THE ULLMANN SYNTHESIS OF BIARYLS, 1945–1963

PAUL E. FANTA

Department of Chemistry, Illinois Institute of Technology, Chicago 16, Illinois

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I. INTRODUCTION

The formation of a biaryl by the condensation of two molecules of an aromatic halide in the presence of finely divided copper is known as the Ullmann reaction. The previous review of this useful preparative procedure covered the literature from the time of the discovery of the reaction by Ullmann (156) up to 1944 (91). In recent years the reaction has enjoyed continued use; for example, in the elucidation of structure of natural products and the mechanisms of organic reactions, in the synthesis of biologically active substances, and in the preparation of biaryls for use in stereochemical studies. The objective of the present review is to supplement, but not to duplicate, any of the material in the earlier review.

II. NATURE AND SCOPE OF THE REACTION

A. THE AROMATIC HALIDE

It has long been known that the reactivity of aryl halides with copper, as measured by the temperature required to initiate the reaction or by the yield of biaryl obtained, is greatly dependent on the structure of the halide. Generalizations about these structural effects, drawn from the earlier literature, were presented in some detail in the previous review. The more recent work supports these conclusions, with some significant modifications.

The results of a study of the Ullmann reaction of the nine *o*-, *m*-, and *p*-chloro-, bromo-, and iodonitrobenzenes are presented in Table I. According to these data, the order of reactivity of the halogens is I > Br > Cl, and the activating effect of the nitro group is *o* > *p* > *m* (74).

Forrest (97) conducted a careful study of the comparative reactivities of 27 halobenzenes with copper. After treatment with copper bronze for 1.5 hr. at 190–195°, the extent of reaction of each compound was determined from three independent measurements: (1) copper halide formed, (2) aryl halide recovered by fractional distillation, (3) biaryl formed. For all but one compound, the extent of reaction as measured by the first and second analytical procedures agreed within 5%. The value obtained by isolation of biaryl was frequently lower, due to difficulties in isolation. These data provide the most coherent basis for the formulation of generalizations regarding the effect of substituents on the Ullmann reaction of halobenzenes.

TABLE I

PERCENTAGE YIELDS OF DINITROBIPHENYLS FROM THE REACTION OF NITROHALOBENZENES WITH COPPER FOR 40 MIN. AT 200–210°

	ortho	*para*	*meta*
I	65	54	36
Br	64	36	15
Cl	40	0	0

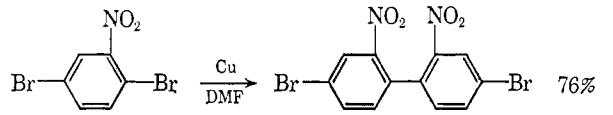
In the earlier review, it was proposed that substituents in the aromatic nucleus which have an effect on the Ullmann reaction of halogenated benzene derivatives fall into four categories. The more recent work requires some modification of these generalizations.

1. *Activating Groups*

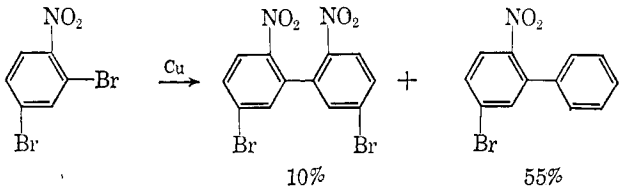
The activating effect of strongly electronegative substituents such as the nitro and carbomethoxyl groups is predominantly at the *ortho* position. For example, whereas *o*-iodonitrobenzene is one of the most reactive aryl halides known in the Ullmann reaction (192), *m*-

and *p*-iodonitrobenzene are hardly more reactive than iodobenzene. The reactivity of *o*-chloronitrobenzene is not significantly enhanced by the presence of an additional nitro group in the *para* position, as in 2,4-dinitrochlorobenzene (97).

A good yield of a single biaryl was obtained from 2,5-dibromonitrobenzene, showing that the bromine atom *meta* to the nitro group is unreactive compared to the *o*-bromine atom (66).



Treatment of a mixture of 2,4-dibromonitrobenzene and iodobenzene with copper gave products resulting only from the reaction of the *o*-bromine; the bromine atom in the *para* position was unreactive (97).



2. *Deactivating Groups*

The hypothesis that since electronegative groups are activating, electropositive groups should be deactivating (91) is not supported by the evidence provided by Forrest (97). Further substitution of iodobenzene by chloro, methyl, or methoxy groups *increases* the reactivity of the halogen, particularly in the *meta* and *para* positions. Examples of bromo- or iodobenzenes which are highly substituted by electropositive groups and give good yields of biphenyls are (substituents and yield are given): 2,6-dimethoxy-, 47%; 2,4,6-trimethoxy-, 64%; 2,3,4,5-tetramethoxy-, 69%; 2,4-dimethoxy-6-methyl-, 90%; 2,6-dimethoxy-4-methyl-, 88%; 2,4-dimethoxy-3,5-dimethyl-, 86%; 3,4-dimethoxy-2,-6-dimethyl-, 63%. Literature references and further examples may be found in Table II.

Conclusions about the effect of "activating groups" are further complicated by the fact that the true rate of the aryl halide-copper reaction is not necessarily measured by the analysis of the products (97). Since the reaction must occur at the metallic surface, a particular type of "activated" compound may conceivably owe its reactivity in part to favorable solvent properties for the copper halide or other reaction products which are formed at the interface.

3. *Inhibiting Groups*

These are defined as those substituents which decrease the yield of biaryl by providing an alternative reaction path for the aryl halide. A quantitative evaluation of the effectiveness of such groups is provided by observations of the influence of diluents on the Ullmann reaction (97). The study was conducted by heating iodobenzene with copper powder at 195° for a fixed period of time (usually 5 hr.), first alone and then in the presence of added substances containing different functional groups. For each reaction, the product was analyzed for percentage yield of copper halide and percentage yield of biaryl. Phenols and aromatic primary amines completely prevented the formation of biaryl and also greatly decreased the formation of copper halide. Addition of benzoic acid also eliminated biaryl formation but increased the yield of copper halide. The treatment of reactive nitrohaloarenes with benzoic acid and copper powder at 200° has been described as a useful dehalogenation procedure (216). Satisfactory yields of dehalogenated products were obtained from haloarenes containing a chlorine or bromine in a position adjacent to a nitro group, or an iodine *ortho*, *meta*, or *para* to a nitro group (217).

Although *o*-bromobenzoic acid reacts rapidly with copper at 160° to give only cuprous benzoate and cuprous bromide, treatment of the potassium salt of the acid with copper in the presence of a little water gives diphenic acid in 43% yield (124). As a protective group for the carboxylic acid, the potassium salt is much inferior to the ester, since dimethyl diphenate is obtained in 82% yield by the conventional Ullmann reaction of methyl *o*-iodobenzoate.

Esterification is a useful method for the protection of the sulfonic acid group. For example, whereas a 12% yield of biaryl was obtained from the reaction of sodium *o*-iodobenzenesulfonate with copper powder in dilute, aqueous copper sulfate solution, an 81% yield was obtained from the reaction of the corresponding phenyl ester with copper in the usual way (5).

Certain *m*-dinitroaryl halides also undergo side reactions which significantly decrease the yield of desired biaryl. The most thoroughly investigated example of this effect is the reaction of 2,4-dinitrochlorobenzene with iodobenzene, which gives an abnormal biaryl and a triphenylamine derivative in addition to the expected biaryl (97).

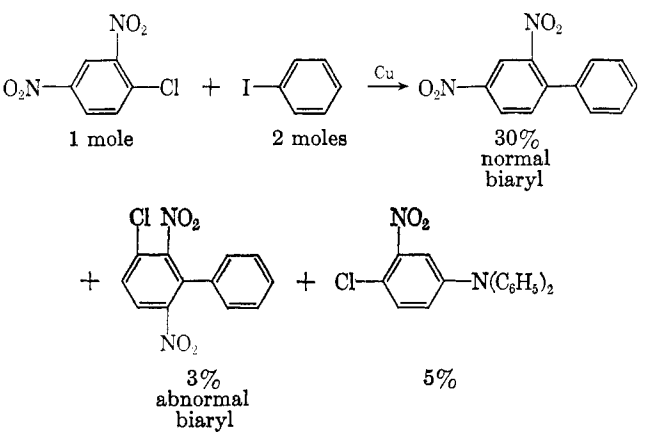


TABLE II
SYMMETRICAL BIARYLS PREPARED BY THE REACTION $2ArX \xrightarrow{Cu} ArAr$

Substituents in Ar	X	Temp., °C.	Special conditions	Yield, %	Reference
Ar = phenyl					
None	I		Reflux	78	97
4-Fluoro	I	220	Reflux		233
2,3,4,5,6-Pentafluoro	Br, I	200–290	Sealed tube	91	169, 189, 190
2-Chloro	I	260		39	172
2-Nitro	Cl	245	Sand	71	160, 251
	I	60		99	49, 111, 192
2-Fluoro-4-nitro	I	218			93
2,4-Difluoro-6-nitro	I	260		75	49
2-Chloro-4-nitro	I	210		43	149
2-Bromo-4-nitro	I	210		23	149
4-Bromo-2-nitro	Br		Dimethylformamide	76	68
5-Bromo-2-nitro	Br	195			97
	I				54, 164
2,6-Dibromo-4-nitro	I	220	Sand	30	51
2,3-Dinitro	I		*p*-Nitrotoluene	53	81
2,6-Dinitro	Cl		Dimethylformamide	51	37, 219
2,4,6-Trinitro	Cl				59
2-Methyl	I	260		65	114, 201
2-Trifluoromethyl	I		Reflux	75	186
3-Trifluoromethyl	I		Reflux	72	186
4-Trifluoromethyl	I		Reflux	41	186
2-Trifluoromethyl-4-nitro	I	300		17	185
3-Trifluoromethyl-4-nitro	I	300		35	185
4-Trifluoromethyl-2-nitro	Cl	165		30	36, 198
3-Chloro-4-methyl	I	220		90	26
5-Chloro-2-methyl	I	290		50	205
2-Methyl-4-nitro	I	280	Sand	25	48, 50
2-Methyl-5-nitro	I	250			205
2-Methyl-6-nitro	Br	280		67	78
	I	200		79	48
3-Methyl-2-nitro	Br	260		1	151
4-Methyl-2-nitro	I	180	Sand	46	48
5-Methyl-2-nitro	Br	235		73	196
2-Bromo-4-methyl-6-nitro	I		Dimethylformamide	58	67, 68
2-Methyl-4,6-dinitro	Cl	230		52	223
2,3-Dimethyl	I	150		45	168
2,5-Di(trifluoromethyl)	I	220	Sand	41	199
3,5-Di(trifluoromethyl)	I	220		30	199
2,4-Di(trifluoromethyl)-6-nitro	Cl		Reflux	Low	36
2-Ethyl	I	240		60	90
4-Ethyl	I				90
4-Isopropyl	I	270		79	90
2-*t*-Butyl	I	235			144
2,6-Dichloro-4-methoxy	I		Sealed tube	79	110
2,6-Dichloro-4-ethoxy	I	190		63	110
2-Methoxy-4-nitro	I	230		50	148
2-Methoxy-3,5-dinitro	I		Nitrobenzene		165
2-Methoxy-3,4-dimethyl	I	260		59	53
2-Methoxy-4,5-dimethyl	I	260		69	53
2,5-Dimethoxy	I	260		90	40, 45
2,6-Dimethoxy	Br	260		47	146
3,4-Dimethoxy	I	235	CO_2 atm.	77	197, 244
3,4-Diethoxy	Br	250		3	103
3,5-Dimethoxy	I	275		70	136, 195
2-Bromo-4,5-dimethoxy	I	230	Nitrobenzene	30	19
2-Chloro-4,6-dimethoxy	I	190		89	110
2,3-Dichloro-5,6-dimethoxy	I	350		30	46
2,4-Dimethoxy-6-methyl	I	200		90	166
2,6-Dimethoxy-4-methyl	Br	290		88	128
	I				1
2-Ethoxy-6-methoxy-4-methyl	Br	290		63	128

TABLE II (*Continued*)

Substituents in Ar	X	Temp., °C.	Special conditions	Yield, %	Reference
4,5-Dimethoxy-2-methyl	I	210		55	71
2,4-Dimethoxy-3,5-dimethyl	I	220		86	22
3,4-Dimethoxy-2,6-dimethyl	I	220		63	22
3-Ethyl-2,4-dimethoxy	I	254			83
2,4-Dimethoxy-6-propyl	I	220	Sealed tube	17	213
5-Cyclohexyl-2,4-dimethoxy	I	220	Sealed tube		100
2,3,4-Trimethoxy	I	270			21, 112
2,4,6-Trimethoxy	I	270		64	194
3,4,5-Trimethoxy	I	270			112
2,3,4,5-Tetramethoxy	I	220		69	21
2-Formyl	I		Dimethylformamide	65	9
2-Formyl-5-nitro	I		Dimethylformamide	65	9
2-Formyl-5-methyl	I	220		50	9
5-Formyl-2,3-dimethoxy	I	250		65	173
6-Formyl-2,3-dimethoxy	Br	230	Sealed tube		138
	I	250		45	173
2-Formyl-4,5-methylenedioxy	I	230	Sealed tube		128
2-Acetyl	I		Dimethylformamide	59	10
4-Acetyl-2-nitro	I	165		22	163
2-Propionyl	I		Dimethylformamide	66	10
2-Benzoyl	Br	360			242
	I		Dimethylformamide	76	10
4-Benzoyl-2-methyl	I	230		77	162
2-Benzoyl-4,5-diethoxy	Br		Dimethylformamide	28	103
2-Mesitoyl	Br	210		95	101, 102
2-Duroyl	Br	250		67	102
4-Carbomethoxy	I	280			116
4-Bromo-2-carbomethoxy	I	220		75	224
2-Carbomethoxy-6-nitro	I	165		79	121, 125
5-Carbomethoxy-2-nitro	Br	205	Nitrobenzene	81	196
4-Carbomethoxy-2,6-dinitro	Cl				158
4-Carbomethoxy-2-methyl-6-nitro	Br	230		70	159
3-Carbomethoxy-6-isopropyl	I	275		81	90
2-*t*-Butyl-5-carbomethoxy	I	235		62	144
2-Carbomethoxy-4,5,6-trimethyl	Br	250			139
2-Carbomethoxy-4-methoxy	I	300			99
5-Carbomethoxy-2-methoxy	Br	250	Sealed tube	7	191
5-(β-Carbomethoxyethyl)-2-methoxy	I	285		58	200
2-Carbomethoxy-4-methoxy-3-methyl	Br	250	2,4-Dimethylsulfolane	85	23
2-Carbomethoxymethyl-4,5-dimethoxy	I	220		38	71
6-Carbomethoxy-2,3-dimethoxy	Br	235	Sealed tube		138
2-Carbomethoxy-4,5-methylenedioxy	I	230	Sealed tube		127
6-Carbomethoxy-2,3,4-trimethoxy	Br		Dimethylformamide, reflux	40	113, 117, 139
2-(β-Carbomethoxyethyl)-4,5,6-trimethoxy	I	270			99
2-Phenylsulfonate	I	210		81	5
4,6-Dimethyl-2-phenylsulfonate	I	180		80	6
2-Phenyl	I			69	65
3-Phenyl	I	260	Sand	83	51
2-Nitro-6-phenyl	I	215			202
2-Methoxy-5-phenyl	I	260		59	32
2-Methyl-4-(trimethyl-*p*-terphenylyl)	I	270		20	137
4-(*p*-Biphenylyl)	I	280		40	175
Ar = 1-naphthyl					
2-Nitro	I		Dimethylformamide	77	37
4-Bromo-2-nitro	I			5	37
2-Nitro-5,6,7,8-tetrahydro	I		Dimethylformamide	23	37
4-Methoxy	I	230			82
2-Carbomethoxy	Br	280		87	11, 31, 115
5-Carbomethoxy-2,3,4-trimethoxy	I	275			119
2-Phenylsulfonate	I	300		83	7
Ar = 2-naphthyl					
1-Nitro	I			80	37
3-Nitro	I	135		31	72, 73
3-Nitro-5,6,7,8-tetrahydro	I	140		72	73, 237

TABLE II *Continued*)

Substituents in Ar	X	Temp., °C.	Special conditions	Yield, %	Reference
1-Methyl	I				132
4,8-Dimethoxy-3-methyl	I	210		45	150
1-Phenylsulfonate	I	210		95	4
Ar = 1-anthraquinolyl					
None	Cl				209
2-Methyl	Br	215	Naphthalene		80
	I		Nitrobenzene	50	29
3-Methyl	Br		Nitrobenzene		30
2-Methoxy	I		Naphthalene	80	39
4-Methoxy-2-methyl	Cl		Naphthalene	40	38, 43
4-Methoxy-3-methyl	Cl		Naphthalene	60	38, 43
2,4-Dimethoxy	Br		Naphthalene	58	214
4,5-Dimethoxy	I		CO_2 atm.	87	44
4,5,7-Trimethoxy-2-methyl	Br	240	Naphthalene	90	41–43
2-Amino	Cl		Structure uncertain		154
4-, 5-, or 8-Benzamido	Cl		Dimethylformamide	90	63
Ar = other carbocyclic groups					
Ferrocenyl	I	60–160	Sealed tube or N_2 atm.	97	184, 192, 193
6-Isopropyl-3-tropolonyl	I		Pyridine		176
2-Fluorononyl	I	230		31	24
10-Nitro-9-phenanthryl	Br			5	37
10-Carbomethoxy-9-phenanthryl	Br	265		80	75
3-Pyrenyl	Br	290			3
6-*meso*-Benzanthronyl					35
Oxygen heterocyclics					
1-Dibenzo-*p*-dioxinyl	I	250		22	108
2-Dibenzo-*p*-dioxinyl	I	250		22	108
Various flavonyls					61, 62, 133, 167, 212
Various coumarinyls					143
Various chromonyls					212
Sulfur heterocyclics					
Ar = 2-thienyl					
None	I		Xylene	70	52, 211, 231
3-Nitro	Br			74	52
5-Nitro	I			39	52, 147
3,5-Dinitro	Cl	220		4	130
	I		Xylene	78	52
3-Methyl	I				231
5-Methyl	I				231
5-*t*-Butyl	I	200		80	222
5-Acetyl-3-nitro	Cl	215		39	130
3-Carbomethoxy	Br	250		24	181
5-Carbomethoxy-3-nitro	Cl	225		53	130
4-Carbomethoxy-2,5-dimethyl	I	260		35	130
Ar = 3-thienyl					
None	I		Dimethylformamide	67	248
5-Methyl-2,4-dinitro	I	155		29	130
4-Carbomethoxy-2,5-dimethyl	Br	280		35	130, 131
Other sulfur heterocyclics					
2-Benzothienyl	I	280		17	210
4-Dibenzothienyl	I	260		30	109
Nitrogen heterocyclics					
Ar = 2-pyridyl					
None	Br	180	Cymene	60	105
5-Chloro	Br	225		8	55
5-Bromo	Br	225		2	55
5-Nitro	I	180		2	55
3-Methyl	Br	240		40	55
4-Methyl	Br	240		33	55
4-Ethyl	Br	220		25	57
4-Phenyl	Br	250	Biphenyl	18	57
Other nitrogen heterocyclics					
2-Methyl-4-pyridyl	I	210		52	188
2-Butyl-6-methyl-4-pyrimidyl	Cl		Cumene		250

TABLE II (*Continued*)

Substituents in Ar	X	Temp., °C.	Special conditions	Yield, %	Reference
2-Benzyl-6-methyl-4-pyrimidyl	I		Cumene		250
8-Ethyl-2-quinolyl	Br	220		3	58
6-Chloro-5-quinolyl	I		Nitrobenzene		123
6-Methoxy-8-quinolyl	I				187
1-Isoquinolyl	Br	230		17	56
3-Isoquinolyl	Br	270		13	56

4. *Steric Effects*

Based on a limited number of observations, it was proposed in the earlier review that the relative hindrance of biaryl formation by bulky groups in positions adjacent to the halogen is the same as the effect of such groups on the restriction of rotation in the resolvable biaryls. The evidence obtained more recently does not provide support for this hypothesis. As can be seen by inspection of Table II, a variety of 2,6-disubstituted halobenzenes gave good yields in the Ullmann reaction. No correlation between size of *ortho* substituent and yield of biaryl can be discerned. The difficulty of generalizing observations about steric effects is illustrated by the observation that although 1-iodo-2-methylnaphthalene gave no biaryl in an attempted Ullmann reaction, methyl 2-bromonaphthoate gave an excellent yield (11), and unsymmetrical biaryls I and II were obtained in respectable yields by the reactions of the corresponding iodomethylnaphthalenes with *o*-bromonitrobenzene (98, 227).

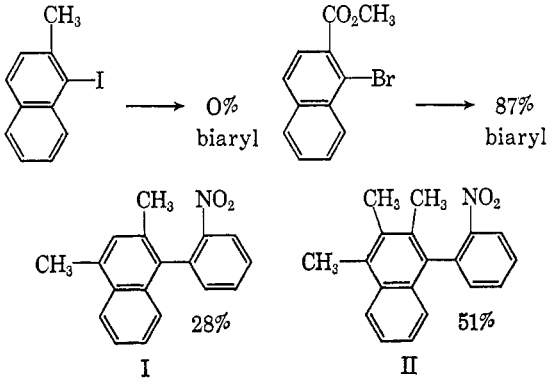


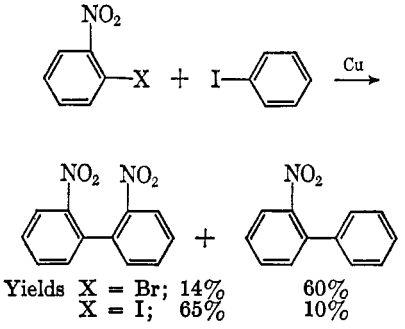
Table II includes all symmetrical biaryls prepared by the Ullmann reaction as found by a systematic search of the literature through *Chemical Abstracts*, Jan., 1945 to June, 1963. Also included are some earlier examples which were overlooked in the previous review. Compounds are listed in an order similar to the Beilstein system; aryl nuclei are in the order: phenyl, naphthyl, anthraquinolyl, other carbocyclics, heterocyclics; substituents are in the order: halogen, nitro, alkyl, alkoxyl, carbonyl, carbomethoxyl, sulfonate, aryl.

B. SYNTHESIS OF UNSYMMETRICAL BIARYLS

In the earlier review, some generalizations were developed regarding the optimum conditions for preparation of unsymmetrical biaryls. It was suggested that the selection of aryl halides of nearly equal reactivity minimized the formation of the symmetrical biaryls, and thus increased the yield of the desired product. Many further examples of the preparation of unsymmetrical biaryls are recorded in Table III, and systematic studies require modification of the earlier generalizations. Forrest (97) has shown that an optimum yield of unsymmetrical biaryl AB is obtained when one of the aryl halides is relatively reactive (A-component) and the other is relatively unreactive (B-component).

$$AX + BX' \rightarrow AA + AB + BB$$

The A-component generally must contain at least one electronegative group, such as nitro or carbomethoxy, *ortho* to the halogen atom. Bromo compounds, and to a lesser extent, chloro compounds are most useful as A-components; the corresponding iodo derivatives undergo predominantly self-condensation with corresponding increase in the formation of the symmetrical biaryl AA. For example, *o*-bromonitrobenzene reacted with iodobenzene to give a much better yield of the unsymmetrical biaryl than was obtained from *o*-iodonitrobenzene (97).



The B components lack electronegative groups in the *ortho* positions and are usually iodo compounds, although in certain instances bromo and chloro compounds have been employed. When both aryl halides are of the B-type, the three possible biaryls are usually obtained in roughly equal yield. For example, the

TABLE III

UNSYMMETRICAL BIARYLS PREPARED BY THE REACTION $ArX + Ar'X' \xrightarrow{Cu} ArAr'$

Substituents in Ar	Substituents in Ar'	X	X'	Temp., °C.	Special conditions	Yield, %	Reference
Ar = phenyl	Ar' = phenyl						
2-Nitro	None	Br	I	190		60	97
3-Nitro	None	I	I	195		25	97
3-Nitro	3-Chloro	I	I	235		23	247
3-Nitro	2-Nitro	I	Br	195		35	97
4-Nitro	None	I	I	195		35	97
4-Nitro	2-Nitro	I	Br	195		35	97
4-Bromo-2-nitro	2-Nitro	Br	Br		Dimethylformamide		68
5-Bromo-2-nitro	None	Br	I	195		55	97
5-Bromo-2-nitro	2-Nitro	I	I				54
5-Bromo-2-nitro	3-Nitro	I	I			2	54
2-Bromo-6-nitro	2-Nitro	I	Br		Dimethylformamide		68
2,6-Dibromo-4-nitro	3-Bromo-2-iodo-5-nitro	I	Br	220	Sand	20	51
2,4-Dinitro	None	Cl	I	200		42	97
		Br	I	175		60	97
2,4-Dinitro	2-Chloro	Cl	I	195		55	97
2,4-Dinitro	3-Chloro	Cl	I	195		24	97
2,4-Dinitro	4-Chloro	Cl	I	195		30	97
2,4-Dinitro	3-Bromo	I	I	260		10	54
2,4-Dinitro	3-Nitro	Cl	Br	195		15	97
2,4-Dinitro	4-Nitro	Cl	Br	195		20	97
2,6-Dinitro	None	Cl	I	180		83	81, 97
2,6-Dinitro	2-Nitro	Cl	Cl		Nitrobenzene	37	81
5-Chloro-2,4-dinitro	None	Cl	I	195		27	97
3-Chloro-2,6-dinitro	None	Cl	I	175		48	97
3-Chloro-2,6-dinitro	2-Chloro	Cl	I	195		7	97
3-Chloro-2,6-dinitro	3-Chloro	Cl	I	195		50	97
3-Chloro-2,6-dinitro	4-Chloro	Cl	I	195		50	97
3,5-Dichloro-2,6-dinitro	None	Cl	I	195		30	97
2-Methyl	2-Nitro	I	I				153
2-Methyl	3-Nitro	I	I	270			153
2-Methyl	2,4-Dinitro	I	Br	175		55	97
2-Methyl	2,6-Dinitro	I	I	230		9	163
4-Methyl	2,4-Dinitro	I	Cl	195		33	97
		I	Br	175		50	97
4-Methyl	2,6-Dinitro	I	Cl	190		60	97
4-Methyl	3-Chloro-2,6-dinitro	I	Cl	195		15	97
4-Methyl	5-Chloro-2,4-dinitro	I	Cl	195		8	97
4-Methyl	3,5-Dichloro-2,6-dinitro	I	Cl	195		15	97
2-Trifluoromethyl	2-Nitro	I	Br	270		14	96
2-Methyl-5-nitro	3-Nitro	I	I	250			205
2-Methyl-6-nitro	2-Nitro	I	I	200	Nitrobenzene	26	18
2-Methyl-6-nitro	2-Methyl-4-nitro	Br	I			16	48
3-Methyl-2-nitro	2-Methyl	Br	I	270			151
4-Methyl-2-nitro	2-Nitro	I	I	180	Nitrobenzene	54	18
4-Methyl-2-nitro	4-Methyl	Br	I	175		40	97
4-Methyl-2-nitro	2-Methyl-4-nitro	I	I	320		35	48
4-Methyl-2-nitro	2-Methyl-6-nitro	I	I	200		32	48
2-Bromo-4-methyl-6-nitro	2-Nitro	I	Br		Dimethylformamide		68
4-Methyl-3,5-dinitro	None	Cl	I	185		45	97
5-Methyl-2,4-dinitro	None	Cl	I	195		13	97
2,5-Dimethyl	2-Nitro-3-methyl	I	Br				152
2-Methoxy	2-Nitro	I	Br	185	Nitrogen atm.	58	64, 218
2-Methoxy	2,4-Dinitro	Br	Cl	195		30	97
3-Methoxy	2-Nitro	Br	Cl	240		27	178
3-Methoxy	2,4-Dinitro	Br	Cl	195		20	97
4-Methoxy	2-Nitro	I	Cl	240		23	178
		I	Br	175		40	97
4-Methoxy	3-Nitro	I	I	235		16	142
4-Methoxy	2,4-Dinitro	Br	Cl	195		25	97
		I	Cl	195		39	97
		I	Br	175		55	97

TABLE III (*Continued*)

Substituents in Ar	Substituents in Ar′	X	X′	Temp., °C.	Special conditions	Yield, %	Reference
4-Methoxy	2,6-Dinitro	I	Cl	190		75	97
4-Methoxy	3-Chloro-2,6-dinitro	I	Cl	195		25	97
4-Methoxy	5-Chloro-2,4-dinitro	I	Cl	195		31	97
4-Methoxy	3,5-Dichloro-2,6-dinitro	I	Cl	195		25	97
4-Ethoxy	2-Nitro	I	I	235	Sand		92
2-Methoxy-6-nitro	2-Nitro	I	I	200	Nitrobenzene	12	18
4-Methoxy-2-nitro	2-Nitro	I	I	200	Nitrobenzene	39	18
5-Methoxy-2,4-dinitro	None	Cl	I	195		34	97
2-Methoxy-5-methyl	4-Methyl	Br	I	245			170
2-Methoxy-6-methyl	2-Nitro	I	Br	185	Nitrogen atm.	81	218
2,3-Dimethoxy	2-Methoxy	Br	I	230		3	129
2,4-Dimethoxy	2-Nitro	I	Br		Nitrobenzene	65	87
2,6-Dimethoxy	2-Methoxy	I	I	230		47	129, 220
2,6-Dimethoxy	2,4-Dimethoxy	I	I	280		3	89, 235
3,4-Dimethoxy	2-Nitro	Br	Cl	240		25	32, 244
2,3-Dichloro-5,6-dimethoxy	None	I	I	350		19	46
4,5-Dimethoxy-2-nitro	None	Br	I	200		38	32
4,5-Dimethoxy-2-nitro	4-Nitro	Br	I	200		54	32
4,5-Dimethoxy-2-nitro	2-Methoxy	Br	I	205		50	33
2,4-Dimethoxy-6-methyl	2,6-Dimethoxy-4-methyl	I	I				1
2,4-Dimethoxy-3,5-dimethyl	3,4-Dimethoxy-2,6-dimethyl	I	I	200		15	22
4,5-Methylenedioxy-2-methyl	2-Nitro	I	Br	230		72	134
4,5-Methylenedioxy-2-methyl	3-Methyl-2-nitro	I	Br	230		50	134
2,4,6-Trimethoxy	2-Nitro	I	Br	185	Nitrogen atm.	30	218
2,4,6-Trimethoxy	2-Methoxy	Br	I	230			135
2,4,6-Trimethoxy	4-Methoxy	Br	I	230			135
2,4,6-Trimethoxy	3,5-Dimethoxy	I	I	230			195
3,4,5-Trimethoxy	2,6-Dimethoxy	I	I	230			183
3,4,5-Trimethoxy	2,3,4-Trimethoxy	I	I	270		21	70
2-Formyl-4,5-methylenedioxy	2-Nitro	Br	Br	245			134
2-Carbomethoxy	None	Br	I	190		45	97
2-Carbomethoxy	3,5-Difluoro	Cl, Br	I	210			93
2-Carbomethoxy	2-Nitro	I	Br	175		65	97, 186
2-Carbomethoxy	2-Fluoro-4-nitro	Br	I	220		43	94
2-Carbomethoxy	3-Fluoro-4-nitro	Cl, Br	I	218		30	93
2-Carbomethoxy	5-Fluoro-2-nitro	Cl, Br	I	218			93
2-Carbomethoxy	3-Methyl	I	I	260		13	120
2-Carbomethoxy	4-Methyl	I	I	260		17	120, 161
2-Carbomethoxy	2-Methyl-6-nitro	I	Br	210	Nitrobenzene	30	77
2-Carbomethoxy	2-*t*-Butyl	I	I	210			144
2-Carbomethoxy	2-Methoxy-4-nitro	Br	I	220		20	182
2-Carbomethoxy	2-Methoxy-5-nitro	Br	I	220		25	182
2-Carbomethoxy	3,4,5-Trimethoxy	Br	I				85
2-Carbomethoxy	2-Formyl-5,6-dimethoxy	I	Br	230	Sealed tube		138
2-Carbomethoxy	2-Formyl-4,5-methylenedioxy	I	Br	230	Sealed tube	7	127
3-Carbomethoxy	2-Formyl-4,5-methylenedioxy	I	Br	250		14	240
4-Carbomethoxy	2-Nitro	I	Br	190		35	97, 178
4-Carbomethoxy	4-Methoxy	I	I	235		9	13, 179
4-Carbomethoxy	4-Methoxy-2-methyl	I	I	290		9	206
4-Carbomethoxy	4-Methoxy-2-ethyl	I	I	290		7	206
4-Carbomethoxy	4-Methoxy-2-propyl	I	I	290		8	206
4-Carbomethoxy	2-Isopropyl-4-methoxy-5-methyl	I	I	280			203
4-Carbomethoxy	2,4-Dimethoxy	I	I	280		21	204
2-Carbomethoxy-4-nitro	None	Br	I	235		37	47
4-Carbomethoxy-2-nitro	None	Br	I	235		59	47
4-Carboethoxy-2-nitro	2-*t*-Butyl	Br	I	240		23	145
2-Carbomethoxy-4,6-dinitro	None	Cl	I	200		69	95
4-Carboethoxy-2-methyl	4-Methoxy	I	I	280		18	203
4-Carboethoxy-2-methyl	4-Methoxy-2-methyl	I	I	280			203
4-Carboethoxy-2-methyl	2-Ethyl-4-methoxy	I	I	280			203
4-Carbomethoxy-3-methyl	4-Methoxy	I	I	280		12	207

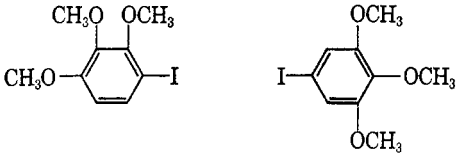
TABLE III (*Continued*)

Substituents in Ar	Substituents in Ar′	X	X′	Temp., °C.	Special conditions	Yield, %	Reference
4-Carbomethoxy-3-ethyl	2-Ethyl-4-methoxy	I	I	280		10	179
4-Carbomethoxy-3-ethyl	4-Methoxy	I	I	280		15	207
4-Carboethoxy-3-ethyl	4-Methoxy-2-methyl	I	I	280		11	208
4-Carboethoxy-3-ethyl	2,4-Dimethoxy	I	I	280		4	204
4-Carbomethoxy-3-propyl	4-Methoxy	I	I	280		16	207
5-Carbomethoxy-2-*t*-butyl	2-Nitro	I	Cl	235		7	145
5-Carbomethoxy-2-*t*-butyl	2-*t*-Butyl	I	I	220			144
4-Carboethoxy-3-ethyl-6-methyl	4-Methoxy	I	I	280		11	208
4-Carboethoxy-3-ethyl-6-methyl	4-Methoxy-2-methyl	I	I	280		6	208
4-Carbomethoxy-2,5-diethyl	4-Methoxy	I	I	280		11	180
3-Carbomethoxy-4-methoxy	None	Br	I	235		11	13
3-Carbomethoxy-4-methoxy	4-Methoxy	Br	I	235		7	13
5-Carbomethoxy-2-methoxy	2-Methoxy	I	I	235		13	13
5-Carbomethoxy-2-methoxy	2,4-Dimethoxy	I	I	280		40	87
5-Carbomethoxy-2-methoxy	3,4,5-Trimethoxy	I	I				85
2-Carbomethoxy-4,5-methylenedioxy	2-Carbomethoxy	Br	I	230	Sealed tube	10	127
2-Carbomethoxy-4,5-dimethoxy	2-Nitro	Br	Br	240		38	245
2-Carbomethoxy-4,5-dimethoxy	3-Methyl-2-nitro	Br	Br				232, 245
2-Carbomethoxy-4,5-methylenedioxy	3-Methoxy	Br	I	235			140
2-Carbomethoxy-4,5-methylenedioxy	4-Methoxy	Br	I	235			140
4-Carbomethoxy-2,5-dimethoxy	4-Methoxy	I	I	280		4	204
6-Carbomethoxy-2,3-dimethoxy	2-Formyl	Br	I	210		10	138
6-Carbomethoxy-2,3-dimethoxy	2-Carbomethoxy	Br	I	235	Sealed tube	8	138
6-Carbomethoxy-2,3-dimethoxy	3-Carbomethoxy	Br	I	235		20	138
6-Carbomethoxy-2,3-dimethoxy	2-Carbomethoxymethyl	Br	I	220	Sealed tube		138
2-Carbomethoxy-4,5,6-trimethoxy	4-Methoxy	Br	I	265		37	99, 157
2-(β-Carbomethoxyethyl)-4,5,6-trimethoxy	4-Methoxy	I	I	270			99
2-(β-Carbomethoxyethyl)-3-bromo-4,5,6-trimethoxy	4-Methoxy	I	I	260			99
2-Methylsulfonyl	2-Carbomethoxy	Br	Br	240		12	84
2-Phenylsulfonate-4,6-dimethyl	2,4-Dimethyl	I	I	190		52	7
2-Phenyl	None	I	I			40	76
2-Phenyl	2-Nitro	I	Cl	270		21	76
2-Phenyl	4-Acetyl	I	I	220		32	2
2-Phenyl	4-Benzoyl	I	Br	240	Sealed tube	6	2
2-Phenyl	2-Carbomethoxy	I	I	250		22	76
2-Carbomethoxy-4,5,6-trimethoxy-3-(6-carbomethoxy-2,3,4-trimethoxyphenyl)	6-Carbomethoxy-2,3,4-trimethoxy	Br	Br	222			113
Ar = 1-naphthyl	Ar′ = phenyl						
None	2-Nitro	I	Br	200		60	97, 98
None	2-Nitro	I	I	240		21	215
None	4-Nitro	I	Br	240		5	97
None	2,6-Dinitro	I	Cl	120		34	118
None	2-Methyl-6-nitro	I	Br	210			228
None	3-Methyl-2-nitro	I	Br	240		16	229
None	4-Methyl-2-nitro	I	Br	150		52	228
None	2-Methoxy	I	I	240			221
None	2-Methoxy-6-nitro	I	Br	250		2	118
None	3-Methoxy-2-nitro	I	Br	230		55	221
None	4-Methoxy-2-nitro	I	Br	170		50	118
None	2-Carbomethoxy-4-nitro	I	I	210			17
None	2-Carbomethoxy-6-nitro	I	Br	120			118
None	4-Carbomethoxy-2-nitro	I	Br	210		42	228
None	2-Carbomethoxy-4,6-dinitro	I	Cl	215	Nitrobenzene	42	236
None	2-Carbomethoxy-5-methyl	I	Br	210		33	17
None	2,3-Dicarbomethoxy	I	I			36	16
2-Nitro	2-Nitro	I	I	200		13	66
8-Nitr	2-Methoxy	Br	I	224		35	221

TABLE III (*Continued*)

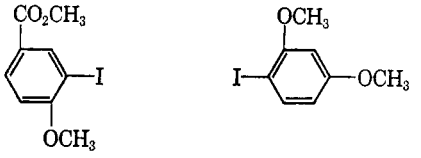
Substituents in Ar	Substituents in Ar′	X	X′	Temp., °C.	Special conditions	Yield, %	Reference
2,4-Dimethyl	2-Nitro	I	Br	270		28	98
2,3,4-Trimethyl	2-Nitro	I	Br	250		51	227
2-Methoxy	2-Nitro	I	Br	230		50	221
2-Methoxy	2-Carbomethoxy	I	I	280			76
2-Methoxy	5-Carbomethoxy-2-methoxy	I	I	235			14
3-Methoxy	2-Carbomethoxy	I	I	210		26	16
4-Methoxy	2-Nitro	I	Br	220		62	221
4-Methoxy	3-Carbomethoxy-4-methoxy	I	Br	240		8	12
4-Methoxy	5-Carbomethoxy-2-methoxy	I	I	270		8	12
6-Methoxy	3-Carbomethoxy-5-methoxy	I	Br	240		10	15
2-Carbomethoxy	3-Methyl	Br	I	200		24	17
2-Carbomethoxy	4-Methyl	Br	I	235		33	17
2-Carbomethoxy	3,5-Dimethyl	Br	I	235		20	17
2-Carbomethoxy	4-Carbomethoxy	Br	I	265		30	16
8-Carbomethoxy	2-*t*-Butyl	I	I	240		11	145
Ar and Ar′ = other aromatic groups							
2-Nitro-1-naphthyl	1-Nitro-2-naphthyl	I	I	175		40	238
1-Nitro-2-naphthyl	2-Nitrophenyl	Br	Br		Dimethylformamide	30	66, 243
4-Methoxy-1-naphthyl	1-Methoxy-2-naphthyl	I	I	240		7	82
2-Carbomethoxy-1-naphthyl	4-Methoxy-1-naphthyl	Br	I	270		20	8
10-Nitro-9-phenanthryl	2-Nitrophenyl	Br	Br	240		31	69
3-Methyl-5-fluoranthryl	2-Nitrophenyl	I	Br	200		42	25
1,2,3,4-Tetrahydro-5-fluoranthryl	2-Nitrophenyl	I	Br	200		10	25
Ferrocenyl	2-Nitrophenyl	I	I			7	192
Various flavonyls, chromonyls, and coumaryls	Phenyl						143, 167, 212
3-Nitro-2-thienyl	2-Methyl-6-nitrophenyl	Br	Br	250		9	181
5-Nitro-2-thienyl	3-Nitro-2-thienyl	I	Br		Xylene	39	52
5-Butyl-2-thienyl	2-Thienyl	I	I				230
4-Carbomethoxy-2,5-dimethyl-3-thienyl	2-Methyl-6-nitrophenyl	I	I	250		30	130, 174
5-(5-Methyl-2-thienyl)-2-thienyl	2-Thienyl	I	I				211
5-(5-Methyl-2-thienyl)-2-thienyl	5-Methyl-2-thienyl	I	I				211

reaction of an equimolar mixture of 4-iodo-1,2,3-trimethoxyiodobenzene and 5-iodo-1,2,3-trimethoxybenzene gave the following distribution of products (70).



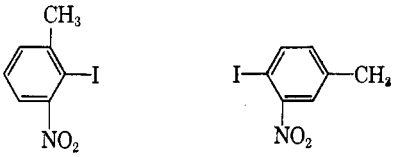
	BI	+	B′I	→	BB	+	BB′	+	B′B′
mmoles	24		24		4.5		5.1		4.5

The reaction of methyl 3-iodoanisate with 2 moles of 2,4-dimethoxyiodobenzene gave the following distribution (87).



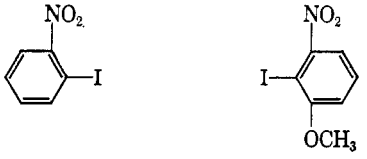
	BI	+	B′I	→	BB	+	BB′	+	B′B′
mmoles	62		124		16		24		34

The same type of product distribution is observed when both components are of a similar A-type, for example, 2-iodo-3-nitrotoluene and 4-iodo-3-nitrotoluene (48).



	AI	+	A′I	→	AA	+	AA′	+	A′A′
mmoles	72		65		10		22		9

Another such example is provided by the reaction of *o*-nitroiodobenzene and 2-iodo-3-nitroanisole (18).



	AI	+	A′I	→	AA	+	AA′	+	A′A′
mmoles	92		77		9		9		12

An exceptionally good yield of unsymmetrical biaryl is usually obtained only from the reaction of an A-component with a B-component. Out of a total of 202 examples of preparations of unsymmetrical biaryls

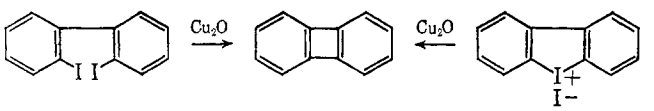
collected in Table III, 74 were obtained in yields of 30% or greater, which may be arbitrarily considered as exceptionally good. Of these, 61 or 82% can clearly be classified as reactions of a typical A-component with a B-component.

Another characteristic of such favorable mixed Ullmann reactions is that they occur at a lower temperature than that at which the B-component alone reacts with copper (97); therefore no biaryl of the type BB is formed. Operation at the lowest practical temperature for the reaction of the A-component with copper gives the best results, and the practice of raising the temperature to complete the reaction may be deleterious. Under ideal conditions, an excess of the B-component can be used and may result in an increased conversion of A-component to unsymmetrical biaryl AB. However, prolonged heating of a product containing nitro groups with excess B-component is harmful, because of the possible occurrence of the reduction–arylation reaction previously mentioned.

The literature coverage of the unsymmetrical biaryls listed in Table III is the same as described for Table II. For each entry, the aryl group Ar is the one which appears later than Ar′ according to the order of precedence used in Table II.

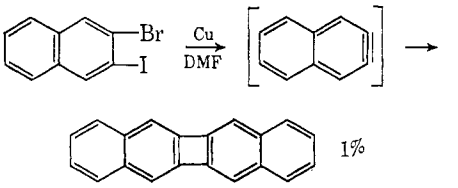
C. CYCLIZATION REACTIONS

In the earlier review, the Lothrop synthesis of biphenylene by the treatment of 2,2′-dihalobiphenyls or 2,2′-biphenyleneiodonium iodides with cuprous oxide was classified as an intramolecular Ullmann reaction. Subsequently, a variety of substituted biphenylenes were prepared by the same method (18–21). In each instance, cuprous oxide and not metallic copper was used, and it was reported that the yield obtained in the cyclization was critically dependent on the quality of the cuprous oxide used (60, 73, 237).

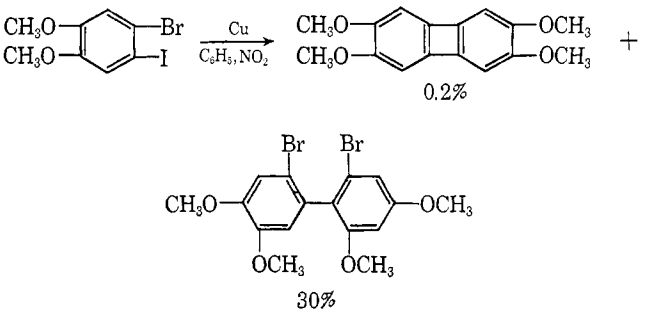


The observation that biphenylene was not obtained by heating *o*-diiodobenzene with cuprous oxide (20) further supported the view that the Lothrop biphenylene synthesis and the Ullmann biaryl synthesis are distinctly different in scope as well as mechanism.

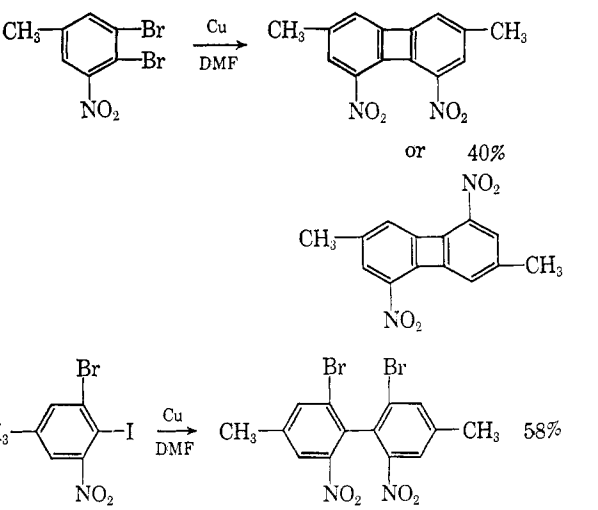
Although only tars were obtained from the reaction of 1,2- or 2,3-dibromonaphthalene with copper (27), more recently it was found that treatment of 2-bromo-3-iodonaphthalene with copper bronze in refluxing dimethylformamide gave a dibenzobiphenylene in very low yield (239). The formation and dimerization of a naphthalyne intermediate was suggested as a plausible mechanism for the reaction.



Similarly, 4-bromo-5-iodoveratrole with copper bronze in nitrobenzene gave a minute yield of a biphenylene derivative (19).



In view of these very low yields, it was surprising that 3,4-dibromo-5-nitrotoluene with copper bronze in refluxing dimethylformamide gave no biaryl but a 40% yield of a dimethyldinitrobiphenylene (67). Under the same reaction conditions, the 4-iodo analog gave a good yield of the expected biaryl and only 2% of the biphenylene. Therefore, the biaryl cannot be an intermediate in the formation of the biphenylene. These results can be interpreted by assuming that the more reactive iodo compound undergoes the Ullmann reaction much more rapidly than it forms a benzyne intermediate, whereas for the less reactive bromo compound the formation of a benzyne intermediate followed by dimerization is the predominant reaction.



D. LINEAR PRODUCTS FROM BIFUNCTIONAL HALIDES

The reaction of a mixture of a bifunctional and a monofunctional aryl halide to give a substituted terphenyl or quaterphenyl may be considered a special

TABLE IV
LINEAR PRODUCTS FROM BIFUNCTIONAL HALIDES

Bifunctional halide (mole)	Monofunctional halide (mole)	Product	Yield, %	Reference
2,6-Dibromo-4-nitroiodobenzene	2,6-Dibromo-4-nitroiodobenzene	2,6-Bis(2,6-dibromo-4-nitrophenyl)-4-nitroiodobenzene	4	51
1,5-Dibromo-2,4-dinitrobenzene (0.005)	1-Iodonaphthalene (0.015)	1,5-Di(1-naphthyl)-2,4-dinitrobenzene	40	226
2,5-Diiodohydroquinone dimethyl ether (0.009)	Iodohydroquinone dimethyl ether (0.074)	2,5-Dimethoxy-1,4-bis(2,5-dimethoxyphenyl)benzene	30	86
2,5-Diiodohydroquinone dimethyl ether (0.1)	Methyl 2-bromobenzoate (0.4)	2,5-Dimethoxy-1,4-bis(2-carbomethoxyphenyl)benzene	48	88
1,4-Diiodo-2,5-dimethoxybenzene (0.10)	*o*-Chloroiodobenzene (0.40)	2,5-Dimethoxy-1,4-bis(2-chlorophenyl)benzene	8	172
1,5-Diiodo-2,4-dimethoxybenzene	2,4-Dimethoxyiodobenzene (excess)	2,4,4′,6′,2″,4″-Hexamethoxy-*m*-terphenyl	"Good"	220
3,6-Diiodo-1,2,4,5-tetramethoxybenzene (0.025)	Methyl 2-bromobenzoate (0.100)	2,3,5,6-Tetramethoxy-1,4-bis(2-carbomethoxyphenyl)benzene	58	171
2,5-Diiodoveratraldehyde ethylene acetal (0.009)	Methyl 2-bromobenzoate (0.08)	2,5-Bis(2-carbomethoxyphenyl)-veratraldehyde ethylene acetal	35	173
4,4′-Diiodo-3,3′-dimethylbiphenyl (0.01)	Iodobenzene (0.10)	2^2,3^3-Dimethyl-*p*-quaterphenyl	28	137
4,4′-Diiodo-2,5,2′,5′-tetramethoxybiphenyl (0.008)	Iodohydroquinone dimethyl ether (0.72)	2,5,2′,5′-Tetramethoxy-4,4′-bis-(2,5-dimethoxyphenyl)biphenyl	68	86
4,4′-Diiodo-3,3′-dimethylbiphenyl	None	Polymer		104
4,4′-Dihalobiphenylsulfone	None	Polymer		241
Fluoro-, methoxy-, and methyl-substituted dihalides	None	Polymers		246

case of the unsymmetrical biaryl synthesis. Ten reported examples are presented in Table IV. Here too, an exceptionally good yield of the desired product is obtained when one of the halides is an activated type and the other an unactivated type (171). A few reported examples of the preparation of low polymers by the Ullmann reaction of dihaloarenes are also included in Table IV.

E. UNSUCCESSFUL REACTIONS

Examples of unsuccessful attempts to use the Ullmann reaction are collected in Table V. In most such cases, the starting material is recovered, or an intractable tar is formed when a higher temperature is used. Some attempted syntheses of unsymmetrical biaryls fail because only symmetrical products are formed.

III. EXPERIMENTAL CONDITIONS

Most Ullmann reactions are conducted by simply heating a mixture of the aryl halide and finely divided copper to the required temperature in an open vessel. In specific instances, various modifications of this procedure are required for optimum results.

A. THE ARYL HALIDE

Special purification of the aryl halide used in the Ullmann reaction is usually unnecessary. An exception to this generalization is the observation that extensive dehalogenation and a poor yield of biaryl was obtained from methyl 1-bromo-2-naphthoate which had been purified by recrystallization, apparently due to the retention of unidentified impurities. When the aryl

TABLE V
UNSUCCESSFUL REACTIONS

Reactants	Reference
A. Attempted syntheses of symmetrical biaryls	
2,5-Dichloro-4-iodonitrobenzene	79
2-Chloro-3,4-dinitrotoluene	223
3,5-Dibromo-4-iodoanisole	110
2,5-Dichloro-4-iodoacetanilide	79
1,2-Dibromonaphthalene	27
2,3-Dibromonaphthalene	27
1-Bromo-5-nitronaphthalene	28
1-Bromo-2-methylnaphthalene	11
1-Iodo-2-methylnaphthalene	11
1-Bromo-2-naphthaldehyde	11
Methyl 5-bromo-1-naphthoate	28
1-Chloroanthracene	29
Halogenated flavanols	62
2-Bromo-8-methylisoquinoline	58
2-Bromo-8-phenylisoquinoline	58
B. Attempted syntheses of unsymmetrical biaryls	
4-Bromo-3-nitroacetophenone and 2,6-dinitroiodobenzene	163
4-Bromopropiophenone and 2-iodo-3-nitrotoluene	163
Methyl β-(2-iodo-3,4,5-trimethoxyphenyl)propionate and methyl 5-methoxy-2-iodobenzoate	99
Iodoferrocene and iodobenzene or 2-iodobiphenyl or 1,4-diiodobenzene	192
6-Methoxy-8-iodoisoquinoline and *p*-chloronitrobenzene	187
C. Attempted ring closures	
1,2-Bis(1-bromo-2-naphthyl)ethane	115
N,N-Di[β-(2-iodophenyl)ethyl]benzenesulfonamide	71

halide was purified by vacuum distillation, an 87% yield of biaryl was obtained (11). The Ullmann coupling of 3-fluoro-4-nitroiodobenzene with an equimolar mixture of methyl *o*-chloro- and *o*-bromobenzoate gave a better yield of the unsymmetrical biaryl than either *o*-halo ester alone (93).

B. THE FINELY DIVIDED COPPER

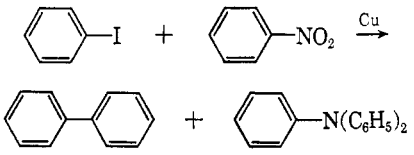
In the older as well as the more recent literature, several different forms of finely divided copper have been advocated as superior reagents for the Ullmann reaction. Unfortunately, no really systematic study of this problem has been reported. Most reactions have been conducted using the commercially available form of mechanically pulverized copper known as copper bronze, either without pretreatment (97) or after "activation" by successive washing with acetone solutions of iodine and hydrochloric acid (234).

On the other hand, it is reported that commercial "lithographic bronze" containing 0.2–0.5% fatty acids, mainly stearic, palmitic, and oleic acids, partly as the copper salts, is a superior reagent for the Ullmann reaction, since reproducible yields are obtained, and usually no unchanged iodo compounds remain from reactions conducted above 220° (172). A U. S. patent has been issued based on the claim of conducting the Ullmann reaction using "electrolytic copper milled with stearic acid" (122).

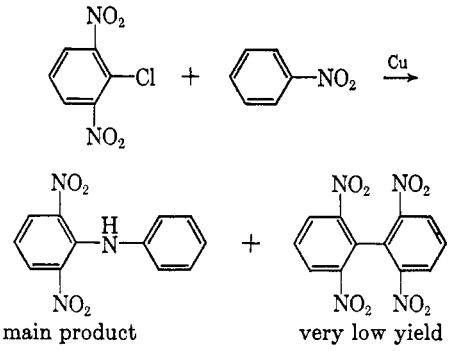
For the preparation of 2,2′-dinitrobiphenyl from *o*-iodonitrobenzene, Gore and Hughes (111) claimed that commercial samples of copper powder gave irreproducible results and that freshly precipitated copper powder obtained by the treatment of oxide-free zinc dust with aqueous copper sulfate was more effective. Using a fourfold ratio of this copper and a temperature of 190–240°, they obtained a 96% yield of the biaryl. Later, Rausch (192) obtained a 99.6% yield of 2,2′-dinitrobiphenyl from *o*-iodonitrobenzene by using a tenfold ratio of commercial copper bronze activated in the traditional way and running the reaction in an atmosphere of nitrogen for 60 hr. at 60°. This is the lowest temperature and highest yield ever recorded for an Ullmann reaction.

C. DILUENTS

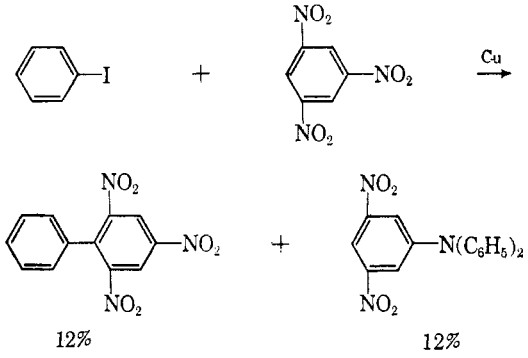
In the older literature, there are many examples of the use of diluents such as nitrobenzene and high-boiling aromatic hydrocarbons in the Ullmann reaction. It was supposed that such substances were chemically inert and served to moderate the vigorously exothermic reaction which occurs when very reactive halides are treated with copper. However, in his study of the effect of diluents, Forrest (97) found that addition of nitrobenzene to the iodobenzene–copper reaction at 195° suppressed the formation of both copper halide and biphenyl to a much greater extent than would be expected from a simple dilution effect. Furthermore, at least a small portion of the nitrobenzene reacted chemically by reduction and arylation to give triphenylamine, and similar side reactions were observed in the Ullmann reactions of other aryl halides in the presence of other mononitroaryls.



The reduction–arylation reaction was even more pronounced when 2,6-dinitrochlorobenzene was treated with copper bronze in boiling nitrobenzene solution. The main reaction product was 2,6-dinitrodiphenylamine, and the yield of biaryl was so small as to render the reaction impractical (34).



In the presence of *m*-dinitroaryls a further side reaction occurs (97). For example, the treatment of a mixture of iodobenzene and 1,3,5-trinitrobenzene with copper gave no biphenyl, but only the abnormal reaction products, 2,4,6-trinitrobiphenyl and 3,5-dinitrotriphenylamine.



In view of all these observations it seems clear that nitroaryls cannot be considered to be inert diluents for the Ullmann reaction.

The use of dimethylformamide, which has a boiling point of 153°, as a diluent in the Ullmann reaction was reported by Kornblum and Kendall (141). Better yields of biaryl have frequently been obtained by conducting the reaction for a prolonged time in refluxing

dimethylformamide, compared to the undiluted reaction at a higher temperature (9, 66, 68). The advantage of this particular diluent has been ascribed to its action as a solvent in keeping the copper surface free of copper halide, reactants, and products (37).

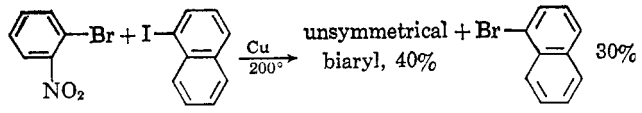
The use of dimethylformamide offers no advantage with most aryl halides which are inert or for some other reason give no biaryl at all under the usual reaction conditions (11, 141). It has been reported to be especially advantageous for the preparation of biaryls containing free aldehyde and ketone groups (9, 103), 2,2′-bithienyl (248), and 2,2′,6,6′-tetranitrobiphenyl (219) and has been mentioned in a patented procedure for the preparation of an acylaminobianthraquinolyl (63). Another convenient property of dimethylformamide is that it can usually be removed from the reaction products by simply pouring the mixture into water.

One of the disadvantages of dimethylformamide is that it seems to cause an increase in the extent of the dehalogenation reaction, ArX → ArH (37, 103, 117). In some instances this side reaction may complicate the isolation of the desired biaryl (117) or actually cause a decrease in yield compared to the usual conditions (37, 126, 176). It is also possible that dimethylformamide facilitates the halogen exchange reaction, as it has been shown that 2,5-diiodohydroquinone dimethyl ether reacts with excess cuprous chloride in boiling dimethylformamide to give a 70% yield of the corresponding chloro compound (172).

Where diluents have been used in the Ullmann reaction, they have been identified in Tables II and III. In most instances, the reaction was conducted at or near the boiling point of the diluent.

D. SIDE REACTIONS

In the preparation of certain unsymmetrical biaryls from a reactive aryl chloride or bromide and unactivated aryl iodide, the conversion of the aryl iodide to an inert chloride or bromide has been observed (97, 151, 172). The extent of the halogen-transfer reaction is usually small, but in specific instances it may be sufficient to detract significantly from the yield of desired biaryl. For example, reaction of an equimolar mixture of *o*-bromonitrobenzene and 1-iodonaphthalene at 200° gave 30% of 1-bromonaphthalene (97).



The yield of biaryl was improved either by using an excess of 1-iodonaphthalene or by conducting the reaction at a lower temperature.

The halogen exchange probably occurs by reaction of the aryl iodide with cuprous chloride or bromide, since it has been observed that 2,5-diiodohydroquinone dimethyl ether reacts with excess cuprous chloride to give a 70% yield of the corresponding chloro compound (172).

As discussed in section IIA, dehalogenation is the predominant reaction in the presence of hydrogen donors such as carboxylic acids. A small amount of dehalogenation also frequently occurs even when no obvious hydrogen source is present (51).

A dibenzofuran derivative has been obtained as a very minor by-product of the Ullmann reaction of the two *o*-dihalobenzene derivatives, 4-bromo-5-iodoveratrole (19) and *o*-chloroiodobenzene (172).

Other side reactions which have been definitely characterized have already been considered in previous sections of this review.

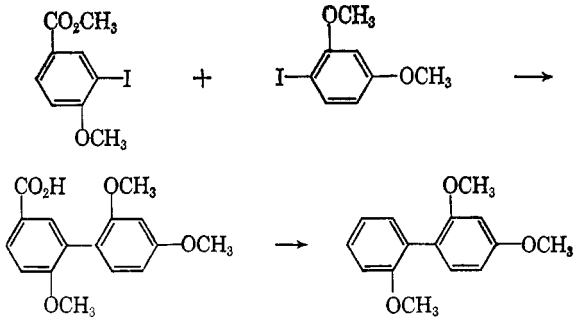
E. PROTECTIVE ATMOSPHERE

In a few instances, the Ullmann reaction has been conducted with exclusion of air, as noted in Tables II and III. Since both the reagents and products of the typical reaction are not known to be particularly sensitive to oxygen, such a precaution is probably of no benefit (51).

F. ISOLATION OF PRODUCTS

Depending on the nature of the products, the traditional techniques of distillation, fractional crystallization, extraction, and chromatography have been employed. The undesired by-products of the reaction are often dark, resinous materials which are readily removed by chromatography on alumina.

The separation of the mixture of products which is often obtained in the preparation of unsymmetrical biaryls is especially facilitated if one aryl residue contains a carboxylate group, since saponification then gives a separable mixture of neutral material, monocarboxylic acid, and dicarboxylic acid. For example, for the preparation of 2,4,2′-trimethoxybiphenyl it was found most convenient to subject a mixture of methyl 3-iodo-4-methoxybenzoate and 4-iodoresorcinol dimethyl ether to an Ullmann reaction, which gave a mixture of products from which the monocarboxylic acid was readily isolated. Decarboxylation gave the desired trimethoxybiphenyl in good yield (87).



IV. MECHANISM

In the earlier review, it was suggested that a useful approach to the study of the mechanism of the Ullmann reaction is the hypothesis that one might find as intermediates either (1) free radicals, (2) moderately stable, isolable organocopper compounds, or (3) metallic complexes of transitory existence.

In support of the free-radical hypothesis, Bell and Morgan (28) observed that it is difficult to envisage the formation of the highly hindered 6,6′-dinitrodiphenate from ethyl 2-iodo-3-nitrobenzoate in a specifically oriented arrangement by way of a transition complex. They felt that the formation and union of free radicals offered a more acceptable interpretation. Nursten (177) studied some Ullmann reactions in the presence of catechol and resorcinol, where dehalogenation is the predominant reaction, and interpreted the results as further evidence for the free-radical mechanism.

The formation of biphenyl by the reaction of bromobenzene and methanol in the presence of potassium hydroxide and palladium catalyst has some superficial resemblance to the Ullmann reaction.

$$2C_6H_5Br + 2KOH + CH_3OH \xrightarrow{Pd} C_6H_5C_6H_5 + 2KBr + 2H_2O + CH_2O$$

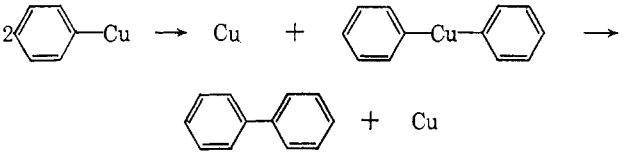
The reaction was studied in some detail by Mayo and Hurwitz (155), who reached the conclusion that "biphenyl was formed by coupling of adsorbed phenyl radicals on a specific surface in the absence of a more adequate source of hydrogen." A significant feature of this hypothesis is the concept of the formation and reaction of adsorbed radicals, and the idea that a specific type of palladium surface is required for the reaction. Analogously, if radicals are intermediates in the Ullmann reaction, they probably cannot be free radicals in the usual sense, but must remain at the metal surface until formation of biaryl is complete.

Arguments in support of the free-radical mechanism have been based on the isolation of abnormal reaction products, such as the traces of biphenyl-2- and -4-carboxylic acids formed in the course of the reaction of iodobenzene with copper in the presence of an excess of ethyl benzoate. It was observed by Forrest (97) that such heterogeneous reactions are characteristic of slow or sterically hindered reactions, usually involving nitro compounds. In the absence of nitro compounds, negligible amounts of such by-products are formed. Therefore the Ullmann reaction probably does not occur *via* a free-radical mechanism.

At first consideration, it appears that 2,6-dinitrobiphenyl, obtained when iodobenzene is treated with copper in the presence of *m*-dinitrobenzene, is a typical product to be expected from the reaction of phenyl radicals with the nitro compound. However, the product distribution shows a greatly different pattern from that obtained in accepted free-radical reactions as shown in Table VI. Thus *m*-dinitrobenzene on treatment with benzoyl peroxide at 100°, or under the conditions of the Gomberg–Bachmann arylation reaction in acetone, gives primarily 2,4-dinitrobiphenyl. From this evidence, Forrest concluded that the mechanism of the abnormal arylation is also in doubt (97).

The study of arylcopper compounds, which might possibly be intermediates in the Ullmann reaction, has been largely neglected since the report of Gilman and Straley (107) on the preparation of phenylcopper from the reaction of phenylmagnesium iodide with cuprous

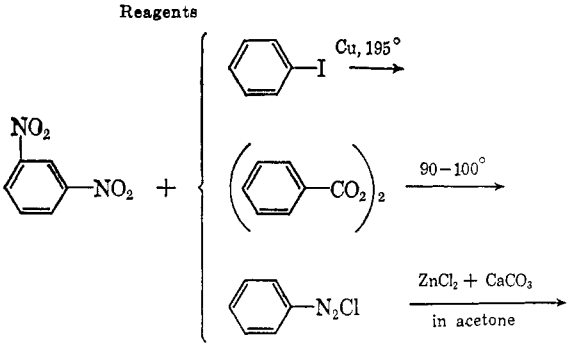
iodide. They observed that there was no experimental evidence for the existence of diphenylcopper, which was proposed as a possible intermediate in the formation of biphenyl from phenylcopper.



More recently it has been reported that diphenyl- and dimesitylcopper are indeed formed by the reaction of cupric chloride with phenyl- or mesitylmagnesium iodide in tetrahydrofuran and are stable at the boiling

TABLE VI

PRODUCT DISTRIBUTION



Percentage yields of the isomeric dinitrobiphenyls	
2,4-	2,6-
0	8
8	1
2	0.2

point of the solvent, which is 66° (225). Hydrolysis of the organocopper compounds gives benzene or mesitylene, but no biaryl. Unfortunately, no other chemical reactions of diarylcopper have been reported.

Evidence against arylcopper as an intermediate in the Ullmann reaction is the observation that phenylcopper undergoes certain reactions typical of the Grignard reagent; for example, it adds to benzaldehyde to give a 24% yield of benzhydrol (107). No evidence has been obtained to indicate that carbonyl or ester groups undergo Grignard-type addition reactions in the ordinary course of the Ullmann reaction.

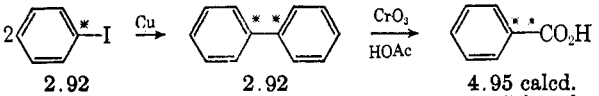
In his study of the effect of diluents, Forrest (97) found that the Ullmann reaction was markedly suppressed by addition of nitro compounds, aldehydes, and esters. However, from a practical synthetic viewpoint, such substituents in the aryl halide can be considered to be inert and compatible with the biaryl synthesis.

On the other hand, the reaction of phenylmagnesium bromide with nitrobenzene to give diphenylamine, among other products (106), has a superficial similarity

$$C_6H_5NO_2 + 4C_6H_5MgBr \rightarrow (C_6H_5)_2NH + C_6H_5OH + (C_6H_5)_2$$

to the formation of triphenylamine derivatives observed when the Ullmann reaction is conducted in the presence of certain aromatic nitro compounds as diluents. Although this resemblance cannot be considered to be very compelling evidence for Grignard-like organocopper compounds in the usual Ullmann biaryl synthesis, it suggests that further studies of the chemistry of organocopper compounds would be of value in the elucidation of the mechanism of the reaction (172).

It has long been known that the Ullmann reaction of substituted halobenzenes results in the formation of biaryl bonds only at the carbon atom from which the reactive halogen has been displaced. With the aid of a radioactive tracer, it has now been demonstrated that this conclusion is also valid for iodobenzene. Biphenyl-1,1′-C^{14} was prepared in 80% yield by the Ullmann reaction of iodobenzene-1-C^{14}. Oxidation of the biphenyl gave benzoic acid which showed no loss in specific activity (249).



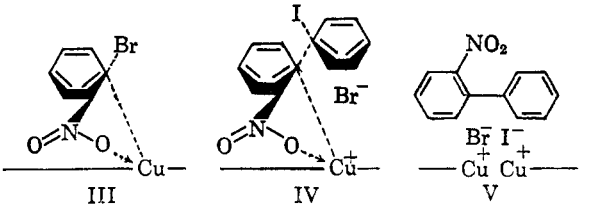
2.92 2.92 4.95 calcd. 4.95 found

activities in mμc./mg. of C

One of the most significant items of evidence regarding the mechanism is the observation that exceptionally good yields of unsymmetrical biaryl can be obtained from the reaction of an activated aryl halide with a relatively unreactive halide at a temperature too low for the second halide alone to react with copper (97). This suggests that the first halide reacts with the copper to form an intermediate which then reacts preferentially with the second halide. The observation is of very general validity, and many examples have been observed. One of the simplest is the reaction of *o*-bromonitrobenzene with a slight excess of iodobenzene to give a 60% yield of 2-nitrobiphenyl (97). The particular role of an *ortho* electronegative group in promoting the reaction may be due to the possibility of chelation as well as electron withdrawal from the aromatic nucleus, which facilitates nucleophilic attack of copper as shown in III for the hypothetical complex formed by reaction of *o*-bromonitrobenzene and copper.

The second stage of the reaction may be envisaged as a nucleophilic attack of the complex on a second molecule of aryl halide, which preferably lacks the activating group and has the more polarizable carbon–iodine bond, such as iodobenzene as shown in IV. It would appear necessary for the complex III to first release the bromide ion while remaining attached to the copper surface; the nucleophilic character of the residue can be maintained by a further flow of electrons from the copper. Such a nucleophilic attack seems plausible, in view of the reported nucleophilic halogen exchange which occurs between aryl iodide and cuprous chloride under conditions similar to those used in the Ullmann reaction (172).

In the final step of the reaction, the covalent biaryl bond is formed, with release of the iodide ion as shown in V. In summary, it appears that the evidence which has been available since the previous review provides further support and a more detailed picture of the activated complex hypothesis as the most acceptable mechanism for the Ullmann reaction.



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