The Ullmann Synthesis of Biaryls

Paul E. FANTA

Department of Chemistry, Illinois Institute of Technology, Chicago, Illinois 60616, U.S.A.

The uses of the Ullmann Biaryl Synthesis – the condensation of two molecules of aryl halide in the presence of copper to form a carbon-carbon bond with elimination of copper halide – for the preparation of symmetrical and unsymmetrical biaryls, biphenylenes, and to effect ring closures are discussed. The cocondensation Ullmann reaction for the formation of oligophenylenes is also mentioned.

1. Selected Examples of Novel Syntheses
2. Tables of Aryl Halides Used
   Table 1, Aryl halides used in the synthesis of symmetrical biaryls
   Table 2, Aryl halides used in the synthesis of unsymmetrical biaryls
3. Synthesis of Biphenylenes
4. Closure of Five-membered and Larger Rings
5. The Cocondensation Ullmann Reaction
6. New Developments in Reaction Techniques
7. Mechanism of the Ullmann Reaction and Related Copper-Promoted Reactions

Es wird die Anwendung der Ullmannschen Biaryl Synthesemethode zur Herstellung symmetrischer und unsymmetrischer Biaryle, Biphenylene und Ringverbindungen abgehandelt. Ausgangsverbindungen sind Arylhalogenide, die mit Kupfer behandelt werden, und unter Abspaltung von Kupferhalogeniden C—C Verknüpfungen eingehen. Die Synthese von Oligophenylenen mit Hilfe der Ullmannschen Cokondensation wird ebenfalls beschrieben.

The Ullmann synthesis of biaryls comprises the reactions in which two molecules of aryl halide are condensed in the presence of finely divided copper to form a new aryl-aryl bond with the elimination of copper halide. The reaction has been used to prepare symmetrical and unsymmetrical biaryls, to effect ring closures at an aryl-aryl bond, and to prepare oligopolyphenylenes. Since the publication of the previous reviews[1,2] the reaction has had continued use, particularly in the elucidation of the structures of natural products, in the preparation of novel heterocyclic biaryls, and for the preparation of compounds for testing as scintillators.

Obviously, the Ullmann synthesis is related to a whole family of reactions in which copper appears as a catalyst or as an isolable organocopper compound. Many such reactions have utility in synthesis and have been comprehensively reviewed in recent years[3,4,5,6].

The previous reviews of this subject have provided a number of generalizations regarding the relationship between the structure of an aryl halide and its reactivity in the Ullmann reaction, which may be briefly summarized as follows: electronegative groups such as nitro and methoxycarbonyl, particularly in the *ortho* position, strongly activate an aryl halogen.

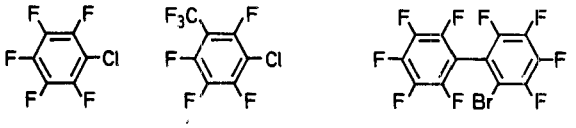
On the other hand, the reaction is greatly inhibited or prevented by the presence of substituents which provide an alternative path for reaction of the aryl halide, such as amino, hydroxy, and free carboxy groups. Bulky groups in the *ortho* positions may inhibit the reaction by steric hindrance. In the synthesis of unsymmetrical biaryls, an optimum yield is usually obtained when one of the aryl halides is activated and the other is relatively unreactive. The data summarized in Tables 1 and 2 provide additional evidence for these structure-activity relationships, but will not be analyzed in detail.

Some of the syntheses collected in Tables 1 and 2 are novel applications of the Ullmann reaction, or illustrate successful uses which may not have been readily predictable by consultation of the previous reviews. A few selected examples of such reactions will be discussed.

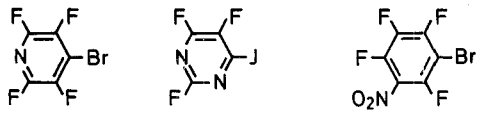
1. Selected Examples of Novel Syntheses

A variety of perfluoroaryl chlorides, bromides, and iodides such as chloropentafluorobenzene (**1**)[7], *m*-chloroheptafluorotoluene (**2**)[8], 2-bromononafluorobiphenyl (**3**)[9], 4-bromotetrafluoropyridine (**4**)[10], 4-iodotrifluoropyrimidine (**5**)[11], and 3-bromotetrafluoronitrobenzene (**6**)[12] have been used in the Ullmann reaction. Good yields of biaryls were usually reported, as indicated below, and in no instance was a fluorine atom eliminated. The reaction of compound **6** is particularly noteworthy, since it shows that fluorine atoms *ortho* to a nitro group remain unreactive relative to a *meta*-nitro bromine atom.

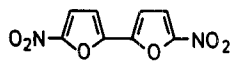
Ullmann reactions of furan derivatives have been reported for the first time. Reactions of a variety of 2-bromo and 2-iodofurans containing methyl, methoxycarbonyl, nitro, and aldehyde groups gave good to fair yields of the expected bifurans under rather mild conditions. The best result was obtained in the reaction with 2-iodo-5-nitrofuran, which gave the dinitrobifuran **7** in 76% yield when treated with copper bronze in dimethylformamide for 12 hours at the unusually low temperature of 100°[13].



1 (75%) 2 (73%) 3



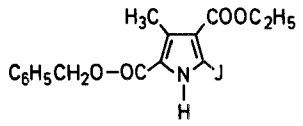
4 (50%) 5 (58%) 6



7 (76%)

5,5'-Dinitro-2,2'-bifuran[13]:
A reaction mixture of 5-iodo-2-nitrofuran (3 g), powdered copper bronze (3 g, BDH laboratory reagent grade), and dimethylformamide (15 g) was stirred and heated at 100° for 12 hours. The solid residue was collected on a filter and washed with chloroform, the combined filtrate and washings were washed with dilute hydrochloric acid, dried, and distilled under reduced pressure to remove solvent. Sublimation of the residue gave the product in the form of yellow prisms; yield: 76%; m.p. 215–217°.

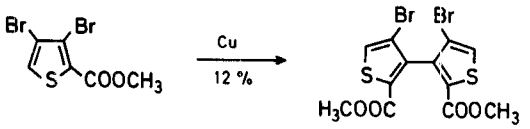
A variety of 2-iodo and 3-iodopyrroles highly substituted with alkyl and ester groups have been successfully used in the Ullmann reaction[14,15,16]. In some cases good yields of bipyrroles were obtained under very mild conditions. For example, the reaction of iodopyrrole **8** gave a 77% yield of the corresponding bipyrrole on stirring with copper bronze in dimethylformamide for 17 hours at room temperature[14].



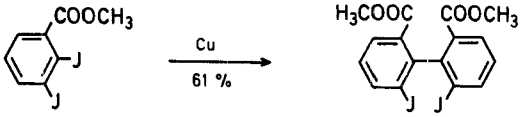
8 (77%)

In the Ullmann reaction of methyl 3,4-dibromo-2-thiophenecarboxylate only the bromine atom at the 3-position was reactive, as shown by the isolation of the bithiophene **9** as the only reaction product[17].

Similarly, only the *ortho*-iodine atom was reactive in methyl 2,3-diiodobenzoate, which gave a good yield of the biphenyl (**10**) on treatment with copper bronze at the relatively low temperature of 110°[18].

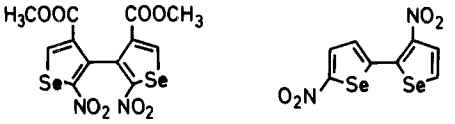


9



10

The Ullmann reaction of selenophene derivatives was reported for the first time in the preparation of the biselenophenes **11** and **12**[19].

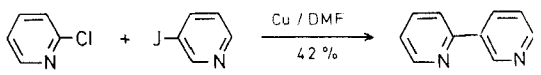


11 (40%) 12

Dimethyl 6,6'-diiododiphenate[18]:
To methyl 2,3-diiodobenzoate (50 g) at 110° was added activated copper bronze (24.6 g) during 1 hr. with stirring. After 1 hr at 110°, another portion of copper (24.6 g) was added in one portion. The mixture was held at 110–115° for 3 hr., cooled, and extracted with dichloromethane. Evaporation of the dichloromethane gave a solid residue which was washed with cold ether to leave a residue of the biphenyl derivative; yield: 20.36 g (61%), m.p. 147–148° (from ethanol). Evaporation of the ether washings gave 15.1 g (31%) of recovered starting material.

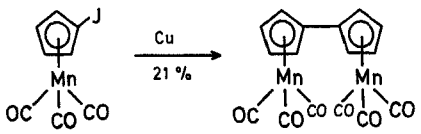
In a study of the optimum conditions for the crossed Ullmann reaction, it was found that the best yield of 2,3'-bipyridine (**13**) was obtained by the slow addition of an excess of 2-chloropyridine to a suspension of copper powder in a boiling solution of 3-iodopyridine in dimethylformamide[20].

[1] P. E. Fanta, *Chem. Rev.* **64**, 613 (1964).
[2] P. E. Fanta, *Chem. Rev.* **38**, 139 (1946).
[3] R. G. R. Bacon, H. A. O. Hill, *Quart. Rev.* **19**, 95 (1965).
[4] J. F. Normant, *Synthesis* **1972**, 63.
[5] M. Nilsson, *Sv. Kem. Tidskr.* **80**, 192 (1968).
[6] M. Nilsson, *Sv. Kem. Tidskr.* **73**, 447 (1961).
[7] G. G. Yakobson, V. D. Shteingarts, A. I. Miroshnikov, N. N. Vorozhtsov, *Dokl. Akad. Nauk SSSR, Chemistry Section (English translation)* **159**, 1347 (1964).
[8] Imperial Smelting Corporation, *Belgian Patent* 659239; *C. A.* **64**, 15792 (1966).
[9] D. E. Fenton, A. J. Park, D. Shaw, A. G. Massey, *Tetrahedron Lett.* **1964**, 949.
[10] R. D. Chambers, J. Hutchinson, W. K. R. Musgrave, *J. Chem. Soc.* **1965**, 5040.
[11] R. E. Banks, D. S. Field, R. N. Haszeldine, *J. Chem. Soc.* (C) **1969**, 1866.
[12] L. F. Belf, D. T. Saggers, *German Patent Application (DOS)* 1904364; *C.A.* **71**, 123908 (1969).
L. J. Belf, M. W. Buxton, J. F. Tilney-Basset, *Tetrahedron* **23**, 4719 (1967).
[13] R. Grigg, J. A. Knight, M. V. Sargent, *J. Chem. Soc.* (C) **1966**, 976.
[14] R. Grigg, A. W. Johnson, J. F. W. Wasley, *J. Chem. Soc.* **1963**, 359.
[15] R. Grigg, A. W. Johnson, *J. Chem. Soc.* **1964**, 3315.
[16] J. L. A. Webb, R. R. Threlkeld, *J. Org. Chem.* **18**, 1406, 1413 (1953).
[17] R. Hakansson, E. Wiklund, *Ark. Kemi* **31**, 101 (1969).
[18] M. S. Newman, M. W. Logue, *J. Org. Chem.* **36**, 1398 (1971).
[19] C. Dell'Erba, D. Spinelli, G. Garbarino, G. Leandri, *J. Heterocycl. Chem.* **5**, 45 (1968).
C. Dell'Erba, G. Garbarino, C. Carpanelli, *Gazz. Chim. Ital.* **100**, 788 (1970).

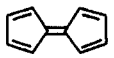


13

The Ullmann reaction of iodocymantrene (**14**), using copper precipitated with zinc dust, gave a 21% yield of the stable biaryl, (fulvalene)-hexacarbonyl-dimanganese (**15**), which is considered to be a metal complex of the extremely unstable hydrocarbon fulvalene (**16**)[21].

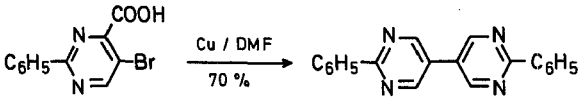


14 **15**



16

The use of the Ullmann reaction for the preparation of bipyrimidine derivatives has been studied in some detail, using a variety of chloro-, bromo-, and iodopyrimidines[22,23]. Although many of these reactions failed or gave poor yields, the reaction of 5-bromo-2-phenylpyrimidine-4-carboxylic acid (**17**) with copper bronze in refluxing dimethylformamide gave a 70% yield of the decarboxylated bipyrimidine (**18**)[22].



17 **18**

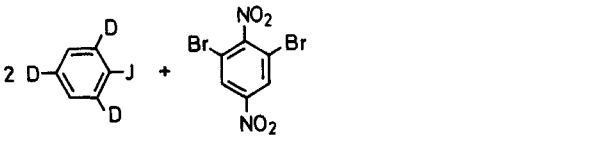
In the cocondensation of excess 2,4,6-trideuteroiodobenzene with 2,6-dibromo-1,4-dinitrobenzene at 200° to give the terphenyl **19** in 35% yield, it was shown that the product retained six atoms of deuterium. Therefore no hydrogen-deuterium exchange occurred under the conditions of the reaction[24]. In contrast, it has been reported that products resulting from hydrogen-deuterium exchange were isolated when the Ullmann reaction of iodobenzene, 4-iodobiphenyl, or 1-iodonaphthalene was carried out in the presence of deuterated benzene or deuterated cyclohexane[25].

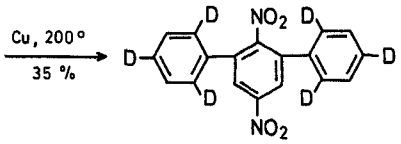
[20] M. Goshaev, O. S. Otroshchenko, A. S. Sadykov, *Tr. Samarkand. Gos. Univ.* **167**, 95 (1969); Ref. *Zh. Khim.* **1970**, 7Zh354; *C.A.* **74**, 53433 (1971).

[21] M. D. Rausch, R. F. Kovar, C. S. Kraihanzel, *J. Amer. Chem. Soc.* **91**, 1259 (1969).

[22] M. P. L. Caton, D. T. Hurst, J. F. W. McOmie, R. R. Hunt, *J. Chem. Soc.* (C) **1967**, 1204, and references cited therein.

[23] J. J. Lafferty, F. H. Case, *J. Org. Chem.* **32**, 1591 (1967).





19

2. Tables of Aryl Halides Used

Table 1 is a list of aryl halides which have been used in the Ullmann synthesis of symmetrical biaryls, as found by a systematic search of the Subject Index of *Chemical Abstracts*, Volumes **59–74** (July, 1963–June, 1971). Additional examples were found with the help of *Science Citation Index*. The aryl groups are listed in an order similar to the familiar *Beilstein* system; nuclei are in the order: phenyl, other carbocyclics, heterocyclics; substituents are in the order: halogen, nitro, alkyl, alkoxy and acyloxy, aryl, carbonyl, and methoxycarbonyl. Attempted reactions which were unsuccessful are noted by the entry 0 in the Yield column.

Table 1. Aryl Halides used in the Ullmann Synthesis of Symmetrical Biaryls.

Substituents in the aryl group	Halogen	Yield (%)	References
aryl = phenyl			
2-chloro	J	53	27
3-chloro	J	64	27
4-chloro	J	48	26, 27
2,3,4,5-tetrafluoro	Br	73	12
pentafluoro	Cl	75	7, 28
pentafluoro	J	72	29
2-nitro-3,4,5,6-tetrafluoro	Br	57	12
2-nitro-2,4,5,6-tetrafluoro	Br		12
2-cyano-3,4,5,6-tetrafluoro	Br	77	12
2-methyl-3,4,5,6-tetrafluoro	Br	61	12
2-methyl-3-nitro	J	0	30
4-methyl-2-nitro-5-bromo	J	77	31
4-methyl-2,6-dinitro	Cl	40	32
3-methyl-2,4,6-trinitro	Br	80	33
3-trifluoromethyl-2,4,5,6-tetrafluoro	Cl	73	8
2,3-dimethyl	J		34
3,4-dimethyl	J		34
2,5-dimethyl-4-nitro-6-bromo	J	0	35
2-phenoxy	J	75	27
3-phenoxy	J	68	27, 36
4-phenoxy	J	45	27
4-methoxy-2,3,5,6-tetrafluoro	J	17	37
5-methoxy-2-nitro	J	80	38
4-acetoxy-2-nitro	J	77	38
4-methoxy-2,6-dinitro	Cl	90	32
3-methoxy-2,4,6-trinitro	Br, Cl	62	39, 40
4-methoxy-2-methyl	J		41
3-methoxy-2-methyl	J	92	30
4-methoxy-2-ethyl	J		41
4-methoxy-2,6-dimethyl	J	18	41, 42

Table 1. continued

Substituents in the aryl group	Halogen	Yield (%)	References
2,3-dimethoxy	J	83	43
2,4-dimethoxy	J	73	44
3,4-methylenedioxy	J	21	45
3,4-methylendioxy-6-nitro	J	57	45
4,5-dimethoxy-2-chloro	J	36	43
2,3-dimethoxy-5-methyl	Br	20	43, 46
2,4-dimethoxy-3-methyl	J		47
2,5-dimethoxy-3-methyl	J		49
2,6-dimethoxy-3-methyl	J		48
2-benzyloxy-5-methoxy-4-methyl	Br	38	49
2-ethoxy-4-methoxy-3-ethyl	J		47
2-methoxy-4-ethoxy-3-ethyl	J		47
2,3-dimethoxy-5,6-dimethyl	Br	20	43
4,5-dimethoxy-2,3-dimethyl	J	13	50
2,5-dimethoxy-3,4-dimethyl	J	36	50
2-phenyl	J	52	51
3-phenyl	J	16	51
4-phenyl	J	97	51, 52
4-pentafluorophenyl-2,3,5,6-tetrafluoro	Br		9
4-phenyl-2-methyl	J	45	53
4-(*m*-tolyl)-2-methyl	J	28	54
3-(2,3,4-trimethoxyphenyl)-4,5,6-trimethoxy	J		55
4-(*p*-(5-alkoxycarbonylpentyl)-phenyl)	J	10	56
2-(*p*-biphenylyl)	J	50	57
2,4-diphenyl	J	10	57
2-(*o*-biphenylyl)	J	0	57
3-formyl-4-methoxy	J		58
2-formyl-5-methoxy	J		59
2-formyl-4,5-dimethoxy	Br		60
2-formyl-5,6-dimethoxy	J, Br	60	61, 62
3-acetyl-2,4-dimethoxy	J		47, 63
3-acetyl-2,6-dimethoxy	J	0	63
3-acetyl-2-methoxy-4-ethoxy	J		64
3-acetyl-2-ethoxy-4-methoxy	J		64
3-methoxycarbonyl	J		65
2-methoxycarbonyl-4-chloro	Br	80	66
2-methoxycarbonyl-6-iodo	J	61	18
2-methoxycarbonyl-4-nitro	Br	51	66
4-methoxycarbonyl-2-bromo-5-nitro	J	40	31
4-methoxycarbonyl-2-nitro-5-bromo	J	0	31
4-methoxycarbonyl-2,6-dinitro	Br	90	32
2-methoxycarbonyl-6-ethyl	J	41	18
2-methoxycarbonyl-4-methoxy	Br	100	67
3-methoxycarbonyl-6-methoxy	J		68
2-methoxycarbonyl-5,6-dimethoxy	Br	70	62
2-methoxycarbonyl-4,6-dimethoxy	J	64	69
3-methoxycarbonyl-2,4-dimethoxy	J		47
3-methoxycarbonyl-2,6-dimethoxy	J		63
4-methoxycarbonyl-2,6-dimethoxy	J	31	69
3-methoxycarbonyl-4,6-dimethoxy	J		48, 63
2-methoxycarbonyl-4,5,6-trimethoxy	Br		65
3-(—CH=CHCO$_2$CH$_3$)-6-methoxy	J	70	70
2-ferrocenyl	J	11	86

Table 1. continued

Substituents in the aryl group	Halogen	Yield (%)	References
aryl = 1-naphthyl, 5,7-dimethoxy-2,4-dimethyl	Br		71
aryl = 3-fluorenonyl, 2-nitro	Br		72
aryl = 3-flavonyl, 4-methoxy and 6-methoxy	J		58
aryl = 3-phenanthryl, and 5-nitro	J		73
aryl = 3-perylenyl	J		75
aryl = 3-benzanthronyl	Cl, Br		74
aryl = 8-benzanthronyl	Cl	8	76
aryl = 11-benzanthronyl	Cl	95	76
aryl = various furanyls			13
aryl = various thienyls			17, 77, 78, 79
aryl = various selenophenyls			19
aryl = various pyrryls			13, 14, 15, 16
aryl = various pyridyls			80, 81, 82
aryl = various pyrimidyls			11, 22, 23, 83
aryl = various ferrocenyls			84, 85, 86

Table 2 is a list of pairs of aryl halides which have been used in the Ullmann synthesis of unsymmetrical biaryls. Aryl groups in column 1 are selected by the principle of latest position, and arranged in the same order as found in Table 1.

[24] P. Otto, F. Stein, G. Suppe, *J. Label. Compounds* **4**, 205 (1968).
[25] I. P. Gragerov, L. F. Kasukhin, *J. Org. Chem. USSR* **5**, 2 (1969).
[26] T. Migata, N. Morikawa, A. Simamura, *Bull. Chem. Soc. Jap.* **36**, 980, 985, 992 (1963); *C.A.* **59**, 13792,3,4 (1963).
[27] W. C. Hammann, R. N. Schisla, *J. Chem. Eng. Data* **17**, 112 (1972), *U.S. Patent* 3406207.
[28] G. M. Brooke, R. D. Chambers, J. Heyes, W. K. R. Musgrave, *J. Chem. Soc.* **1964**, 729.
[29] J. M. Birchall, R. Hazarc, R. N. Haszeldine, W. W. Wakalski, *J. Chem. Soc.* (C) **1967**, 47.
[30] M. Lounasmaa, *Acta Chem. Scand.* **22**, 2388 (1968).
[31] R. E. Carter, L. Dahlgren, *Ark. Kemi* **27**, 257 (1967).
[32] R. N. Castle, W. D. Guither, P. Hilbert, F. E. Kempter, N. R. Patel, *J. Heterocycl. Chem.* **6**, 533 (1969).
[33] J. C. Dacons, H. G. Adolph, M. J. Kamlet, *Tetrahedron* **19**, 791 (1963).
[34] A. R. Urbanik, *Dissertation*, West Virginia University (1967); *Diss. Abstr. B* **28**, 1865 (1967).
[35] S. Gronowitz, G. Hansen, *Ark. Kemi* **27**, 145 (1967).
[36] British Petroleum Co. Ltd. and C. F. Forster, *British Patent* 1062261; *C.A.* **67**, 11335 (1967).
[37] L. A. Wall, W. J. Pummer, J. E. Fearn, J. M. Antonucci, *J. Res. Natl. Bur. Std.* **67A**, 481 (1963).
[38] F. E. Kempter, R. N. Castle, *J. Heterocycl. Chem.* **6**, 523 (1969).
[39] R. E. Oesterling, J. C. Dacons, L. A. Kaplan, *U.S. Patent* 3404184; *C.A.* **70**, 37444 (1969).
[40] D. W. Hein, S. J. Radkowski, *U.S. Patent* 3402202; *C.A.* **70**, 47077 (1969).
[41] Y. Osawa, *Nippon Kagaku Zasshi* **84**, 140 (1963); *C.A.* **59**, 13860 (1963).

Table 2. Pairs of Aryl Halides used in the Ullmann Synthesis of Unsymmetrical Biaryls.

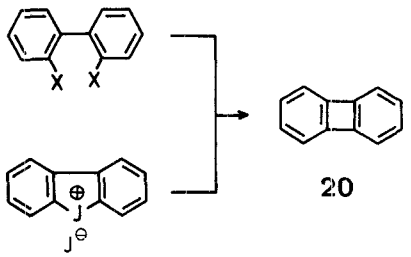
Substituents in aryl group 1	Substituents in aryl group 2	Halogen 1	Halogen 2	Yield (%)	References
aryl = phenyl	aryl = phenyl				
2-nitro	2-fluoro	Br	J	57	87
2-nitro	3-fluoro	Br	J	45	87
2-nitro	4-fluoro	Br	J	36	87
2-nitro-4-fluoro	none	Br	J	43	87
2-nitro-5-fluoro	none	Br	J	59	87
2,4,6-trinitro	2-nitro	Cl	J	67	88
2,4,6-trinitro	3-nitro	Cl	J	45	88
2,4,6-trinitro	4-nitro	Cl	J	86	88
2-methyl	2,4,6-trinitro	Br	Cl	69	33
2-methyl-6-nitro	2-fluoro	J	J	29	89
3-methyl-2,4,6-trinitro	2,4,6-trinitro	Br	Cl		33
4-methyl	2-chloro, and 3-chloro	J	J		26
3-methyl	4-chloro	J	J		26
2-methoxy	4-methyl	J	J		26
3-methoxy	4-chloro, and 4-methyl	J	J		26
4-methoxy	3-chloro, 4-chloro, 2-methyl, 3-methyl, and 3-methoxy	J	J		26
2-methoxy	2-isopropyl, and 2-isopropyl-4-nitro	J	J		91
3-phenoxy	2-chloro	J	J	19	27
3-phenoxy	3-chloro	J	J	37	27
4-phenoxy	3-chloro	J	J		27
2-methoxy-4-nitro	2-isopropyl, 2-isopropyl-4-nitro, and 4-methoxy-2-isopropyl	J	J		91
4-methoxy-2-isopropyl	2-methoxy	J	J		91
4-methoxy-2-methyl	2-methyl-4-nitro	J	Br	6	90
2,4-dimethoxy	2-isopropyl, 2-isopropyl-4-nitro, and 4-methoxy-2-isopropyl	J	J		91
3,4-dimethoxy	4-nitro	J	J		92
3,6-dimethoxy	none	Br	J		93
2,6-dimethoxy	2-methoxy	J	J	40	94
2,4-dimethoxy-3-ethyl	2,4-dimethoxy	J	J		47
3,4-dimethoxy-6-ethyl	3-methyl-2-nitro	J	Br		95
2,4-dimethoxy-3-ethyl	2,4-dimethoxy-3-ethyl	J	J		47
2-ethoxy-4-methoxy-3-ethyl	2-methoxy-4-ethoxy-3-ethyl	J	J		47
3,4,5-trimethoxy	none	J	J		96
2,3,4,6-tetramethoxy	none	Br	J	16	97
4-phenyl	none	J	Br, J	82	52, 98
4-phenyl	2,4-dinitro	J	Cl	6	99
4-phenyl	2,6-dinitro	J	Cl	46	99
4-phenyl	2,4,6-trinitro	J	Cl	80	99
4-phenyl	2-methyl, 4-methyl, and 4-isopropyl	J	J		100
4-phenyl	2-phenyl	J	J	20	101
4-(*p*-biphenylyl)	2-methyl	J	J	34	102
4-(*p*-biphenylyl)	3-methyl	J	J	37	102
4-(*p*-biphenylyl)	4-methyl	J	J	17	102
3-formyl-5,6-dimethoxy	2-formyl-5,6-dimethoxy	J	J	18	61
3-acetyl-2,4-dimethoxy	2,4-dimethoxy	J	J		47
3-acetyl-2-ethoxy-4-methoxy	3-acetyl-2-methoxy-4-ethoxy	J	J		64
2-methoxycarbonyl	3,4-dimethoxy	Br	J	47	103
2-methoxycarbonyl	3,4,5-trimethoxy	Br	J	21	96
4-methoxycarbonyl	4-methyl-2-nitro	J	Br	42	104
4-methoxycarbonyl	4-*t*-butyl-2-nitro	J	Br	61	104
4-methoxycarbonyl	4-methoxy-2-nitro	J	Br	42	104
2-methoxycarbonyl-5-fluoro	none	Br	J	52	87
2-methoxycarbonyl-6-methyl	2-fluoro	J	J	76	89
3-methoxycarbonyl-6-methoxy	2,6-dimethoxy	J	J	35	105
3-methoxycarbonyl-6-methoxy	2,3,6-trimethoxy	J	J	36	105
3-methoxycarbonyl-6-methoxy	2,4,5-trimethoxy	J	J	29	105
3-methoxycarbonyl-6-methoxy	3,4,5-trimethoxy	J	J		96
2-methoxycarbonyl-4,6-dimethoxy	4-methoxycarbonyl-2,6-dimethoxy	J	J	4	69
2-methoxycarbonyl-5,6-dimethoxy	2-methoxycarbonyl-5-methoxy	Br	J		59
2-methoxycarbonyl-5,6-dimethoxy	5-methoxy-2-methyl	Br	J		59
2-methoxycarbonyl-5,6-dimethoxy	2-acetyl-5-methoxy	J	J		106
3-methoxycarbonyl-5,6-dimethoxy	2-methoxy	J	J	69	105
3-methoxycarbonyl-5,6-dimethoxy	2-formyl-5,6-dimethoxy	J	Br	34	62
3-methoxycarbonyl	3-formyl-5,6-dimethoxy	Br	J	7	62

Table 2 continued

Substituents in aryl group 1	Substituents in aryl group 2	Halogen 1	Halogen 2	Yield (%)	References
2-methoxycarbonyl-4,5,6-trimethoxy	2-methoxycarbonyl	Br	J		65
2-methoxycarbonyl-3,4,5-trimethoxy	3-methoxycarbonyl	J	J		65
2-methoxycarbonyl-4,5,6-trimethoxy	4-nitro	Br	J	18	107
2-methoxycarbonyl-4,5,6-trimethoxy	4-methoxy-2-nitro	Br	J	11	107
aryl = 2-pyridyl	aryl = 3-pyridyl	Br	Br	19	20
		Cl	J	42	20
aryl = 2-pyridyl	aryl = 4-pyridyl	Br	Cl	14	108
aryl = 2-selenophenyl, 5-nitro	aryl = 2-selenophenyl, 3-nitro	J	Br		19
aryl = ferrocenyl, 2-methoxycarbonyl and 2-acetyl	aryl = ferrocenyl	J	J		85

3. Synthesis of Biphenylenes

Work summarized earlier[109] suggested that the synthesis of a biphenylene (**20**) from a 2,2′-dihalobiphenyl or a 2,2′-biphenyleneiodonium iodide required copper(I) oxide (the Lothrop synthesis) and not metallic copper and differed distinctly in scope and mechanism from the Ullmann synthesis. Further examples of this ring-closure, summarized in Table 3, show that copper can be used and in some cases gives a better yield than copper(I) oxide.



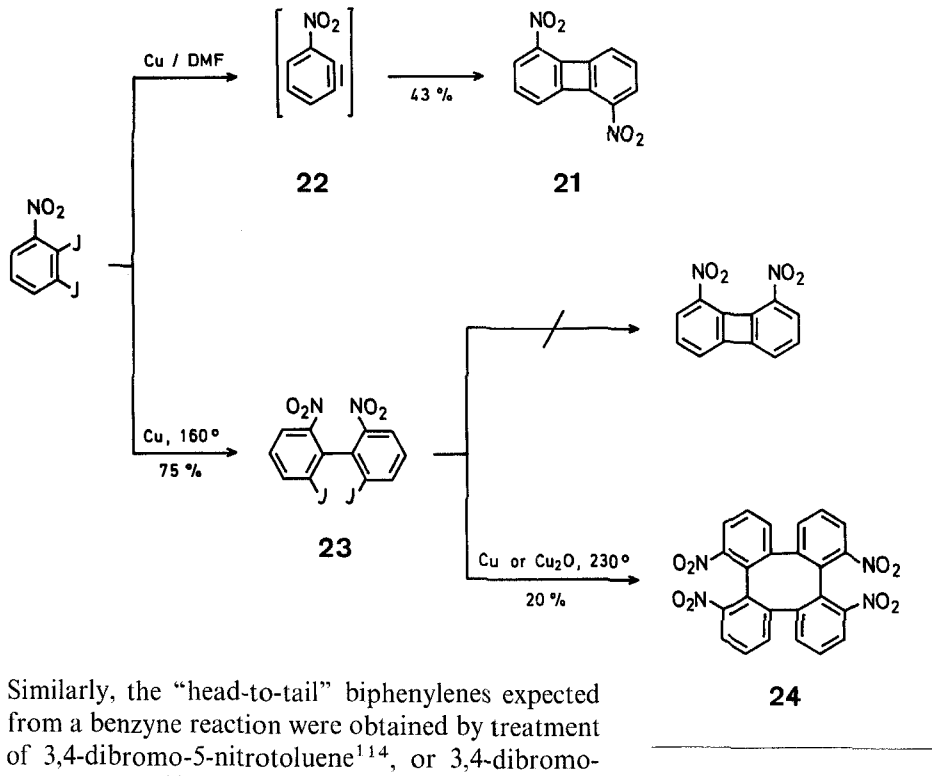
20

Table 3. Biphenylenes Prepared from 2,2′-Diiodobiphenyls or 2,2′-Biphenyleneiodonium Iodides by Heating with Copper(I) Oxide or Metallic Copper.

Substituents in the biphenylene	Reagent	Yield (%)	References
none	Cu_2O	31	44
	Cu	44	44
octafluoro	Cu	10	111
1-fluoro-8-methyl (from diiodobiphenyl)	Cu_2O	27	89
(from iodonium iodide)	Cu_2O	74	89
1,8-dinitro	Cu_2O	0	113
2,7-dimethyl	Cu_2O	35	110
3,6-dimethyl-1,8-dinitro	Cu_2O	0	114
2,3,6,7-tetramethyl	Cu_2O	5	110
2,7-dimethoxy-1,3,4,5,6,8-hexamethyl	Cu_2O	7	50
2,3,6,7-tetramethoxy-1,8-dimethyl	Cu_2O	18	50
1,2,3,6,7,8-hexamethoxy	Cu_2O	18	44
	Cu	46	44
2,7-diacetoxy-1,3,6,8-tetramethoxy	Cu_2O	0	112
2-phenyl	Cu_2O	15, 17	110
1,8-dimethoxycarbonyl	Cu	11	18

2,3-Diiodonitrobenzene was used in a detailed study of the competition between the formation of a biphenyl and a biphenylene. The highest yield of the "head-to-tail" biphenylene **21** was obtained when the reaction was run in dimethylformamide, with slow addition of the aryl halide to an excess of copper bronze. The product has the structure expected if the reaction occurs by way of a benzyne intermediate (**22**). The highest yield of the normal Ullmann product, biphenyl **23**, was obtained in the absence of solvent at moderate temperatures. At a higher temperature, with either copper or copper(I) oxide, the reaction of biphenyl **23** gave the tetraphenylene **24** in a yield of 20%, but 1,8-dinitrobiphenylene, the expected product of a Lothrop reaction, was not formed[113].

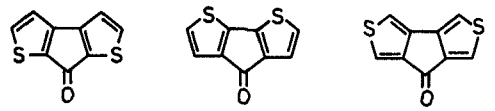
[42] Y. Nomura, Y. Takeuchi, *J. Chem. Soc.* (B) **1970**, 956.
[43] L. Horner, K. H. Weber, *Chem. Ber.* **96**, 1568 (1963).
[44] J. C. Salfeld, E. Baume, *Tetrahedron Lett.* **1966**, 3365.
[45] F. Dallacker, G. Adolphen, *Liebigs Ann. Chem.* **694**, 110 (1966).
[46] M. Tomita, T. Kikuchi, K. Bessho, T. Hori, Y. Inubushi, *Chem. Pharm. Bull.* **11**, 1484 (1963); *C.A.* **60**, 9321 (1964).
[47] J. W. Apsimon, N. G. Creasey, W. Marlow, K. Y. Sim, W. B. Whalley, *J. Chem. Soc.* **1965**, 4156.
[48] B. Kanakalakshmi, K. P. Mathai, S. Sethna, *J. Indian Chem. Soc.* **43**, 469 (1966).
[49] D. F. Bowman, F. R. Hewgill, B. R. Kennedy, *J. Chem. Soc.* (C) **1966**, 2274.
[50] D. W. Lawson, J. F. W. McOmie, D. E. West, *J. Chem. Soc.* (C) **1968**, 2414.
[51] J. A. Cade, A. Pilbeam, *Tetrahedron* **20**, 519 (1964).
[52] A. N. Novikov, T. A. Khalimova, *Tr. Tomskogo Gos. Univ., Ser. Khim.* **170**, 45 (1964); *C.A.* **63**, 533 (1965).
[53] R. L. Taber, G. H. Daub, F. N. Hayes, D. G. Ott, *J. Heterocycl. Chem.* **2**, 181 (1965).
[54] I. L. Kotlyarevskii, M. S. Shvartsberg, S. F. Vasil'evskii, V. N. Andrievskii, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1966**, 302; *C.A.* **64**, 19792 (1966).
[55] H. Erdtman, G. Moussa, A. Timell, *Acta Chem. Scand.* **24**, 235 (1970).
[56] H. Dehne, R. Zahnow, H. G. Steinhagen, *Z. Chem.* **11**, 305 (1971).
[57] J. A. Cade, A. Pilbeam, *J. Chem. Soc.* **1964**, 114.
[58] K. P. Mathai, S. Sethna, *J. Indian Chem. Soc.* **41**, 347 (1964).
[59] J. Koizumi, S. Kobayashi, S. Uyeo, *Chem. Pharm. Bull.* **12**, 696 (1964); *C.A.* **61**, 13357 (1964).
[60] S. Kobayashi, M. Azekawa, *Tokushima Daigaku Yakugaku Kenkyu Nempo* **18**, 11 (1969); *C.A.* **73**, 98558 (1970).
[61] Y. Omote, Y. Fujinama, N. Sugiyama, *Bull. Chem. Soc. Japan* **44**, 572 (1971).



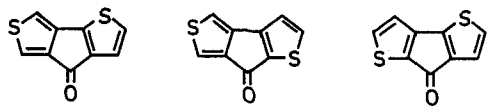
Similarly, the "head-to-tail" biphenylenes expected from a benzyne reaction were obtained by treatment of 3,4-dibromo-5-nitrotoluene[114], or 3,4-dibromo-5-nitroanisole[114], or methyl 2,3-diiodobenzoate[18] with copper in dimethylformamide. Very poor yields of the expected biphenylenes were obtained from 2,3-diiodonaphthalene[115] or 2,3-dibromo-1-nitronaphthalene[115].

4. Closure of Five-membered and Larger Rings

The facility of an Ullmann reaction leading to the closure of a five-membered ring is illustrated by the synthesis of the six thiophene analogs of fluorenone (**25**–**30**). These compounds were prepared in the yields indicated by reaction of the appropriate thiophene analog of 2,2′-dibromo- or 2,2′-diiodobenzophenone with copper powder in dimethylformamide[116]. The tetramethyl derivatives of **25** (75% yield), **26** (89% yield), and **29** (92% yield) were prepared in a similar manner[117].

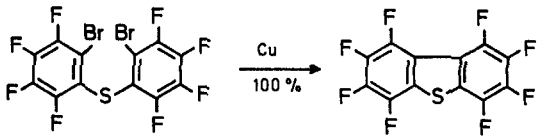


25 (100%) **26** (99%) **27** (37%)



28 (38%) **29** (57%) **30** (39%)

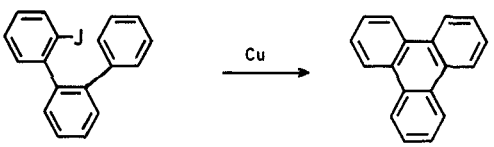
Octafluorodibenzothiophene (**31**) was obtained in quantitative yield by heating bis-(*o*-bromotetrafluorophenyl) sulfide with copper in a sealed, evacuated tube[118]. The reaction failed when it was attempted in a dimethylformamide solution.



31

Octafluorodibenzothiophene (31)[118]:
A mixture of bis(*o*-bromotetrafluorophenyl) sulfide (3.0 g) and copper powder (1.8 g) was heated at 200° for 5 days in a sealed, evacuated Carius tube. The product, isolated in quantitative yield by extraction with ether followed by sublimation, was a white solid; m.p. 99–100°. Attempts to conduct the reaction in dimethylformamide at temperatures below 150° lead to recovery of starting material, and above this temperature a complex product containing CH bonds (N.M.R. spectrum) was obtained.

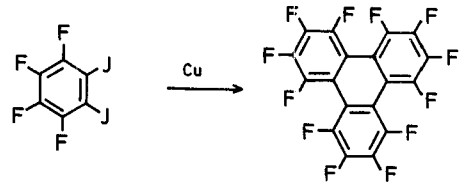
Triphenylene (**32**) was the only product isolated from the attempted Ullmann coupling of 2-iodo-*o*-terphenyl[57].



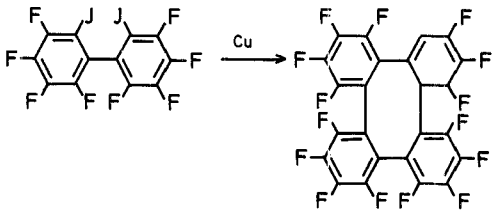
32

[62] R. F. Chapman, G. A. Swan, *J. Chem. Soc.* (C) **1970**, 865.
[63] T. Miyazaki, S. Mihashi, K. Okabayashi, *Chem. Pharm. Bull.* **12**, 1236 (1964); *C.A.* **62**, 2755 (1965).
[64] J. W. Hooper, W. Marlow, W. B. Whalley, *J. Chem. Soc.* (D) **1971**, 111.
[65] S. Ozeki, *Yakugaku Zasshi*, **85**, 206 (1965); *C.A.* **63**, 643 (1965).
[66] H. L. Pan, T. L. Fletcher, *J. Med. Chem.* **13**, 567 (1970).
[67] C. A. Bunton, G. W. Kenner, M. J. T. Robinson, B. R. Webster, *Tetrahedron* **19**, 1001 (1963).
[68] K. P. Mathai, S. Sethna, *J. Indian Chem. Soc.* **40**, 347 (1963).

The reaction of 1,2-diiodotetrafluorobenzene on heating with copper gave mainly perfluorotriphenylene (**33**), and a mixture of higher polyphenylenes. Under the same conditions, the reaction of 2,2′-diiodooctafluorobiphenyl gave perfluorotetraphenylene (**34**) in about 10% yield in addition to the expected biphenylene[111].

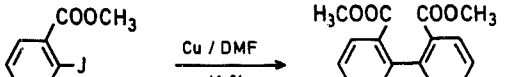


33

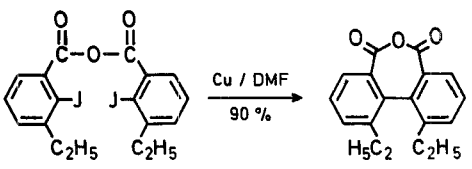


34

Similarly, it has been demonstrated that an intramolecular Ullmann reaction leading to the closure of a seven-membered diphenic anhydride ring occurs much more readily than the analogous open-chain reaction. On refluxing with copper bronze in dimethylformamide for 15 minutes, the ester **35** gave a 41% yield of the expected biphenyl (**36**), while the corresponding benzoic anhydride (**37**) gave the cyclic anhydride (**38**) in 90% yield[18].

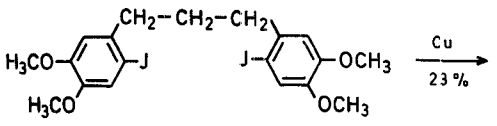


35 **36**

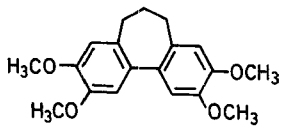


37 **38**

On the other hand, cyclization of **39**, which lacks an activating group, gave only a 23% yield of the seven-membered ring compound **40**[92].

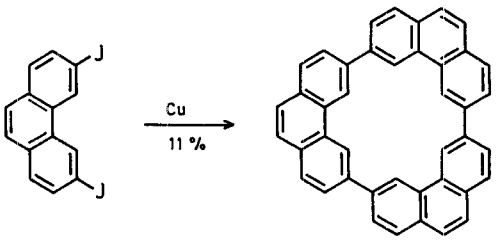


39

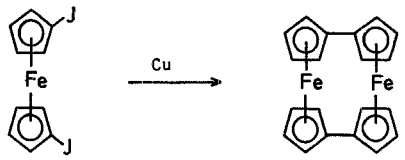


40

The Ullmann reaction of 3,6-diiodophenanthrene gave triphenanthrylene (**41**) in 11% yield[73]. 1,1′-Biferrocenylene (**42**) was obtained from the Ullmann reaction of 1,1′-diiodoferrocene, using *n*-butylferrocene or diethylbenzene as a solvent[119].



41



42

5. The Cocondensation Ullmann Reaction

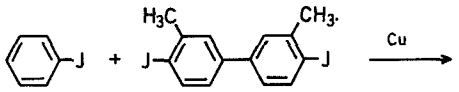
The use of the Ullmann reaction to give linear polyphenylenes has recently been comprehensively reviewed and compared with other methods of synthesis[120]. Wirth proposed the term cocondensed Ullmann reaction to designate those reactions in which a large excess of a monofunctional component reacts with a bifunctional diiodo compound in the presence of copper to give an oligopolyarylene. He developed a special apparatus equipped with a low speed stirrer and a nitrogen atmosphere and used standardized conditions to obtain consistently good yields of the desired products[122]. For example, the reaction of 4,4′-diiodo-3,3′-dimethylbiphenyl with a tenfold excess of iodobenzene, a 3.5 fold excess of copper powder, biphenyl as an inert solvent, and a few drops of mercury as an activator, gave a 43% yield of the purified dimethylquaterphenyl **43**, based on the biphenyl used[122].

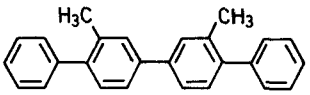
[69] D. D. Ridley, E. Ritchie, W. C. Taylor, *Aust. J. Chem.* **23**, 147 (1970).

[70] E. Fujita, K. Fuji, K. Tanaka, *Tetrahedron Lett.* **1968**, 5905.

[71] E. Moreshita, S. Shibata, *Chem. Pharm. Bull.* **15**, 1765 (1967); *C.A.* **68**, 68823 (1968).

[72] K. Suzuki, E. K. Weisburger, J. H. Weisburger, *J. Org. Chem.* **26**, 2236 (1961).

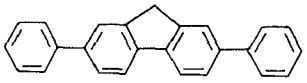




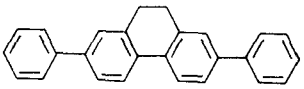
43

Together with the conventional symmetrical and unsymmetrical Ullmann reactions[124] the cocondensation reaction was used to prepare a great variety of oligopolyphenylenes. In a brief review of his work, Wirth stated that more than 70 such compounds had been prepared in his laboratory in the period 1962–1965[121] These products will not be individually itemized in the present review, instead a few selected examples will be given to illustrate the variety of compounds prepared.

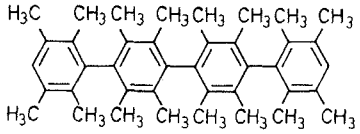
The cocondensation proved to be particularly advantageous for the preparation of certain bridged polyphenylenes such as **44**[122] and **45**[123], highly methylated products such as the hexadecamethyl-*p*-quaterphenyl **46**[126], and oxido-bridged or dibenzofuran derivatives such as **47**[127]. In dimethylformamide in the absence of a monofunctional component, 4,4′-diiodo-3,3′-dinitrobiphenyl gave a well-characterized nitropolyphenylene **48**, with iodo end groups and an average degree of polymerization of 52[125].



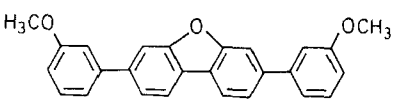
44



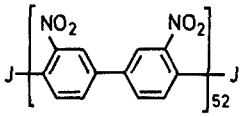
45



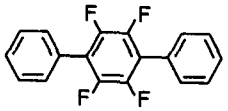
46



47



48

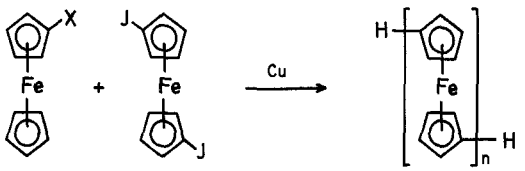


49

In addition to the examples cited in the review[120], the cocondensation technique has been used in the preparation of several highly methoxylated terphenyls[92,129,130,131], an octamethoxyquaterphenyl[132], and the tetrafluoroterphenyl **49**[133]. A French Patent reports the use of Wirth's procedure for the preparation of 46 polyphenylenes with various alkyl and alkoxy side chains[128].

2′,3′,5′,6′-Tetrafluoro-*p*-terphenyl (49)[133]:
A mixture of 1,4-dibromotetrafluorobenzene (3.0 g), bromobenzene (6.0 g), and copper bronze (10.0 g) was heated in a sealed tube at 200° for 24 hrs. The ether insoluble portion of the reaction product was sublimed to give the desired terphenyl; yield: 0.5 g, 17%; m.p. 259–260°.

Nesmeyanov and coworkers[84] reported that the cocondensation of bromoferrocene and 1,1′-dibromoferrocene gave a mixture containing a 14% yield of terferrocene (**50**) and other higher condensation products. Later Rausch expanded this study to include the reactions of chloro-, bromo-, and iodoferrocene with 1,1′-diiodoferrocene. He found that optimum yields of terferrocene were obtained by using bromoferrocene in the reaction, and he also isolated and characterized quaterferrocene, quinquiferrocene, and sexiferrocene (**51**, **52**, and **53**) from the reaction mixture[86].

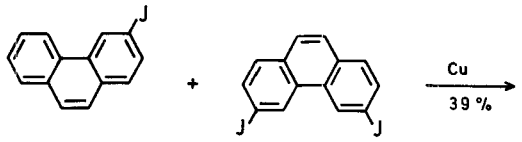


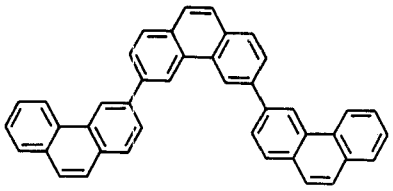
X = Cl, Br, J

50, n = 3
51, n = 4
52, n = 5
53, n = 6

The terphenanthrene **54** was obtained by the cocondensation of 3-iodophenanthrene and 3,6-diiodophenanthrene[73].

[73] H. A. Staab, H. Bräunling, K. Schneider, *Chem. Ber.* **101**, 879 (1968).
[74] Y. Nagai, K. Nagasawa, *Kogyo Kagaku Zasshi* **69**, 666 (1966); *C.A.* **66**, 37696 (1967).
[75] N. Gotoh, Y. Koga, *Seisan-Kenkyu* **19**, 175 (1967); *C.A.* **69** 58980 (1968).
[76] Y. Nagai, N. Gotoh, S. Ogawa, *Yuki Gosei Kagaku Kyokai Shi* **28**, 930 (1970); *C.A.* **74**, 43506 (1971).
[77] S. Gronowitz, K. Dahlgren, *Ark. Kemi* **21**, 201 (1963).
[78] R. Hakansson, *Acta Chem. Scand.* **23**, 952 (1969).
[79] C. Dell'Erba, G. Garbarino, G. Guanti, *Gazz. Chem. Ital.* **100**, 916 (1970).
[80] A. Etienne, G. Izoret, *French Patent* 1369401; *C.A.* **62**, 570 (1965).
[81] Z. Kulicki, W. Karminski, *Zesz. Nauk. Politech. Slask. Chem.* **16**, 11 (1963); *C.A.* **62**, 4001 (1965).
[82] W. Karminski, Z. Kulicki, *Chem. Stosow. Ser. A* **9**, 129 (1965); *C.A.* **63**, 18018 (1965).





54

6. New Developments in Reaction Techniques

Commercial copper powder is substantially activated for use in the Ullmann coupling of *p*-iodotoluene by washing it with a 0.02 *M* aqueous solution of the disodium salt of ethylenediaminetetraacetic acid. This treatment gives a reagent which compares favorably in reactivity with freshly prepared, chemically precipitated copper[134]. The use of five different copper preparations in the Ullmann synthesis of 2,2′-bipyridyl from 2-bromopyridine has been carefully studied. „Naturkupfer C", copper activated by treatment with iodine, copper precipitated from copper sulfate solution with zinc, copper precipitated with chromyl chloride, and electrolytically purified copper were compared. Electrolytic copper powder gave the best results and the purest product[81]. In a variety of Ullmann reactions of haloferrocenes, copper powder manufactured by the Schuchardt Co. of Germany gave better yields than a product of the U.S. Bronze Powder Co.[86].

In a study of the reaction of aryl halides with various copper(I) species, it was found that yields of up to 70% of 2,2′-dinitrobiphenyl were obtained when the reaction of 2-bromonitrobenzene and copper(I) oxide was conducted for 24 hours in boiling pyridine. Since the reaction of this halide with copper bronze in the conventional Ullmann procedure gives yields as high as 75%, this modification lacks any practical advantage[135].

Although copper free of copper oxide is generally specified in the Ullmann reaction, metallic copper containing a small amount of copper oxide was found suitable for the preparation of terphenyl from a mixture of bromobenzene and 4-iodobiphenyl[98]. On the other hand, the reaction of iodohydroquinone dimethyl ether gave a better yield of the expected tetramethoxybiphenyl with copper (73%) than with copper(I) oxide (47%)[44].

In a preliminary study, it was found that when 2-bromonitrobenzene in pyridine was heated with one mol of copper for six hours at 80°, the inclusion in the reaction mixture of one mol of copper(I) iodide raised the yield of 2,2′-dinitrobiphenyl from 3% to 12%. Parallel kinetic studies indicated that the promoting effect of the copper(I) iodide was due to exchange of iodine for bromine in the organic molecule prior to condensation. These results suggest that halogen-halogen exchange with copper(I) iodide may be a general procedure to permit bromoarenes to be used in the Ullmann reaction at temperatures where the reaction rate is otherwise too slow[136].

The use of dimethylformamide as a diluent in the Ullmann reaction was reported twenty years ago, and it has since been used more often than any other solvent. In a careful comparison of the effect of different solvents on the synthesis of 1,1′-bipyridyl from 2-bromopyridine, it was found that dimethylformamide permits the use of lower temperatures and a lower proportion of copper and results in a higher yield than various aromatic, aliphatic, and alicyclic hydrocarbon solvents[82]. The Ullmann reaction of methyl 3-bromo-5-nitro-2-thiophenecarboxylate was erratic in xylene, sometimes almost complete dehalogenation was observed, whereas in dimethylformamide, using electrolytically prepared copper powder, reproducible yields of 70–75% of the desired biaryl were obtained[77].

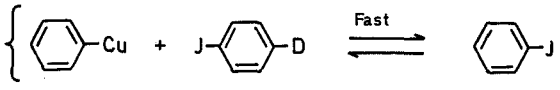
It has also been suggested, without experimental evidence, that tetramethylurea may be a superior diluent for the Ullmann reaction, since it would not be expected to cause reductive dehalogenation, and its boiling point is 23° higher than that of dimethylformamide[137].

---

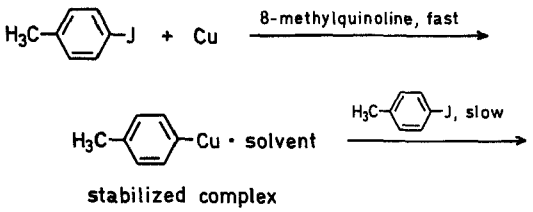
[83] D. D. Bly, M. G. Mellon, *J. Org. Chem.* **27**, 2945 (1962). D. D. Bly, *J. Org. Chem.* **29**, 943 (1964).
[84] A. N. Nesmeyanov, et al., *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* **1963**, 667; *C.A.* **59**, 7556 (1963).
[85] R. F. Kovar, *Dissertation*, University of Massachusetts (1969); *Diss. Abst. Int. B* **30**, 2090 (1969).
[86] P. V. Roling, M. D. Rausch, *J. Org. Chem.* **37**, 729 (1972), and references cited therein.
[87] M. J. S. Dewar, P. J. Grisdale, *J. Org. Chem.* **28**, 1759 (1963).
[88] G. P. Sharnin, I. F. Falyakhov, *Izv. Vyssh. Ucheb. Zaved., Khim. Khim. Technol.* **12**, 1057 (1969); *C.A.* **72**, 31346 (1970).
[89] G. W. Gribble, J. R. Douglas, Jr., *J. Amer. Chem. Soc.* **92**, 5764 (1970).
[90] M. Oki, H. Iwamura, G. Yamamoto, *Bull. Chem. Soc. Japan* **44**, 262 (1971).
[91] M. Oki, G. Yamamoto, *Bull. Chem. Soc. Japan* **44**, 266 (1971).
[92] L. Horner, K. H. Weber, *Chem. Ber.* **100**, 2842 (1967).
[93] H. I. Joschek, S. I. Miller, *J. Amer. Chem. Soc.* **88**, 3269 (1966).
[94] N. E. Stjernström, *Acta Chem. Scand.* **16**, 553 (1962).
[95] J. R. Merchant, D. D. Vaghani, C. S. Kallianpur, *J. Indian Chem. Soc.* **40**, 315 (1963).
[96] H. Erdtman, G. Eriksson, T. Norin, *Acta Chem. Scand.* **17**, 1151 (1963).
[97] J. M. Blatchly, J. W. McOmie, *J. Chem. Soc.* **1963**, 5311.
[98] K. Fujimoto, S. Arita, K. Takeshita, *Yuki Gosei Kagaku Kyokai Shi* **22**, 390 (1964); *C.A.* **61**, 4245 (1964).
[99] R. L. Hansen, *J. Phys. Chem.* **70**, 1646 (1966).
[100] C. H. Wu, H. C. Hsu, *Hua Hsueh Hsueh Pao* **28**, 388 (1962); *C.A.* **59**, 12664 (1963).

7. Mechanism of the Ullmann Reaction and Related Copper-Promoted Reactions

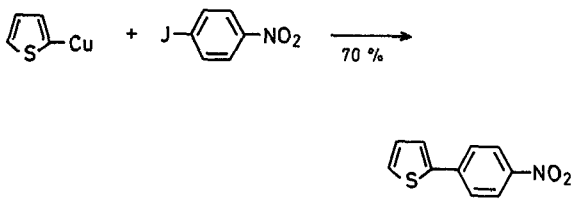
In recent years compelling evidence has been found to support the view that an arylcopper compound is an intermediate in the Ullmann synthesis of biaryls. Data obtained from a careful study of the reaction of *p*-iodotoluene with copper in 8-methylquinoline at 190° is best explained by the assumption



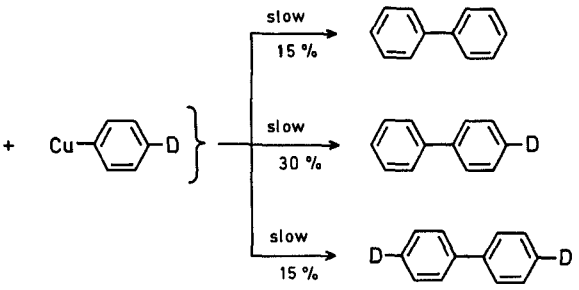
that tolylcopper is rapidly formed and stabilized in the form of a complex with the solvent, followed by a relatively slow reaction with additional *p*-iodotoluene to give 4,4'-dimethylbiphenyl[138].



This observation suggested that the preparation of unsymmetrical biaryls could be effectively accomplished in a two-step procedure consisting in the preparation of an arylcopper, followed by treatment with a different aryl halide, thus avoiding the formation of undesired symmetrical biaryls. This procedure indeed proved to be very successful for the preparation of arylthiophenes. The reaction of crude (~70% pure) 2-thienylcopper with nine different iodoarenes gave fair to excellent yields of 2-arylthiophenes. The best yield (70%) was obtained by the reaction with *p*-iodonitrobenzene in pyridine at 50° [139].

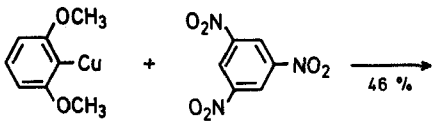


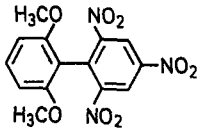
When a similar coupling reaction was tried, using phenylcopper and nine different iodoarenes, relatively large amounts of the symmetrical biaryls were obtained in addition to the desired unsymmetrical product. This is the result to be expected if copper-iodine exchange is rapid compared to the coupling reaction. For example, the reaction of phenylcopper and *p*-deuteroiodobenzene in pyridine at 50° gave biphenyl, monodeuterobiphenyl, and dideuterobiphenyl in a ratio of 1:2:1, showing that equilibration due to copper-iodine exchange was much faster than the coupling reaction[140].



A group of copper-promoted arylation reactions closely related to the Ullmann synthesis has been investigated in recent years[141]. Some of these reactions occur in good yield and may have synthetic utility superior to the conventional Ullmann reaction for the preparation of certain types of unsymmetrical biaryls. These reactions will not be reviewed systematically here, but a few examples will be cited to illustrate their relationship to the conventional Ullmann reaction.

The arylation of polynitroarenes by aryl copper compounds may be illustrated by the reaction of 2,6-dimethoxyphenylcopper with 1,3,5-trinitrobenzene in pyridine at 50° to give a 46% yield of the unsymmetrical biaryl **55**[141].

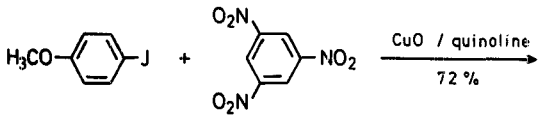


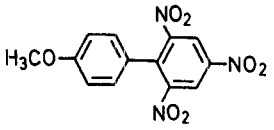


55

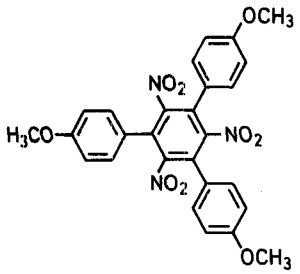
[101] J. Dale, *Acta Chem. Scand.* **11**, 640 (1957).
[102] G. Drefahl, K. Winnefeld, *J. Prakt. Chem.* **28**, 242 (1965).
[103] L. Horner, K. H. Teichmann, K. H. Weber, E. Geyer, *Chem. Ber.* **98**, 1233 (1965).
[104] D. J. Byron, G. W. Gray, R. C. Wilson, *J. Chem. Soc.* (C) **1966**, 840.
[105] E. Pettersson, N. E. Stjernström, *Ark. Kemi* **21**, 49 (1963).
[106] S. Kobayashi, C. Kuraishi, *Chem. Parm. Bull.* **10**, 1137 (1962); *C.A.* **59**, 3814 (1963).
[107] K. P. Sarbhai, K. B. L. Mathur, *Indian J. Chem.* **4**, 81 (1966).
[108] M. Goshaev, O. S. Otroshchenko, A. S. Sadykov, N. Kuznetsova, *Izv. Akad. Nauk Turkm. SSR, Ser. Fiz.-Tekh., Khim. Geol. Nauk* **1970**, 114; *C.A.* **74**, 3480 (1971).
[109] M. P. Cava, M. J. Mitchell, *Cyclobutadiene and Related Compounds*, Academic Press, New York, 1967, p. 255 and p. 317.
[110] P. R. Constantine, G. E. Hall, C. R. Harrison, J. F. W. McOmie, R. J. G. Searle, *J. Chem. Soc.* (C) **1966**, 1767.
[111] S. C. Cohen, A. G. Massey, *J. Organometal. Chem.* **10**, 471 (1967).
[112] W. Baker, N. J. McLean, J. F. W. McOmie, *J. Chem. Soc.* **1964**, 1067.

The copper(I) oxide promoted arylation of a polynitroarene by an iodoarene is illustrated by the reaction of one mol of *p*-iodoanisole, 1,3,5-trinitrobenzene, and copper(I) oxide in quinoline to give a 72% yield of the biphenyl **56**. By increasing the proportion of iodoanisole and the duration of the reaction, and also raising the temperature, the course of the reaction can be directed to give up to a 16% yield of the triarylated product **57**[142].



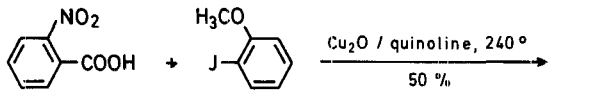


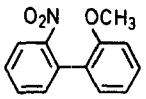
56



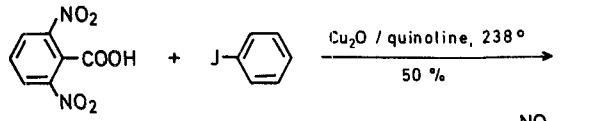
57

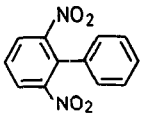
The utility of arylation by decarboxylative coupling is illustrated by the reaction of *o*-nitrobenzoic acid and *o*-iodoanisole with copper(I) oxide in quinoline at 240° to give a 50% yield of the unsymmetrical biphenyl **58**[143]. Similarly, 2,6-dinitrobenzoic acid, iodobenzene, and copper(I) oxide react in quinoline at 238° to give a 50% yield of 2,6-dinitrobiphenyl (**59**)[144].





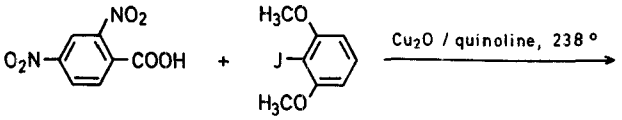
58

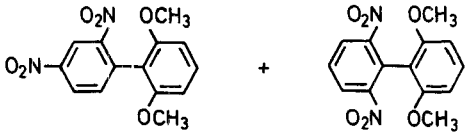




59

Unlike the conventional Ullmann coupling reaction, the biaryl bond is not formed exclusively at the position from which the carbonyl group is displaced. For example, the reaction of 2,4-dinitrobenzoic acid and 2,6-dimethoxyiodobenzene with copper(I) oxide in quinoline gave two isomeric unsymmetrical biphenyls, **60** and **61**, thus complicating the problem of isolation and purification and reducing the usefulness of this reaction in synthesis[144].





60 (45 %) **61** (10 %)

This review was completed in the library of Argonne National Laboratory during an appointment as a Resident Associate under the Faculty Research Participation Program of the Argonne Center for Educational Affairs, June–August, 1972. The search of Chemical Abstracts was aided by students in the chemical literature course at Illinois Institute of Technology. Several important references were found with the help of Science Citation Index (1961 and 1964–1971).

Received: August 14, 1972.

Note added in Proof

Another review of the Ullman reaction has been published recently[145].

[113] K. Iqbal, R. C. Wilson, *J. Chem. Soc.* (C) **1967**, 1690.
[114] C. R. Harrison, J. F. W. McOmie, et. al., *J. Chem. Soc.* (C) **1966**, 1769.
[115] E. R. Ward, J. E. Marriott, *J. Chem. Soc.* **1963**, 4999.
[116] P. Jordens, G. Rawson, H. Wynberg, *J. Chem. Soc.* (C) **1970**, 273.
[117] A. K. Wiersema, S. Gronowitz, *Acta Chem. Scand.* **24**, 2593 (1970).
[118] R. D. Chambers, J. A. Cunningham, J. D. Spring, *Tetrahedron* **24**, 3997 (1968); *British Patent* 1180743; *C.A.* **72**, 132501 (1970).
[119] F. L. Hedberg, H. Rosenberg, *J. Amer. Chem. Soc.* **91**, 1258 (1969).
[120] J. G. Speight, P. Kovacic, F. W. Koch, *Synthesis and Properties of Polyphenyls and Polyphenylenes*, in *Reviews in Macromolecular Chemistry*, Vol. 6, edited by G. B. Butler, K. F. O'Driscoll, and M. Shen, Marcel Dekker, Inc., New York, 1971, p. 295.
see also W. Ried, D. Freitag, *Angew. Chem.* **80**, 932 (1968); *Angew. Chem. Internat. Ed. Engl.* **7**, 835 (1968).
[121] H. O. Wirth, *Chem. Ztg.* **89**, 517 (1965).
[122] H. O. Wirth, K. H. Gönner, R. Stück, W. Kern, *Makromol. Chem.* **63**, 30 (1963).

[123] H. O. Wirth, K. H. Gönner, W. Kern, *Makromol. Chem.* **63**, 53 (1963).
[124] H. O. Wirth, W. Kern, E. Schmitz, *Makromol. Chem.* **68**, 69 (1963).
[125] H. O. Wirth, R. Müller, W. Kern, *Makromol. Chem.* **77**, 90 (1964).
[126] H. O. Wirth, F. U. Herrmann, W. Kern, *Makromol. Chem.* **80**, 120 (1964).
[127] H. O. Wirth, G. Waese, W. Kern, *Makromol. Chem.* **86**, 139 (1965).
[128] E. Merck, A. G., *French Patent* 1488494; *C.A.* **69**, 43621 (1968).
[129] M. Lounasmaa, *Acta Chem. Scand.* **19**, 540 (1965).
[130] N. E. Stjernström, *Acta Chem. Scand.* **14**, 1274 (1960).
[131] J. Gripenberg, M. Lounasmaa, *Acta Chem. Scand.* **20**, 2202 (1966).
[132] H. Erdtman, M. Granath, G. Schultz, *Acta Chem. Scand.* **8**, 1442 (1954).
[133] M. T. Chaudhry, R. Stephens, *J. Chem. Soc.* **1963**, 4281.
[134] A. H. Lewin, M. J. Zovko, W. H. Rosewater, T. Cohen, *Chem. Commun.* **1967**, 80.
[135] R. G. R. Bacon, S. G. Pande, *J. Chem. Soc.* (C) **1970**, 1967.
[136] C. Björklund, *Acta Chem. Scand.* **25**, 2825 (1971).
[137] A. Lüttringhaus, H. W. Dirksen, *Angew. Chem.* **75**, 1059 (1963); *Angew. Chem. Internat. Ed. Engl.* **3**, 260 (1964).
[138] A. H. Lewin, T. Cohen, *Tetrahedron Lett.* **1965**, 4531.
[139] M. Nilsson, C. Ullenius, *Acta Chem. Scand.* **24**, 2379 (1970).
[140] M. Nilsson, O. Wennerström, *Acta Chem. Scand.* **24**, 482 (1970).
M. Nilsson,, O. Wennerström, *Tetrahedron Lett.* **1968**, 3307.
[141] C. Björklund, M. Nilsson, O. Wennerström, *Acta Chem. Scand.* **24**, 3599 (1970), and references cited therein.
[142] C. Björklund, M. Nilsson, *Acta Chem. Scand.* **22**, 2581 (1968).
[143] M. Nilsson, *Acta Chem. Scand.* **20**, 423 (1966).
[144] C. Björklund, M. Nilsson, *Acta Chem. Scand.* **22**, 2585 (1968).
[145] M. Goshaev, O. S. Otroshchenko, A. A. Sadykov, *Russian Chemical Reviews* **41**, 12 (1972).