *J. Chem. Soc.*, 2235 (1950).

(49) (a) J. Elvidge and P. D. Ralph, *J. Chem. Soc. C*, 387 (1966). (b) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy", Pergamon Press, New York, 1959, p 95.

(50) J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 684 (1942).

(51) E. J. Corey and D. Seebach, *J. Org. Chem.*, **40**, 231 (1975).

Ullmann Reaction to Form Biaryl 10, $n = 3$. The bis(aryl iodide) **9**, $n = 3$ (0.38 g, 0.75 mmol), and copper (0.4 g, 0.063 mol) were heated at 240 °C under argon for 3 h. The crude solid was triturated with dichloromethane and filtered through Celite, and the filtrate was concentrated to yield a colorless solid (0.16 g, 84%). Preparative layer chromatography (30% dichloromethane in cyclohexane) provided crystals, mp 99–101 °C, identical with the product from Ni(0) cyclization.

1,6-Diiodo-1,5-hexadiyne (11). A 1000-mL three-neck flask which was equipped with a stopcock, rubber septum, and 125-mL addition funnel was filled with argon in the usual manner. Anhydrous ether (200 mL) was added to the flask, and a 1.65 M solution (55 mL, 91 mmol; Foote Mineral Co.) of methyllithium in ether was transferred to the addition funnel. After the flask was cooled to 0 °C, 1,5-hexadiyne (3.51 g, 45.5 mmol; Farchan Research Laboratories) was added to the flask, and the methyllithium solution was added over a 1-h period. The reaction mixture was stirred at 25 °C for 5 h and then cooled to 0 °C. Then the 125-mL addition funnel was replaced by a 250-mL additional funnel containing a solution of iodine (23.1 g, 91 mmol) in anhydrous ether (200 mL). After the iodine solution had been added dropwise, the resulting deep red solution was warmed to 25 °C, diluted with 300 mL of ether, washed sequentially with several 50-mL portions of water, 10% aqueous sodium thiosulfate, and saturated aqueous sodium chloride, dried, and concentrated in vacuo. Remaining was 13.26 g (89%) of yellow solid which became dark red on standing: mp 88–91 °C; ^{1}H NMR ($CDCl_3$): δ 2.54 (s). This material was used in the preparation of **12a** without further purification.

1,6-Diiodo-*cis*,*cis*-1,5-hexadiene (12a). By the general method of Zweifel,[33] 1,6-diiodo-1,5-hexadiyne was converted to **12a**. A 250-mL, three-neck flask which was equipped with a stopcock, rubber septum, and a thermometer was filled with argon in the usual manner. To the flask at 25 °C were added THF (25 mL) and cyclohexene (4.52 g, 54.0 mmol), and, after the flask was cooled to 0 °C, a 1 M solution (27 mL, 27 mmol; Alfa Products) of diborane in tetrahydrofuran was added with a syringe at such a rate that the temperature was maintained below 5 °C. After the mixture had been stirred at 0 °C for 2 h, 1,6-diiodo-1,5-hexadiyne (5.00 g, 13.5 mmol) in 17 mL of THF was added rapidly via syringe. The reaction mixture was stirred at 25 °C for 2 h and then cooled to 0 °C, and acetic acid (12.4 mL, 96 mmol) was added with a syringe. The mixture was then stirred for 5 h at 25 °C, diluted with 120 mL of ether, washed sequentially with 30 mL of water, 30 mL of aqueous sodium thiosulfate, and 30 mL of water, dried, and concentrated in vacuo. The crude product was stirred with 50 mL of hexane, the mixture was filtered, and the filtrate was concentrated in vacuo, affording 8.16 g of clear, colorless liquid. Short-path distillation at 25 °C (0.025 torr) into a trap cooled to −78 °C gave 3.093 g (62%) of a pink liquid which was redistilled. Obtained as the major fraction was 2.16 g (43%) of light pink liquid: bp 56–58 °C (0.005 torr); ^{1}H NMR ($CDCl_3$) δ 5.80–6.20 (m, 4 H), 1.80–2.50 (m, 4 H); mass spectral mol wt 334, calcd for $C_6H_8I_2$ 334.

Reaction of 12a with Ni(COD)$_2$. To a suspension of Ni(COD)$_2$ (0.899 g, 3.27 mmol) in DMF (15 mL) at −78 °C under argon was added neat **12a** (0.955 g, 2.98 mmol) all at once. The mixture was warmed at 38 °C for 16 hr and then cooled to 25°. Short path distillation at 25°/0.01 torr into a liquid nitrogen cooled trap afforded a clear liquid which was analyzed by GLPC (10-ft × 0.375-in, 20% FFAP, 100°) with cyclohexane as the internal standard. A 64% yield of 1,3-cyclohexadiene was detected. Neither benzene nor cyclohexene was detected (<2% yield).

In a similar experiment the reaction mixture was stirred at 0 °C for 5 h, 25 °C for 12 h, and 35 °C for 2 h. Obtained was a 61% yield of 1,3-cyclohexadiene, with <2% of benzene or cyclohexene.

Reaction of 1,3-Cyclohexadiene with Ni(COD)$_2$. Neat 1,3-cyclohexadiene (0.103 g, 1.34 mmol) was added all at once to a suspension of Ni(COD)$_2$ (0.203 g, 0.736 mmol) in DMF (7 mL) at −78 °C under argon. The mixture was then stirred at 35 °C for 15 h, cooled to 25 °C, and subjected to short-path distillation at 25 °C (0.01 torr) into a liquid-nitrogen-cooled trap. The clear, colorless distillate was analyzed by GLPC (10-ft × 0.375-in., 20% FFAP, 100 °C) with cyclohexane as the internal standard. Cyclohexene and benzene were detected in yields of 42% and 43%, respectively.

Preparation of *trans*,*trans*-1,6-Dibromo-1,5-hexadiene (12b). According to Zweifel's procedure,[34] to 0.050 mmol of 1,5-hexadiyne in 20 mL of hexane was added 0.10 mmol of diisobutylaluminum hydride (20% solution in hexane, Alfa Inorganics) while the temperature was maintained below 40 °C by means of a water bath. After the initial exothermic reaction had subsided, the mixture was heated at 50 °C for 2 h. The hexane was then removed at reduced pressure, and the residue was diluted with 40 mL of THF and cooled to −50 °C. A solution of bromine (5.47 mL, 15.98 g, 0.10 mmol) in dichloromethane (40 mL) was added slowly to the vinylalane solution. The mixture was allowed to warm to 25 °C and treated by dropwise addition of 20% aqueous sulfuric acid followed by pouring into a slurry of ice and 20% sulfuric acid. Extraction with pentane as usual, drying, and concentrating by rotary evaporation produced 7.6 g of crude dibromide. Fractional distillation gave a center cut, 2.04 g (17% yield), bp 34–43° (0.01 torr), which was homogeneous by GLPC analysis (6-ft × 0.25-in. column of 20% Versamide on Chromosorb W at 175 °C): ^{1}H NMR ($CDCl_3$) δ 5.72–6.50 (m, 4 H), 1.78–2.54 (m, 4 H). Mass spectral mol wt 238, calcd for $C_6H_8{}^{79}Br_2$ 238.

Reaction of 12b with Ni(COD)$_2$. Exactly according to the procedure for reaction of **12a**, the dibromide **12b** reacted with Ni(COD)$_2$ and produced no detectable 1,3-cyclohexadiene, benzene, or cyclohexene according to quantitative GLPC analysis (<2% yield).

Preparation of Compounds Related to the Attempted Synthesis of Steganone. Compounds 21–26. These starting materials and products were prepared in simple ways. The details and characterization data are given in the supplementary material unless given immediately below.

Reaction of 21 with Ni(COD)$_2$ in DMF. To a suspension of Ni(COD)$_2$ (0.209 g, 0.73 mmol) in 20 mL of DMF at −78 °C under argon was added solid 6-bromo-3,4-methylenedioxyacetophenone (**21**, 0.17 g, 0.70 mmol) in one portion. The mixture was stirred at 25 °C for 10 min and then heated at 35 °C for 12 h. Isolation of the organic products as usual produced a colorless solid. Preparative layer chromatography (silica gel, dichloromethane) gave a major component of $R_f = 0.15$ (60 mg, 61%) and a minor component of $R_f = 0.4$ (45 mg, 39%). The major product was identified as biaryl **24** through ^{1}H NMR and mass spectral data: ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 6 H), 6.0 (s, 4 H), 6.55 (s, 2 H), 7.2 (m, 2 H); mass spectral mol wt 202, calcd for $C_{18}H_{14}O_2$ 202. The minor component was tentatively identified as **25**: ^{1}H NMR ($CDCl_3$): δ 2.5 (s, 3 H), 6.0 (s, 2 H), 6.8 (d, $J = 7$ Hz, 1 H), 7.3–7.6 (m, 2 H).

Reaction of 22 with Ni(0) Reagents. (a) With One Equivalent of Ni(COD)$_2$ in DMF. To a suspension of Ni(COD)$_2$ (0.13 g, 0.473 mmol) in 20 mL of DMF at −78 °C under argon was added 1-ethyl-2-iodo-3,4,5-trimethoxybenzene (**22**, 0.30 g, 0.473 mmol) in one portion via syringe. The mixture was warmed to 25 °C over 15 min and heated at 40 °C for 18 h. The yellow suspension gradually became homogeneous green-brown. The mixture was partitioned between ether and 1 M hydrochloric acid. From the ether was isolated a pale yellow oil, 0.23 g. Two major components were isolated by preparative layer chromatography ($R_f = 0.5$ and $R_f = 0.2$, silica gel and dichloromethane). The component of $R_f = 0.5$ was identified as the starting material (**22**, 0.11 g, 37% recovered) by ^{1}H NMR analysis, and the component of $R_f = 0.2$ was identified as reduction product (**26**, 80 mg, 44% yield) by ^{1}H NMR comparison with a sample prepared earlier (see supplementary material). No other significant components were apparent by TLC and ^{1}H NMR analysis.

(b) With Two Equiv of Ni(COD)$_2$ in DMF. In a reaction exactly as described above, but with a mole ratio of 1:1 for Ni(COD)$_2$:**22**, the crude product consisted of starting material (**22**, 23% recovered) and reduction product (**26**, 77% yield).

(c) With Two Equivalents of Ni(COD)$_2$ and *n*-Bu$_3$P in THF. A mixture of Ni(COD)$_2$ (0.15 g, 0.55 mmol), THF (10 mL), tri-*n*-butylphosphine (0.13 g, 1.09 mmol), and **22** (80 mg, 0.25 mmol) was heated at reflux for 48 h. The mixture was partitioned between ether and 1 M hydrochloric acid, and from the ether was isolated a colorless oil. Analysis as before indicated the absence of starting iodide (**22**) and complete conversion to reduction product **28**.

(d) With Tetrakis(triphenylphosphine)nickel(0) in DMF. By using tetrakis(triphenylphosphine)nickel (0.40 g, 0.36 mmol) in 8 mL of DMF under argon at −78 °C was added iodide **22** in one portion via syringe. After 18 h at 55 °C, the organic products were isolated and shown to be a mixture of **22** (30%) and reduction product **26** (70%).

Attempted Cyclizations of 23 (X = Br, Y = I). (a) With Tetrakis(triphenylphosphine)nickel(0). To a suspension of tetrakis(triphenylphosphine)nickel (0.59 g, 0.53 mmol) in 7 mL of DMF at −78 °C under argon was added **23** (X = Br, Y = I; 0.20 g, 0.35 mmol) in 2 mL of DMF. The mixture was stirred at 45 °C over 38 h and then partitioned between ether and 1 M hydrochloric acid. From the ether solution was isolated a yellow oil, 0.62 g. Preparative layer chromatography (silica gel, dichloromethane) allowed isolation of two major components, triphenylphosphine ($R_f = 0.7$) and **23** (X = H, Y = I) at $R_f = 0.3$ (60 mg, 35% yield): ^{1}H NMR ($CDCl_3$): δ 1.7–2.3 (quint, 2 H, $J = 7$ Hz), 2.5–3.1 (overlapping t, $J = 7$ Hz, 4 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 3.81 (s, 3 H), 5.98 (s, 2 H), 6.64 (s, 2 H), 6.83 (d, $J = 8$ Hz, 1 H), 7.4 (d, $J = 2$ Hz, 1 H), 7.51 (dd, $J = 8$ Hz, 1 H); mass spectral mol wt 484, calcd for $C_{20}H_{21}IO_6$ 484. The starting material (**23**, X = Br, Y = I) was clearly absent by TLC analysis, and none of several minor components were characterized.

(b) With Ni(COD)$_2$ and Tri-*n*-butylphosphine in Ether. To a suspension of Ni(COD)$_2$ (0.155 g, 0.564 mmol) in 7 mL of ether under argon at −78 °C was added tri-*n*-butylphosphine (0.238 g, 1.13 mmol)

in one portion via syringe. A solution of **23** (X = Br, Y = I; 0.20 g, 0.36 mmol) in 3 mL of ether was added in one portion. After 14 h at 0 °C, the mixture was partitioned between ether and water, and from the ether solution was isolated a yellow oil. Preparative layer chromatography (silica gel, dichloromethane) produced three pure compounds: tri-*n*-butylphosphine (R_f = 0.8), **23** (X = H, Y = I; R_f = 0.4, 66 mg, 39%), and **23** (X, Y = H, R_f = 0.3, 30 mg, 24% yield). The latter product was identified by ^{1}H NMR and mass spectral analysis. ^{1}H NMR($CDCl_3$): δ 1.7–2.3 (quint, J = 7 Hz, 2 H), 2.6–3.1 (overlapping t, J = 7 Hz, 4 H), 3.81 (s, 3 H), 3.82 (s, 3 H), 3.85 (s, 3 H), 6.0 (s, 2 H), 6.4 (s, 2 H), 6.83 (d, J = 8 Hz, 1 H), 7.43 (d, J = 1 Hz, 1 H), 7.55 (dd, J = 2, 8 Hz, 1 H). Mass spectral mol wt: 358. Calcd for $C_{20}H_{22}O_6$: 358.

(c) Isolation Involving D_2O/D_2SO_4. An experiment identical with b was carried out except a 1 M solution of D_2SO_4 (>98% D) in D_2O (>99.9% D) was added immediately before ether extraction. The reduction product (**23**, X = H, Y = H) was isolated and shown to contain <1% deuterium above natural abundance by mass spectral analysis.

Preparation of 3-(4-Methoxyphenyl)propanal (30). To a suspension of lithium aluminum hydride (13.6 g, 36 mmol) in 600 mL of ether at 0 °C was added solid 3-(4-methoxyphenyl)propionic acid (25 g, 138 mmol, Aldrich Chemical Co.) in small portions over 0.5 h. The reaction mixture was stirred at 25 °C for 5 h (drying tube). Successive portions of water (13.6 mL), 15% aqueous potassium hydroxide (13.6 mL), and water (45 mL) were added slowly. The precipitate was removed by filtration and washed with ether. From the combined ether solution was isolated a colorless oil which was distilled to give a center cut of bp 113 °C (0.45 torr) (22.5 g, 97.5%) of 3-(4-methoxyphenyl)propanol which was used in the next step without further purification.

To a solution of chromium trioxide (36 g, 0.36 mmol) and pyridine (57 mL, 0.72 mmol) at 25 °C was added all at once a solution of the distilled alcohol (above, 10 g, 0.060 mol) in 5 mL of dichloromethane. The mixture was stirred for 10 min and then filtered through a column of Florisil (3.5 cm × 30 cm) with dichloromethane as eluant.[37] The solution was concentrated by rotary evaporation, and the residue was dissolved in 150 mL of ether. The ether solution was washed sequentially with two 50-mL portions of cold 0.5 M hydrochloric acid and 25 mL of saturated aqueous salt solution, dried, and concentrated to leave a pale yellow liquid. Short-path distillation (air bath at 80 °C, 0.005 torr) afforded 8.2 g (83%) of colorless aldehyde which was homogeneous by analytical TLC but did not give a proper analysis: ^{1}H NMR $CDCl_3$) δ 2.55–2.85 (m, 4 H), 3.75 (s, 3 H), 6.6–7.05 (AA′BB′ pattern, J = 8 Hz, 4 H), 9.80 (br s, 1 H). Ir (neat) 1735 (s), 1615 (m), 1515 (s), 1225 (s), 1145 (s) cm^{-1}.

Preparation of the 1,3-Dithiane Derivative 31. According to the method of Corey,[51] boron trifluoride etherate (15 drops) was added in one portion to a solution of aldehyde **30** (4 g, 24.4 mmol) and propane-1,3-dithiol (2.86 g, 26.4 mmol) in 50 mL of dichloromethane at 0 °C. After being stirred at 0 °C for 0.5 h and at 25 °C for 1.5 h, the mixture was poured into 125 mL of ether. The ether solution was washed sequentially with three 50-mL portions of 20% aqueous sodium hydroxide solution and 25 mL of saturated aqueous salt solution. From the ether solution was isolated by concentration and recrystallization (methyl alcohol) 5.8 g (94%) of fine colorless needles: mp 46–47 °C; ^{1}H NMR ($CDCl_3$) δ 1.75–2.3 (m, 4 H), 2.6–3.0 (m, 6 H), 3.80 (s, 3 H), 3.98 (t, J = 7 Hz, 1 H), 6.75–7.21 (AA′BB′, J_{AB} = 8 Hz, 4 H); IR ($CHCl_3$) 1600 (s), 1500 (s), 1320 (m), 1300 (m) cm^{-1}; mass spectral mol wt 254, calcd 254.

Anal. Calcd for $C_{13}H_{18}S_2O$: C, 61.37; H, 7.13; S, 25.21. Found: C, 61.26; H, 7.15; s, 25.00.

Preparation of 4-(4-Methoxyphenyl)-1-butene Oxide (32). According to the method of Corey,[38] a 57% oil dispersion of sodium hydride (3.49 g, 82.5 mmol) under argon was washed with three 10-mL portions of dry pentane and dried at 0.001 torr. To the sodium hydride was added 30 mL of dimethyl sulfoxide (Me_2SO), and the suspension was heated at 65 °C for 1.5 h (hydrogen evolution ceases). The pale green homogeneous solution was diluted with 30 mL of THF and cooled to 0 °C. A solution of trimethylsulfonium iodide[38] (16.9 g, 82.6 mmol) in 75 mL of Me_2SO was added dropwise via syringe over 5 min. The reaction mixture was stirred for 10 min, and then a solution of aldehyde **30** (8.1 g, 49.3 mmol) in 5 mL of THF was added dropwise via syringe over 1 min. The mixture was stirred at 0 °C for 0.5 h and at 25 °C for 2 h, and then partitioned between water and ether. From the ether was isolated a pale yellow liquid which was distilled to give a center cut: bp 82 °C (0.02 torr); 7.50 g (86% yield); ^{1}H NMR ($CDCl_3$) δ 1.52–2.5 (m, 2 H), 2.24–4.00 (m, 5 H), 3.70 (s, 3 H), 6.8–7.21 (AA′BB′, J_{AB} = 8 Hz, 4 H); IR(film): 1620 (m), 1510 (s), 1400 (w), 1300 (m) cm^{-1}; mass spectral mole wt 178, calcd for $C_{11}H_{14}O_2$ 178.

Preparation of 1,7-Bis(4-methoxyphenyl)-5-hydroxyhept-3-one (34). According to the method of Corey and Seebach,[39] to a stirred solution of the dithiane derivative **31** (4.0 g, 15.8 mmol) in 40 mL of THF under argon at −30 °C was added *n*-butyllithium in ether (7.9 mL of 2.0 M, 15.8 mmol) dropwise via syringe over 10 min. The resulting pale yellow solution was stirred at −30 °C for 1.5 h and then warmed to 0 °C. A solution of epoxide **32** (2.81 g, 15.8 mmol) in 4 mL of THF was added dropwise over 2 min. After being stirred at 0 °C for 12 h, the mixture was partitioned between ether and water and the ether solution was washed sequentially with water (2×) and saturated aqueous salt solution, dried, and concentrated to afford 7.6 g of a nearly colorless liquid (**33**). The product was hydrolyzed by treatment with a mixture of methyl alcohol (360 mL), water (36 mL), yellow mercuric oxide (6.9 g, 32 mmol), and mercuric chloride (8.65 g, 32 mmol) at reflux for 18 h. The suspension was filtered through Celite, and the filtrate was concentrated by rotary evaporation. The residue was dissolved in ether, and the solution was washed with water and saturated aqueous salt solution and concentrated again to yield a fluffy white solid. Recrystallization from ether gave 5.4 g (99% yield) of **34**: mp 69–70 °C; ^{1}H NMR ($CDCl_3$) δ 2.4–3.15 (m, 10 H), 3.8 (s, 6 H), 3.8–4.2 (m, 1 H), 6.7–7.2 (AA′BB′, J = 8 Hz, 8 H); IR ($CHCl_3$) 3600 (w), 1705 (s), 1605 (m), 1570 (s) cm^{-1}; mass spectral mole wt 342, calcd for $C_{21}H_{26}O_4$ 342.

Preparation of 1,7-Bis(4-methoxyphenyl)-4-hepten-3-one (35). The hydroxy ketone **34** (0.80 g, 2.3 mmol) was dissolved in 18 mL of pyridine and 9 mL of acetic anhydride and stirred at 25 °C for 12 h. Ice (20 g) was added slowly, and the mixture was partitioned between ether and water. The ether solution was washed sequentially with water, 1.0 M hydrochloric acid, water, and saturated aqueous salt solution. From the ether was obtained a colorless liquid (acetate of **34**, 0.91 g, 99% yield): ^{1}H NMR ($CDCl_3$) δ 1.95 (s, 3 H), 2.35–2.90 (m, 10 H), 3.75 (s, 6 H), 5.0–5.4 (quint, J = 6 Hz, 1 H), 6.71–7.21 (AA′BB′, J_{AB} = 9 Hz, 4 H).

The crude acetate (3.0 g, 7.8 mmol) was dissolved in a mixture of chloroform (20 mL) and diazabicyclononane (0.99 g, 8.0 mmol). After 0.5 h at 25 °C, the mixture was partitioned between water and ether and the ether solution was washed sequentially with 1 M hydrochloric acid, water, saturated aqueous sodium bicarbonate, and saturated aqueous salt solution, then dried, and concentrated to give a fluffy white solid which was recrystallized from ether to yield pure **35**: 2.20 g, 81% yield; mp 48–49 °C; ^{1}H NMR ($CDCl_3$) δ 2.35–2.75 (m, 4 H), 2.84 (br s, 4 H), 3.72 (s, 3 H), 3.76 (s, 3 H), 6.09 (d, J = 15 Hz, 1 H), 6.67–7.30 (overlapping multiplet and AA″BB″ pattern, 9 H). IR (CCl_4) 1680 (s), 1620 (s), 1500 (s), 1460 (s), 1440 (s), 1360 (m), 1290 (s), 1240 (br, s), 1175 (s), 1100 (s), 1020 (s); mass spectral mol wt 324, calcd 324.

Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.58; H, 7.49.

Preparation of 1,7-Bis(3-iodo-4-methoxyphenyl)-4-hepten-3-one (36). Solid silver trifluoroacetate (0.64 g, 2.9 mmol) was added to a solution of **35** (0.20 g, 0.93 mmol) in 15 mL of chloroform. To the stirred suspension was added a solution of iodine (0.74 g, 2.9 mmol) in 50 mL of chloroform dropwise over 15 min. The yellow suspension was stirred an additional 0.5 h and then filtered through Celite. From the filtrate was isolated 0.63 g of a yellow oil which was purified by preparative layer chromatography (silica gel, dichloromethane) to yield a major component of R_f = 0.5: 0.40 g, 75% yield, as a colorless liquid; ^{1}H NMR ($CDCl_3$) δ 2.3–2.8 (m, 4 H), 2.8 (s, 4 H), 3.8 (s, 6 H), 6.06 (d, J = 16 Hz, 1 H), 6.55–7.25 (m, 5 H), 7.51–7.67 (m, 2 H); mass spectral mole wt 576, calcd for $C_{21}H_{19}I_2O_3$, 576.

Cyclization of 36 to Give Alnusone Dimethyl Ether (28). A mixture of tetrakis(triphenylphosphine)nickel(0) (0.20 g, 0.18 mmol), 12.5 mL of DMF, and diiodide **36** (68 mg, 0.12 mmol) was stirred at 25 °C for 20 min and at 50 °C for 40 h. Then it was partitioned between ether and water, and from the ether solution was isolated a yellow oil. Preparative layer chromatography (2×, silica gel, dichloromethane) provided a major component of R_f = 0.25, 40 mg, as a colorless solid, 52% yield. Recrystallization from ether afforded the analytical sample: 30 mg, 40% yield; mp 150–151 °C; ^{1}H NMR ($CDCl_3$) δ 2.2–3.35 (m, 8 H), 3.82 (s, 6 H), 6.35 (d, J = 16 Hz, 1 H), 6.7–7.3 (m, 7 H); IR ($CHCl_3$): 1700 (s), 1625 (s), 1510 (s), 1270 (s), 1210 (s), 1130 (m), 1200 (m), 1030 (m) cm^{-1}; mass spectral mol wt 322, calcd 322.

Anal. Calcd for $C_{21}H_{22}O_3$: C, 78.23; H, 6.87. Found: C, 78.10; H, 6.87.

Conversion of Alnusone (27) to the Dimethyl Ether (28). A sample of natural alnusone (**27**)[40] (10 mg, 0.034 mmol) was dissolved in 3 mL of acetone containing potassium carbonate (0.20 g, 0.15 mmol) and methyl iodide (2 mL). The suspension was stirred at 25 °C for 2 days and then filtered. From the filtrate was isolated alnusone dimethyl ether (**28**) as a colorless solid, 10 mg. This sample was identical with that obtained from the nickel-promoted cyclization (^{1}H NMR, IR, mass spectra, analytical TLC).

Attempted Demethylation of Alnusone Dimethyl Ether (28). A series of experiments was carried out in a failed effort to obtain alnusone (**27**) from the dimethyl ether (**28**). A summary is presented here.

(a) The dimethyl ether (**28**) dissolved in dichloromethane was treated with an equimolar amount of boron tribromide.[52] After 25 min at 25

°C, water was added and the usual aqueous extraction procedure led to a crude product which contained no aromatic methyl ether (^{1}H NMR) and no alnusone (TLC). Shorter reaction times led to incomplete reaction but no detectable alnusone.

(b) A sample of the dimethyl ether (0.031 mmol) was heated at reflux in 2.5 mL of 48% aqueous hydrobromic acid. After the usual isolation procedures, the starting alnusone dimethyl ether was recovered (>90%) in high purity (^{1}H NMR, TLC).

(c) A sample of the dimethyl ether (0.031 mmol) and sodium iodide (0.10 g, 0.15 mmol) in 2.5 mL of acetic acid was heated at reflux for 4 h. The usual isolation procedures produced 8.0 mg of alnusone dimethyl ether (80% recovery) of high purity.

(d) A sample of the dimethyl ether (8 mg) and sodium iodide (0.20 g, 1.2 mmol) in 1.0 mL of HMPA was stirred at 90 °C for 10 h under argon. The usual isolation procedures produced recovered alnusone dimethyl ether. A similar experiment carried out in HMPA at reflux for 10 h led to recovered dimethyl ether, unidentified products, and no detectable alnusone (TLC).

(e) A mixture of the dimethyl ether (5 mg, 0.015 mmol), quinuclidine (4 gm, 0.36 mmol), and 2 mL of benzene was heated at reflux for 18 h under argon. The usual isolation procedures produced recovered starting alnusone dimethyl ether.

(f) A mixture of alnusone dimethyl ether (2 mg), sodium dodecylmercaptide (0.1 g), and HMPA (0.75 mL) was heated at 80 °C for 12 h. The usual isolation procedures afforded only unreacted starting material.

(g) A sample of alnusone dimethyl ether (5 mL) was dissolved in 1.5 mL of 50% aqueous hydroiodic acid and heated at reflux for 4 h. The usual isolation procedures afforded a crude product mixture which contained no aromatic methyl ethers (^{1}H NMR) and no alnusone (TLC).

Characterization of the Methoxymethyl Ether Series of Intermediates in the Alnusone Synthesis. A series of procedures exactly parallel with that described immediately above (starting with **30**) was carried out with a methoxymethyl group in place of the methyl unit on the phenolic hydroxyl groups. Characterization data and significant differences in procedures are presented here.

3-(4-(Methoxymethoxy)phenyl)-1-propanol: ^{1}H NMR ($CDCl_3$) δ 1.55–2.17 (m, 2 H), 2.60 (m, 2 H), 3.45 (s, 3 H), 3.30–3.86 (m, 2 H), 5.15 (s, 2 H), 7.00 (AA'BB', 4 H); IR (neat) 3610–3030 (m), 1613 (m), 1585 (w), 1510 (s), 1235 (s) cm^{-1}; bp 126–129 °C (0.1 torr).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.06; H, 8.10.

3-(4-(Methoxymethoxy)phenyl)propanal (37): bp 113–116 °C (0.1 torr); ^{1}H NMR ($CDCl_3$) δ 2.40–3.00 (m, 4 H), 3.35 (s, 3 H), 4.99 (s, 2 H), 6.94 (AA'BB', 4 H), 9.81 (br s, 1 H); IR (neat) 1720 (s), 1615 (m), 1585 (w), 1515 (s), 1230 (s) cm^{-1}; mass spectral mol wt 194.230, calcd for $C_{11}H_{14}O_3$ 194.231.

3-(4-(Methoxymethoxy)phenyl)-1-propene Epoxide (39): short-path distillation, 95–120 °C (0.03 torr); ^{1}H NMR ($CDCl_3$) δ 1.56–1.98 (m, 2 H), 2.32–3.08 (m, 5 H), 3.46 (s, 3 H), 5.13 (s, 2 H), 7.02 (AA'BB', 4 H). IR (neat) 1640 (m), 1610 (w), 1535 (s), 1230 (s), 1195 (m) cm^{-1}.

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.11; H, 7.74. Found: C, 68.80; H, 7.58.

1-[3-(4-(Methoxymethoxy)phenyl)propyl]-1,3-dithiane (38): purified by column chromatography on silica gel by using 1:1 ether:hexane, mp ca. 25 °C; ^{1}H NMR ($CDCl_3$) δ 1.59–2.37 (m, 4 H), 2.62–2.95 (m, 6 H), 3.45 (s, 3 H), 3.95 (t, J = 7 Hz, 1 H), 5.14 (s, 2 H), 7.03 (AA'BB', 4 H); IR (neat) 1615 (w), 1590 (w), 1515 (s), 1235 (s), 1195 (m) cm^{-1}.

Anal. Calcd for $C_{14}H_{20}O_2S_2$: C, 59.12; H, 7.09; S, 22.54. Found: C, 59.08; H, 7.09; S, 22.51.

1,7-Bis(4-(methoxymethoxy)phenyl)-5-hydroxy-3-heptanone (40): mp 64–65 °C; ^{1}H NMR ($CDCl_3$) δ 1.35–1.93 (m, 2 H), 2.30–2.90 (m, 8 H), 3.44 (s, 6 H), 3.98 (t, J = 5.5 Hz, 1 H), 5.09 (s, 4 H), 6.70–7.20 (m, . H); IR ($CHCl_3$) 3440 (br, w), 1706 (w), 1616 (m), 1513 (s), 1229 (s), 1180 (m) cm^{-1}.

Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.66; H, 7.46. Found: C, 68.88; H, 7.24.

1,7-Bis(4-(methoxymethoxy)phenyl)-4-hepten-3-one (41): colorless oil purified by column chromatography on silica gel, 3:2 hexane:ether; ^{1}H NMR ($CDCl_3$) δ 2.30–3.00 (m, 8 H), 3.49 (s, 6 H), 5.19 (s, 4 H), 5.89–6.26 (m, 1 H), 6.50–7.33 (m, 9 H); IR ($CHCl_3$) 1690 (m), 1665 (m), 1625 (m), 1613 (m), 1510 (s) cm^{-1}.

Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.88; H, 7.29. Found: C, 71.88; H, 7.11.

1,7-Bis(3-iodo-4-(methoxymethoxy)phenyl)-4-hepten-3-one (42). Pale yellow oil purified by column chromatography (silica gel, 2:3 ether:hexane); ^{1}H NMR ($CDCl_3$) δ 2.35–3.08 (m, 8 H), 3.53 (s, 6 H), 5.28 (s, 4 H), 5.87–6.30 (m, 1 H), 6.50–7.35 (m, 6 H), 7.53 (br s, 1 H); IR ($CHCl_3$) 1725 (w), 1700 (m), 1675 (m), 1640 (m), 1610 (w), 1575 (w) cm^{-1}; mass spectral mol wt 636, calcd for $C_{23}H_{26}I_2O_5$ 636.

Bis(*O*-methoxymethyl)alnusone (29): crystals from ethyl acetate; mp 167–169 °C; ^{1}H NMR ($CDCl_3$) δ 2.20–3.40 (br m, 8 H), 3.47 (s, 6 H), 5.14 (s, 4 H), 6.15–7.22 (m, 8 H); IR ($CDCl_3$) 1695 (m), 1615 (s), 1505 (s), 1260 (m), 1230 (s), 1150 (s) cm^{-1}; mass spectral mol wt 382, calcd 382.

Anal. Calcd for $C_{23}H_{26}O_5$: C, 72.23; H, 6.81. Found: C, 72.05; H, 6.74.

Conversion of 29 to Alnusone (27). The bis(methoxymethyl) ether **27** (22 mg, 0.057 mmol) was added to 2 mL of 1:1 acetic acid:water containing 0.011 mL of sulfuric acid. The heterogeneous mixture was heated at reflux for 12 min, cooled, and treated with sodium bicarbonate solution to pH 8, and then extracted with chloroform. From the chloroform was obtained a yellow oil, 15 mg. Purification by preparative layer chromatography (silica gel, ether) afforded a colorless solid, 12 mg (72% yield), mp 252–254 °C (lit.[24a] mp 253–255 °C), which was in ^{1}H NMR, IR, and TLC properties identical with those of the natural sample.

Preparation of 6-Bromopiperonyl Alcohol-*O*-*d* (49). A sample of 6-bromopiperonyl alcohol (**43**) was dissolved in dichloromethane, and the solution was shaken vigorously with D_2O (>99.9% D) at 25 °C. The dichloromethane layer was separated and shaken vigorously with another portion of D_2O. Then the dichloromethane layer was dried over anhydrous magnesium sulfate and concentrated by rotary evaporation. The residue showed an ^{1}H NMR spectrum ($CDCl_3$) identical with that of 6-bromopiperonyl alcohol, except for an abnormally small signal due to -OH (-OD). Careful integration determined that the hydroxyl group was 60 ± 5% labeled with deuterium. Mass spectral analysis showed the presence of 54% d_1 and 46% d_0. Repeated attempts to increase the percent labeling failed.

Reaction of 6-Bromopiperonyl Alcohol-*O*-*d* (49) with Ni(COD)$_2$. Under the general conditions of biaryl formation [Ni(COD)$_2$/DMF], a mixture of labeled and unlabeled piperonyl alcohol was obtained (**50**), in 59% yield. Integration of the ^{1}H NMR spectrum, comparing the $-OCH_2O-$ signal with the C-6 proton signal, indicated the presence of 32 ± 4% deuterium at C-6. Mass spectral analysis showed 2% d_2, 40% d_1, and 58% d_0.

Preparation of 6-Bromopiperonyl Methyl Ether α,α-Dideuterio (51). Piperonylic acid (Aldrich Chem. Co.) was reduced to piperonyl alcohol α,α-dideuterio by using lithium aluminum deuteride (>99% D, Ventron). Then bromination and conversion to the methyl ether (as for the unlabeled analogue, see supplementary material) produced a colorless oil, in chromatographic properties identical with 6-bromopiperonyl methyl ether. The ^{1}H NMR ($CDCl_3$) showed no detectable signal at δ 4.44, indicating >95% deuterium at the α-position. Mass spectral analysis: 94% d_2, 3% d_1, 3% d_0.

Reaction of 6-Bromopiperonyl Methyl Ether α,α-Dideuterio (51) with Ni(COD)$_2$. As reported in the supplementary material for the unlabeled analogue, **51** was allowed to react with Ni(COD)$_2$ in DMF. Obtained was the biaryl (77% yield) and reduction product **52** (8%) isolated by preparative layer chromatography. Careful integration of the signal at δ 4.50 against the singlet due to the methylenedioxy group (δ 6.00) indicated the presence of 29% deuterium above natural abundance.

Reaction of Ni(0) with Aryl Halides in the Presence of Acid. General Procedure for Table V. A 100-mL Schlenk flask[41] was placed under argon and a sample of Ni(COD)$_2$ was transferred in under a flow of argon. The vessel was cooled at -78 °C and the other reactants, solvents, and ligands were added. The system was again evacuated and filled with argon and then warmed quickly to the specified temperature. After the specified reaction time (Table V), the solution (usually green) was partitioned between ether and 1 M hydrochloric acid. From the ether solution was obtained the crude product which was analyzed for the reduction product by quantitative GLPC by using a pure sample of the expected product for calibration. The reduction product was then isolated and fully characterized by comparison of spectral data (^{1}H NMR, IR) with those of a sample from alternative synthesis or commercial sources.

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Supplementary Material Available: Experimental procedures and characterization data for compounds in Tables I and IV and compounds **9**, **21**, **22**, and **23** (X = Br, Y = I) (17 pages). Ordering information is given on any current masthead page.

(52) F. L. Benton and T. E. Dillon, *J. Am. Chem. Soc.*, **64**, 1128 (1942).