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MODERN METHODS OF ARYL–ARYL BOND FORMATION

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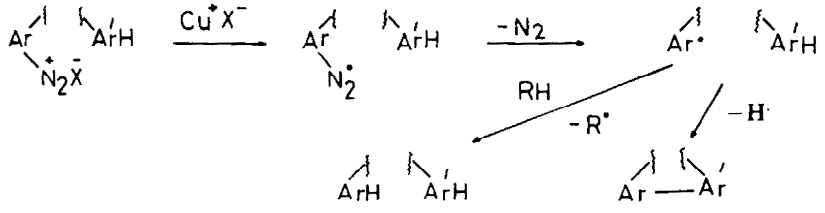
INTRODUCTION

The requirement to introduce a bond between two aromatic rings, either intra- or inter-molecularly, is a problem familiar to many organic chemists. Fortunately there is a wide variety of procedures that may be adopted, some of which are based upon named reactions. Needless to say, these traditional approaches are individually well documented so that it is not the intention in this report to deal with them in depth, but rather to describe most of them together with some of the newer oxidative techniques which have emerged in the last decade or so. Where possible the various methods will be critically examined against one another so that the choice between them is, hopefully, made easier for the synthetic organic chemist. The extent of the coverage is not uniform and a somewhat heavier emphasis is laid on those areas which are within the direct interests of the author and where the review literature is out of date.

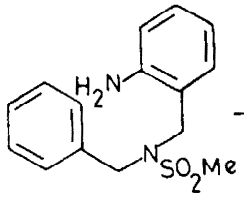
1. PSCHORR REACTION

The Pschorr reaction has a long history;[1] it involves the intramolecular substitution of arenes by aryl radicals which are generated by the reduction of arene diazonium salts with copper(I) ion.[2–4] Aryl diazenyl radicals are intermediates in the reaction, and these rapidly eliminate nitrogen affording the required aryl radicals for C–C bond formation.[5–10] Yields may be lowered when protic solvents are employed, for hydrogen abstraction from the solvent now competes with arylation:[11–15]



The application of the Pschorr technique to organic synthesis has been comprehensively reviewed,[16–19] so that only a few examples need be cited here. These are selected so that comparisons may be made later with similar reactions which utilise modern reagents.

Typical Pschorr cyclisations are illustrated by the synthesis of 6-mesyl-6,7-dihydro-(5H)-dibenz[c,e]azepine (**2**) from the diazonium salt of 2-amino-N-methanesulphonyl dibenzylamine[20] (**1**) and (±)-thalicsimidine (**4**) from the corresponding salt of the 2′-aminotetrahydroisoquinoline (**3**).[21]



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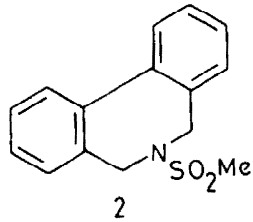

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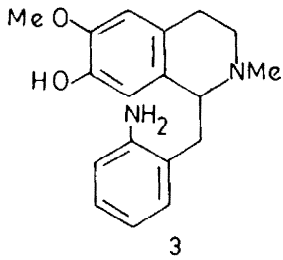

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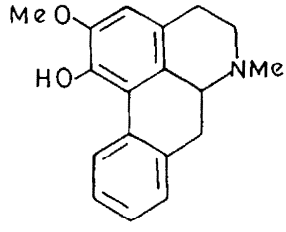

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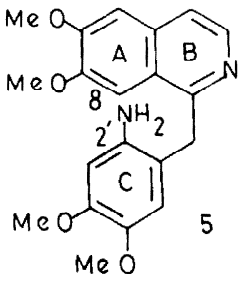
Starting compounds for Pschorr cyclisations are not always easily prepared and the yields of ring-closed products are modest, on the other hand the position of bond formation is usually unambiguous. Naturally steric effects are important thus in the case of 2′-aminopapaverine (**5**) for example, a Pschorr reaction gives the imidazole **6** and the indenoisoquinoline **7** rather than the dehydroaporphine that might have been expected. Unlike that of the tetrahydroisoquinoline **3**, however, the B ring of 2′-aminopapaverine is rigid and direct C2′–C8 attack is no longer favoured.[22]



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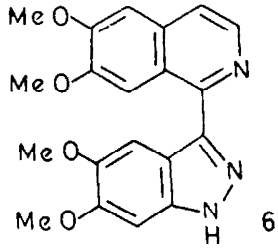

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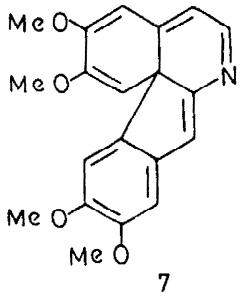

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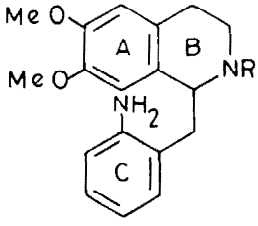
In a similar manner the size of the N substituent in 1-benzyltetrahydroisoquinolines (**8**) influences the amount of aporphine formed.[23] The larger the group the more ring C is forced to assume a position underneath and close to ring A, thus the yield of the aporphine (**9**) increases in the order R = H(7.2%) > R = Me(23%) > R = CH_2Ph(25.4%). A further increase in substituent size is not advantageous, and when R = $CH(Ph)_2$ the yield falls to 15.7%.



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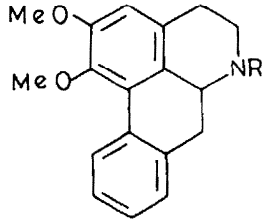

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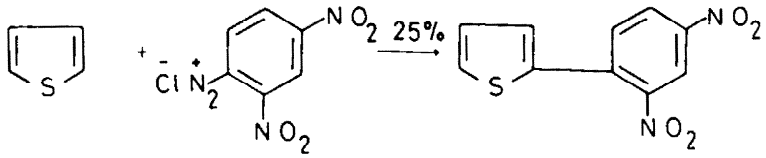
Modifications to the Pschorr reaction include the decomposition of diazonium salts by thermal and photochemical means,[24] and these techniques may be used to form intermolecularly coupled products.[25] Electrochemical reduction has also been employed,[26] but yields in all these procedures are poor. On the other hand a Pschorr-type reaction between aryl diazonium salts and phenols promoted by titanium(III) ion gives rather better yields of arylphenols than are obtained with traditional Pschorr or photo-Pschorr methods.[27]

2. GOMBERG, BACHMANN, HEY REACTION

The Gomberg, Bachmann, Hey reaction is another of the classical routes to biaryls, the scope and limitations of which have been reviewed.[28–30] Recent references to the so-called "G–B–H" reaction are few since yields are generally poor. Formally this and the Pschorr procedure are related: they both require the decomposition of diazonium salts, one typically in alkaline solution and the other in acid. A comparatively recent example of the "G–B–H" reaction is provided by the synthesis of 2-(2,4-dinitrophenyl)thiophene (**10**) from thiophene and the diazonium salt of 2,4-dinitroaniline.[31]



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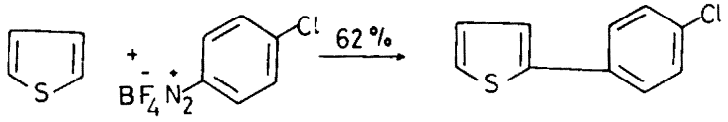
An improvement on the classical approach has been reported by Gokel *et al*,[32] whereby the reaction is conducted in a non-aqueous solvent making use of the phase-transfer catalyst 18-crown-6. Productivity is significantly greater and in an illustrative experiment 4-chlorophenyldiazonium tetrafluoroborate was reacted with thiophene to produce 2-(4-chlorophenyl)thiophene (**11**) in 62% yield.



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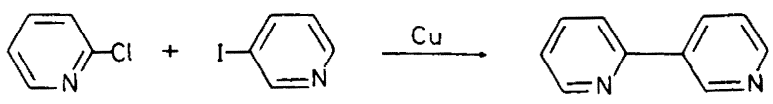
3. ULLMANN BIARYL SYNTHESIS AND RELATED REACTIONS

The Ullmann reaction like the Pschorr reaction has long been employed by chemists to generate a bond between two aromatic nuclei. Typically two molecular equivalents of aryl halide are reacted with one of finely divided copper to form a biaryl and copper halide. This procedure which is closely related to other reactions employing copper or organo-copper compounds has been extensively surveyed,[33–37] and it seems that electronegative functions such as nitro or methoxycarbonyl groups, especially when substituted *ortho* to the halogen atom in the aryl halide, provide an activational effect. Some others particularly amino, hydroxyl or free carboxyl groups limit the reaction by providing alternative sites at which the second aryl halide can attack. Large functions in the *ortho* positions exert an inhibitive steric influence.

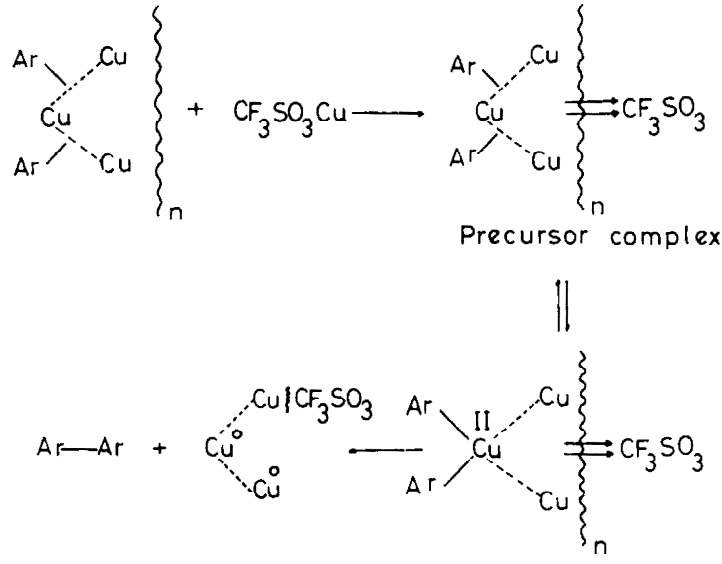
One major advantage of the Ullman reaction is that unsymmetrically substituted arenes may be coupled and it is common practice to react an activated aryl halide with another which is relatively inert. Thus the slow addition of excess 2-chloropyridine to a suspension of copper powder in N,N-dimethylformamide containing 3-iodopyridine affords 2,3′-bipyridyl in 42% yield.[38]



Scheme 1.

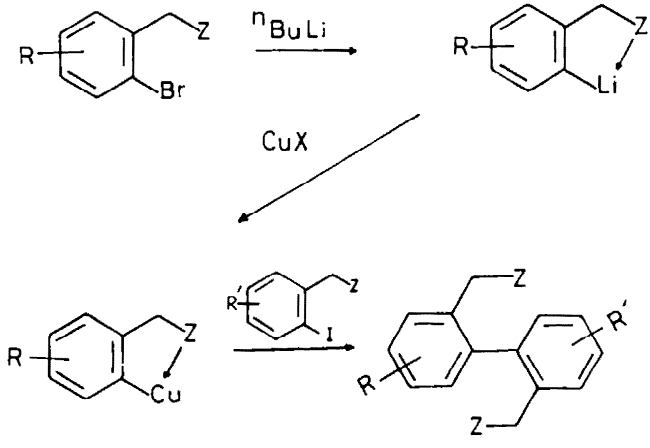
Another route to unsymmetrical biaryls requires a two-step sequence and stems from the generally held view that mechanistically the Ullmann reaction proceeds through the agency of aryl-copper intermediates.[39,40] A development of this approach has been used by van Koten and Noltes[41] to prepare symmetrical biaryls in very high yields. Here an aryl copper compound is reacted with copper(I)trifluoromethanesulphonate in an exact 1:1 molar ratio to give copper metal and the biaryl.

This reaction is thought to require the formation of a precursor complex by a process involving valence disproportionation inside the Cu_n core, followed by the reductive elimination of the biaryl:



Scheme 2.

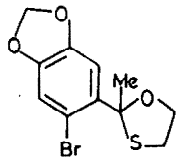
In yet another varient, Zeigler *et al*[42] have developed a technique which achieves a low temperature and consistently productive coupling reaction between unsymmetrical aryl halides. Here a copper(I) aryl species **12**, stabilized intramolecularly by a heteroatom, is generated from one aryl halide and reacted with another bearing an *ortho* substituent which may also function as a ligand. The strategy is summarized in the following sequence:



12 . Z = N or S

Scheme 3.

This concept is not new and intramolecular ligand-stabilized aryl–Cu,[43] –Pt,[44] –Pd[45] and –Ag[46] complexes have been used before, but only to couple symmetrically substituted aryl halides. As an illustration of the new method the oxathiolane **13** was reacted with the imine **14**. Hydrolysis of the product **15** gave the biaryl aldehyde **16** as a mixture of diastereoisomers in 82% yield. The aldehyde was then employed as an intermediate en route to the cytotoxic lignan (±)steganacin (**17**).



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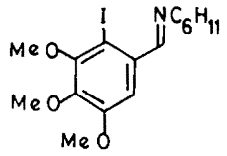

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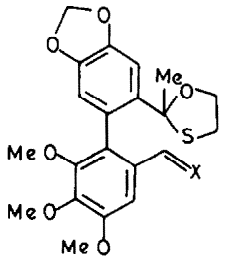
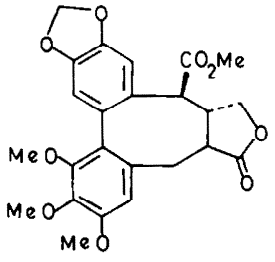


15, X = NC_6H_{11}
16, X = O

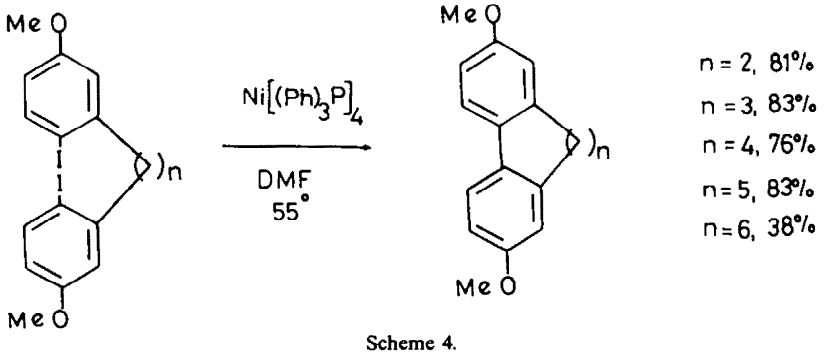


17

Improved yields in traditional Ullmann reactions can be achieved through the use of an activated form of Cu powder, made by the reduction of copper(I) iodide with K.[47] The major advantage, however, is that the reaction can now be carried out at lower temperatures than normally employed: thus pentafluorophenyl iodide in 1,2-dimethoxyethane solution at 85° with this catalyst affords decafluorobiphenyl in 83% yield. Hitherto a sealed vessel and temperatures of 300° were necessary in order to achieve a 72% conversion.[48]

Classical Ullmann reaction procedures are still commonplace in the literature of organic chemistry, but for symmetrical biaryl syntheses, at least, the use of zerovalent Ni appears to be more productive. The original method discovered by Semmelhack[49] utilises isolable bis(1,5-cyclooctadiene) nickel (0), or tetrakis(triphenylphosphine) nickel (0) as catalysts—both of which are air sensitive and rather difficult to prepare. By reacting bis(triphenylphosphine) nickel(II) dichloride and triphenylphosphine in N,N-dimethylformamide solution the more stable tris-(triphenylphosphine) nickel (0) can be prepared and Kende *et al.* have recommended[50] this compound as an Ullmann catalyst. It may be, however, that interest in the original procedure will be revitalized now that Mori *et al.* have shown[51] that tetrakis(triphenylphosphine) nickel (0) can be prepared *in situ*. Additionally, Zembayashi *et al.* claim[52] that aryl–aryl coupling can be achieved between aryl halides with catalytic amounts of nickel(II) ion and Zn powder as the ultimate reductant, and Takagi *et al.*, suggest[53] the use of Ni species derived from the reduction of nickel(II) chloride with Zn in tris(trimethylamino)phosphine oxide solution.

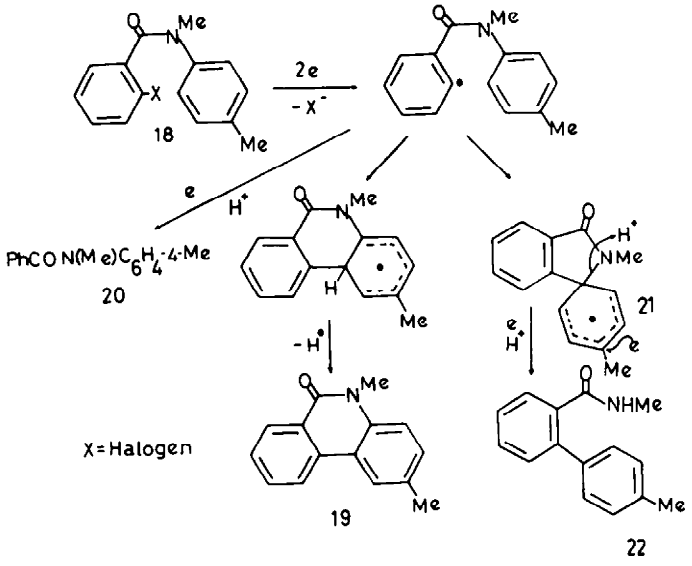
Whatever eventually turns out to be the best system Semmelhack and Rono's[54] yields (shown in brackets below) for the cyclisation of bis(2-iodophenyl)alkanes are impressive:



Scheme 4.

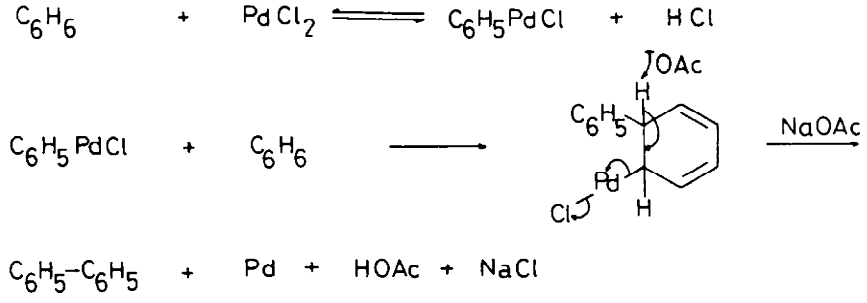
The mechanism by which nickel (0) alkylphosphine complexes react with aryl halides has been analysed in detail by Tsou and Kochi[55] and consequently this topic will not be discussed here.

Grimshaw *et al.*[56] have shown that the electrochemical coupling of aryl halides is possible. Cathodic reduction of the amide **18**, for example, gives the phenanthridone **19**, accompanied by the dehalogenated products **20** and **22**. The last compound is presumed to arise *via* a spiro radical intermediate **21** which is further reduced and then cleaved by protonation. In this and similar reactions[57,58] the nature of the halogen atom is important and the optimum yields of phenanthridones are obtained with chlorocompounds.



4. COUPLING OF ARENES WITH PALLADIUM(II) COMPLEXES[59]

Biphenyl can be obtained by heating benzene with palladium(II) chloride and sodium acetate at 90° in acetic acid solution.[60] As the reaction proceeds Pd metal is deposited, but no coupling occurs unless acetate ion is present. The rate determining step is considered to be the formation of a σ-bonded aryl–Pd(II) complex, followed by a fast breakdown of the complex. The latter is initiated by attack of acetate anion.

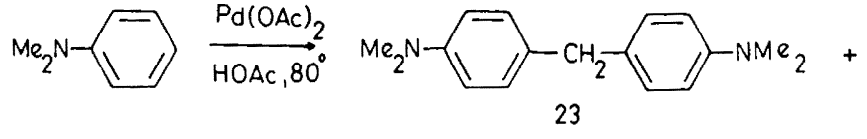


Scheme 5.

Arylation of substituted benzenes follows the usual orientation pattern expected for electrophilic attack, but the total reaction is extremely rapid in trifluoroacetic acid solution.[61,62] However, the obvious extension to the use of palladium(II) trifluoroacetate as a reagent for arene coupling is not

always practical since polynuclear complexes containing Pd(I) and Pd(II) are formed, as well as polyarenes.[63]

Palladium(II) acetate, on the other hand, is a very useful oxidant and may be employed, usually in acetic acid solution, to couple arenes and heteroarenes. Benzylic oxidation can be a problem with alkylbenzenes, however, and toluene, for example, yields benzylacetate, benzaldehyde and benzylidine diacetate, as well as 4,4'-dimethylbiphenyl.[64,65] In the case of N,N-dialkylanilines intermolecular coupling is replaced by carbon abstraction, probably from a Me group of palladium(II) acetate. N,N-Dimethylaniline, for example, yields N,N,N',N'-tetramethyldiaminodiphenylmethane (**23**; 72%), crystal violet (**24**; 16%) and a trace of N,N-dimethyl-4-toluidine[66] (**25**).



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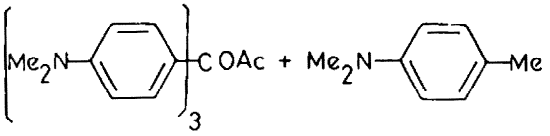

24 25

1-Benzoylpyrrole couples normally to give 1,1'-dibenzoyl-2,2'-bipyrrole (**26**)[67] and carbazoles afford dicarbazyls (**27**)[68] in about 50% yields.

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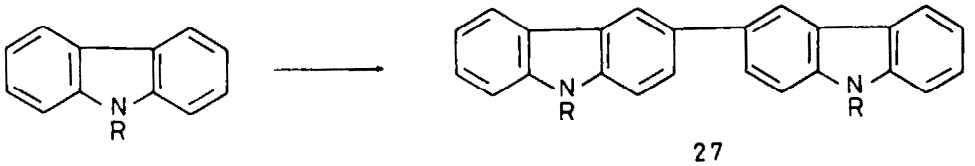


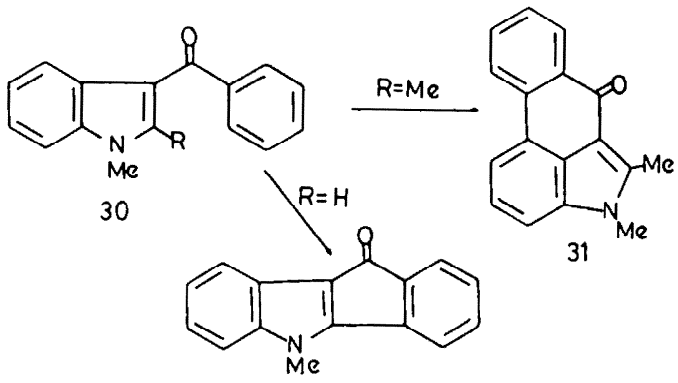
27

Intramolecular cyclisations are in general much more successful, and in a clear demonstration of the versatility of the approach Eberson *et al.*[69] have ring-closed a number of compounds of the general formula **28** (Percentage yields of products **29** are shown in brackets).

28 29

X=O (90%), X=NH (70%), X=NMe (80%), X=CO (65%), X=CONH (75%)

Coupling between systems of differing oxidation potentials is also possible; thus the 3-benzoylindole **30** (R = Me) affords the tetracycle **31**. When R = H the linear compound **32** is produced.[70] In similar substrates other oxidants often yield dehydrodimers rather than stimulating intramolecular coupling, the new bond forming from the more easily oxidised unit (see p. 14).



Biaryl synthesis can be made catalytic with respect to Pd if oxygen is present. It is claimed,[71] for example, that bitolyls can be made in 20,600% yield (based on palladium(II) acetate) from toluene and oxygen at 150° for 16 hr. Radical species are probably involved, but the precise mechanism is uncertain. Thiophene dimerizes to 2,2'-dithienyl and 2,3'-dithienyl under similar circumstances.[72] Palladium(II) salts react with arylmercury(II) compounds to afford biaryls, the following mechanisms are proposed.[73]

$$ArHgX + PdX_2 \rightarrow ArPdX + HgX_2$$

$$ArPdX + ArH \rightarrow Ar\text{-}Ar + Pd + HX$$

or

$$ArPdX + ArHgX \rightarrow Ar\text{-}Ar + Pd + HgX_2$$

Arylmercury(II) derivatives are readily available and may be purified by crystallisation. When reacted with copper and a catalytic amount of palladium(II) chloride in pyridine these compounds are readily converted to biaryls under mild conditions. This, together with the fact that the reaction is effective with substrates containing amino and substituted amino substituents, makes it a useful adjunct to the Ullmann procedure (see section 3).

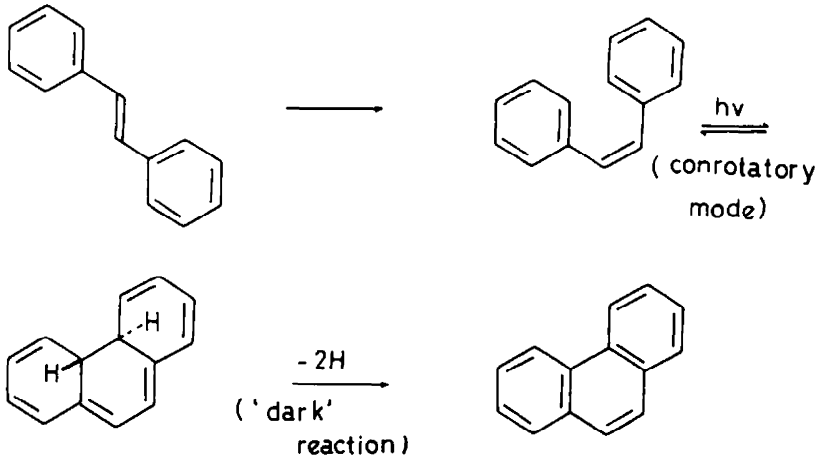
Using this technique 4,4'-dichlorobiphenyl is obtained from 4-chlorophenylmercuric acetate in 62% yield and 4,4'diacetamidobiphenyl from 4-acetamidophenyl mercuric acetate in 69% yield.[74] However, substrates bearing free hydroxyl or carboxylic acid functions fail to couple.

5. PHOTOCHEMICAL METHODS OF ARYL–ARYL BOND FORMATION

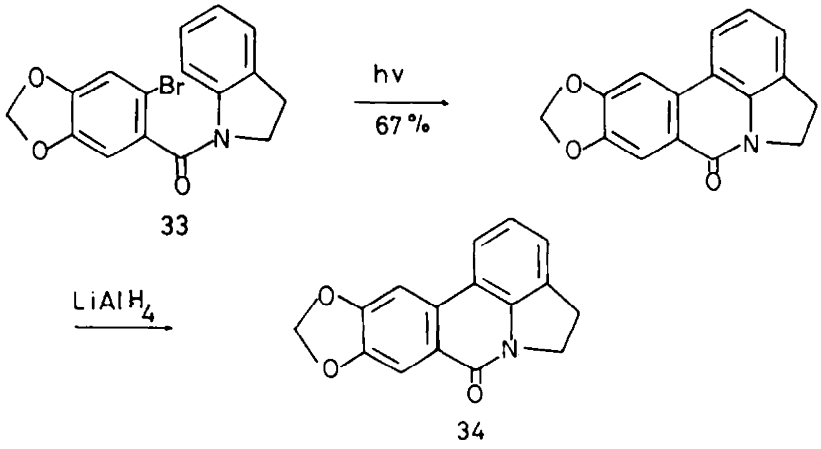
One of the earliest examples of photochemical aryl–aryl bond formation is the conversion of *trans*-stilbene in cyclohexane solution to give phenanthrene.[75] Since stilbenes are readily available, photocyclisation forms the basis of a very convenient route to phenanthrenes and related compounds. Mechanistically the irradiation of stilbenes involves *trans–cis* isomerisation and reversible ring-closure to a *trans*-4a,4b-dihydrophenanthrene which then undergoes dehydrogenation to the fully aromatic species. The relative stereochemistry of the dihydrophenanthrene intermediate follows from simple orbital symmetry considerations which have been discussed by many authors.[76–78]

Various "so called" hydrogen abstractors are sometimes added to improve the yield, the commonest being iodine, although Bendig *et al.*[79] recommend tetracyanoethene as the most effective reagent. The range and limitations of the photochemical synthesis has been surveyed a number of times,[80–82] and an interesting and useful modern development has been the utilisation of the double bond character of amides to produce phenanthridones.[83,84] For example, anhydrolycorine (**34**) has

been synthesised by photolysis of the *o*-bromobenzanilide (**33**) derivative, followed by reduction of the product tetracycle with lithium aluminium hydride.[85]

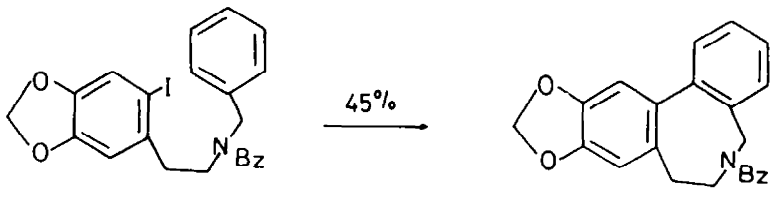


Scheme 6.



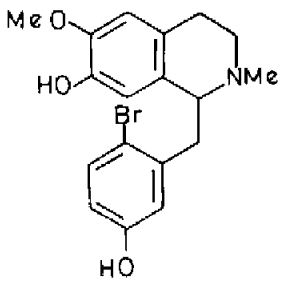
33 34

Trienic systems or their aza-equivalents are not always necessary where the intramolecular cyclisations of aryliodides and bromides are concerned. Presumably aryl radicals are now generated and Kihara and Kobayashi have shown,[86] for example, that the photolysis of N-benzyl-2-iodo-4,5-methylenedioxy-β-phenylethylamine (**35**) affords the corresponding dibenzoazocine (**36**) directly.



35 36

Similarly, irradiation of the 2′-bromo-1-benzyltetrahydroisoquinoline (**37**) in alkaline solution furnishes the aporphine **38** in a significantly higher yield than is possible by chemical oxidation of the 2′-debromo analogue.[87]



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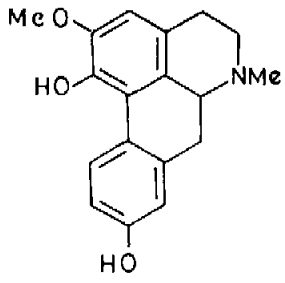
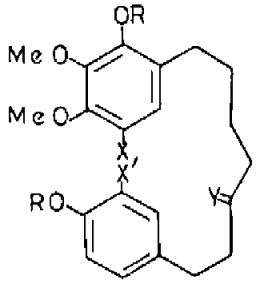


38

In the case of amines the success of most other methods of coupling depends upon the need to protect the N atom. This is not required here, so that the photocyclisation of the appropriate halogeno derivatives is a valuable technique, despite the fact that extra steps are necessary in order to introduce the halogen substituent. An interesting comparison of the effectiveness of a number of aryl–aryl coupling methods is provided by the synthesis of myricanone (**40**, Y = O) and (±)-myricanol (**40**, Y = H, OH).[88] Direct oxidation of the parent phenol **39** (R = X = X′ = H, Y = O) with potassium hexacyanoferrate(III) (p. 3337), silver(I) oxide, (p. 3337), manganese(IV) oxide, or vanadium oxytrichloride (p. 3347) gave only tars, whereas thallium tris(trifluoroacetate) (p. 3352) caused C–O coupling within the substrate affording the 14-oxa[7,1]metaparacyclophane **41** analogous to the natural products acerogenin-A (**42**)[89] and gleon (**43**).[90]

Reductive coupling of the bisiodide **39** (R = Bz; X = X′ = I; Y = O) with tetrakis-(triphenylphosphine) nickel (0) (p. 3331) led, after debenzylation, to myricanone in ~10% yield. The acetate (R = Bz; X = X′ = I; Y = H,OAc) similarly gave (±)-myricanol.

Irradiation of the bromide **39** (R = Bz; X = Br; X′ = H, Y = O) also afforded myricanone, after debenzylation. The yield being almost the same as with the nickel reagent.



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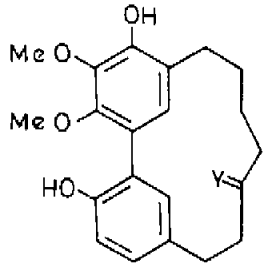

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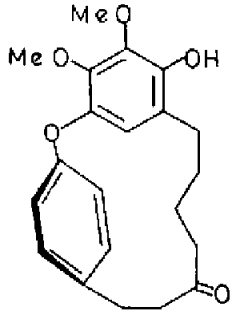

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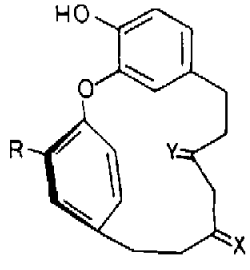


42; X = H, OH : Y = H_2 : R = H

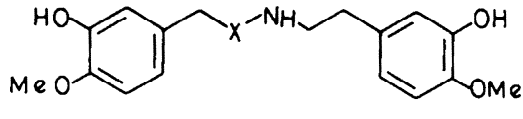
43; X = H_2 : Y = O : R = OMe

6. PHENOLIC OXIDATIVE COUPLING

The biogenesis of many natural products occurs through the oxidative coupling of phenols, and the recognition of this fact has stimulated an immense amount of work aimed at achieving biomimetic syntheses, particularly of alkaloids, lignans and their cogeners. Fortunately there are numerous reviews and monographs on this subject[91-95] and it is not the object of the present work to do more than comment upon some modern developments.

The major drawback to the use of traditional oxidants such as iron(III) chloride or potassium hexacyanoferrate(III) to achieve coupling between hydroxylated arenes in aqueous alkaline solution is the probability of over oxidation of the products which are themselves phenols. Nowadays, two phase systems are frequently utilized in which the phenolate anion is oxidised in the aqueous layer and, hopefully, the products are then protected from further oxidation by rapid diffusion into the organic phase. The addition of a phase transfer catalyst is helpful and with cetyltriethylammonium bromide and using a two phase system a 44% conversion of the bisphenol **44** (X = CH_2) into the crysodienone **45** has been achieved.[96]

However, with the corresponding amide **44** (X = CO) only 5% of the azoninone **46** was obtained.[97] Iron(III)chloride-N,N-dimethylformamide (DMF) complex[98] $[Fe(DMF)_3Cl_2]^+[FeCl_4]^-$ failed to yield any azoninone. Manganese(IV)oxide with silica as diluent caused over oxidation,[99] but vanadium oxytrichloride[100] effected a 16% yield (see Section 8).



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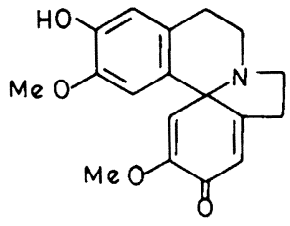

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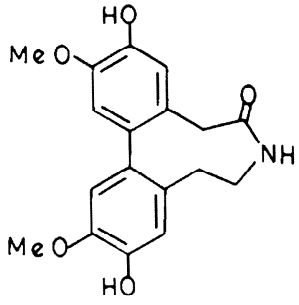
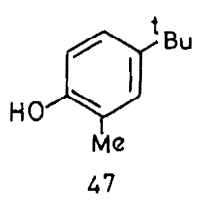


46

Part of the problem with this particular substrate is undoubtedly the adverse geometry of the amide unit (see p. 3342) but such a low yield in the phenolic oxidation reaction is quite common and emphasises most dramatically the differences between reactions *in vivo* and *in vitro*. Indeed the general assumption that the oxidative coupling of phenols in Nature always proceeds through the dimerization of aryloxy radicals has been challenged.[101,102] Silver(I) oxide has found some application in phenolic coupling, but it is a more vigorous oxidant than potassium hexacyanoferrate(III). Thus, whereas the latter reacts with 4-t-butyl-2-methylphenol (**47**) to give the C–C coupled biaryl **48**, silver(I) oxide brings about two further C–O couplings with the incorporation of a third molecule of the phenol to furnish the tetracycle **49**.[103]

Copper(II)benzoate is sometimes used as an oxidant, affording in the case of 2-t-butyl-4-methylphenol the *ortho–ortho* coupled dehydrodimer **50**,[104] but when copper(II)amine complexes are employed in the presence of oxygen the *ortho–para* coupled Pummerer's ketone **51** is obtained.[105] This last compound is also a by-product of the potassium hexacyanoferrate(III) oxidation of the same phenol.[106] With other phenols, copper-amine complexes may cause polymerisation.[107,108]

Bis(salicylidene)ethylenediimino cobalt functions as a catalyst in the oxidative coupling of tocopherol models[109] (e.g. **52** → **53**) and in a series of patents Rutledge has demonstrated that it is possible to oxidatively "dimerize" simple phenols using as catalysts first row transition metal chelates of diketones,[110a] dicarboxylic acids,[110b] aminoketones,[110c] guanidine[110d] and polyimino acids.[110e]



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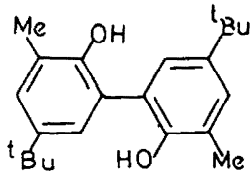

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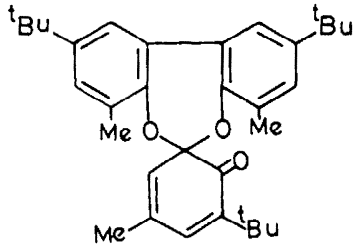

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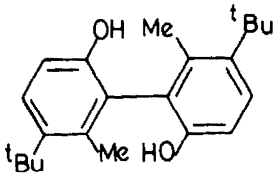

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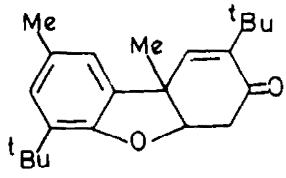

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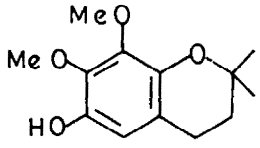

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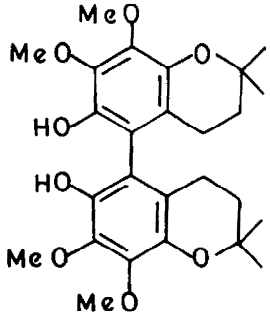

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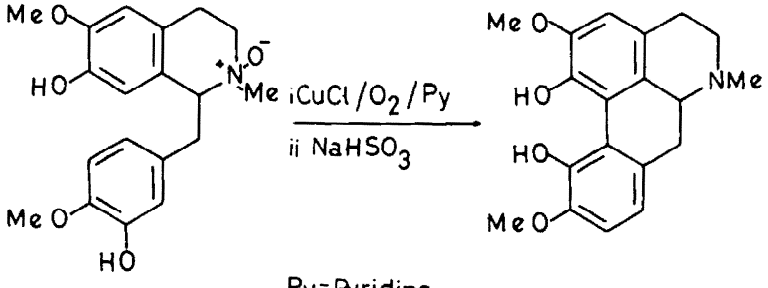
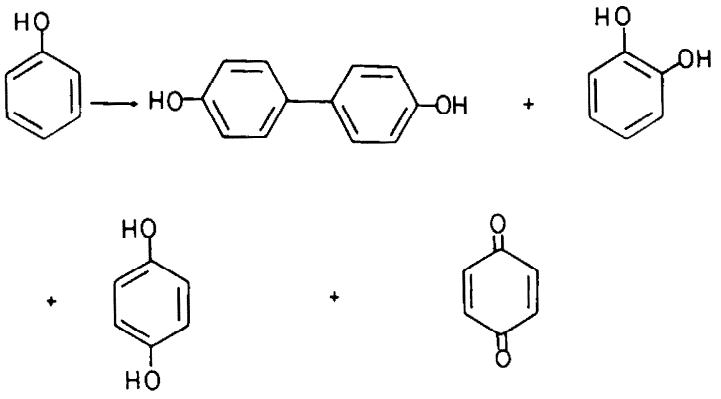


54 55

Kametani[111] claims that copper(I)chloride, pyridine and molecular oxygen[112] is the system of choice for phenolic coupling, especially with isoquinoline substrates. For example, reticuline N-oxide (**54**) affords corytuberine (**55**) in 28% yield.[113] The regiospecificity of the coupling reaction is assumed to be due to the participation of a copper-organo complex.

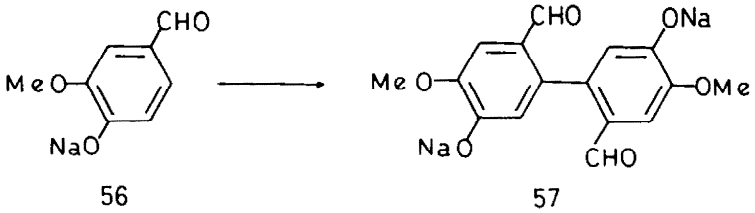
7. ANODIC OXIDATION

In 1916 Fitcher showed[114] that oxidation of phenol in dilute sulphuric acid solution at a lead dioxide anode gave a small yield of 4,4′-dihydroxybiphenyl, together with catechol, quinol and *p*-benzoquinone.

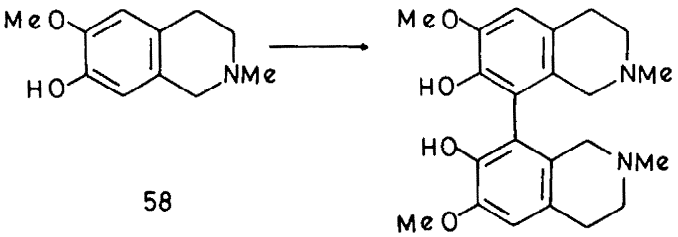


Scheme 7.

Later, the same author reported[115] that methoxylated benzenes also underwent oxidative coupling to form the corresponding methoxylated biaryls in moderate amounts, thus providing the basis for a very versatile route to a wide variety of biaryl derivatives. However, this information was largely ignored until Vermillion and Pearl studied[116] the oxidation of phenols by voltammetric analysis and demonstrated that sodium vanillate (**56**) could be coupled to the biaryl **57**. In a parallel study Bobbitt *et al.*[117] produced the dehydrodimer **59** by anodic oxidation of the alkaloid corypalline **58** at a carbon electrode.



56 57

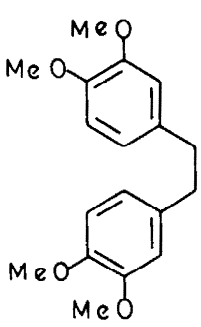


58 59

In these and related pioneering studies,[118] intermolecular reactions were being considered. However, the greatest application of anodic coupling to date has centred on intramolecular cyclisations. Thus Ronlán and Parker[119] were the first to describe the synthesis of the phenanthrene **61** by the oxidation of 3,4,3′,4′-tetramethoxybibenzyl (**60**) in acetonitrile solution containing lithium perchlorate as supporting electrolyte at a Pt electrode.

It will be noted that here, in addition to ring-closure, further oxidation of the alkyl chain has occurred, illustrating a problem common to all oxidative procedures, namely how to prevent over oxidation of products as, or more, easily oxidised than the starting materials. In this case it was overcome simply by reversing the current direction at the end of the reaction, and in this way the 9,10-dihydrophenanthrene **62** was obtained.[120]

This type of cyclisation procedure is not restricted to the formation of 6-membered rings, and bis-(3,4-dimethoxyphenyl)alkanes of the type **63** where n ranges from 1–16 have been oxidised to afford varying yields of tetracyclic products.[121]



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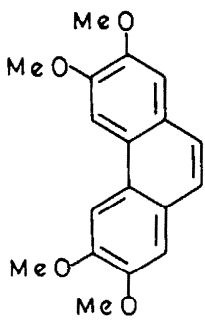

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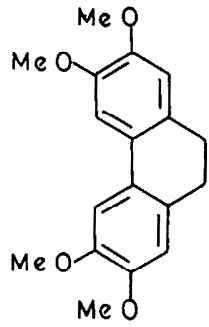

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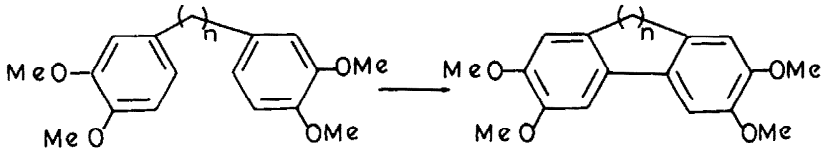
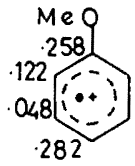


63

The mechanism by which methoxylated diarylalkanes undergo coupling is the subject of much debate. In the first place the aryl–aryl bond usually forms *para* to existing OMe groups. This is a fairly obvious result which corresponds with electron density calculations made by Zweig *et al.*[122] from data provided by electron spin resonance spectra of various methoxylated benzenes (see formulae **64**, **65** and **66**).



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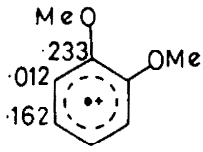

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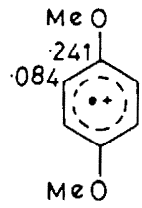
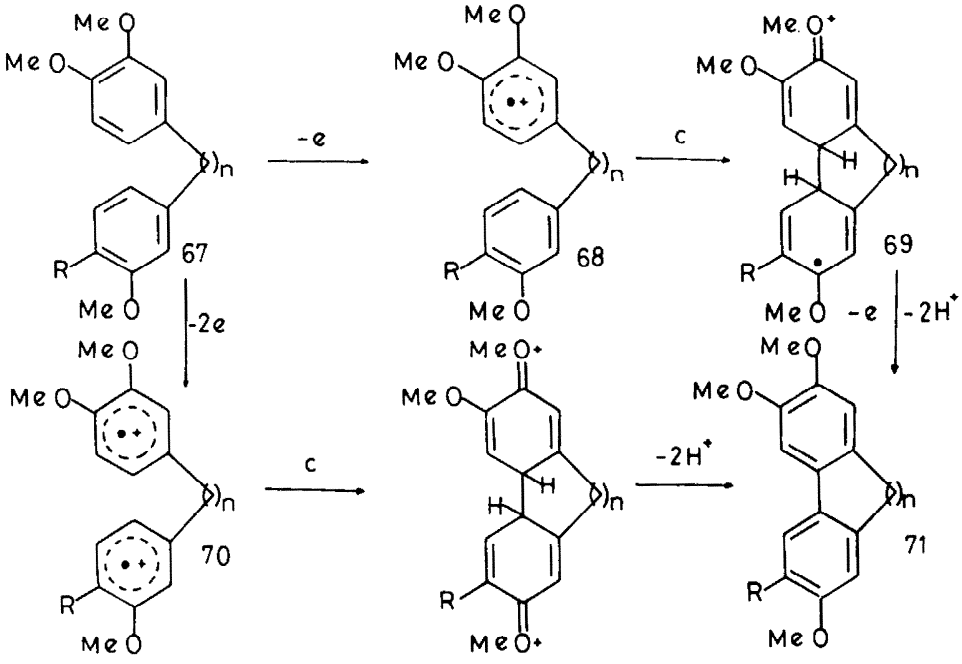


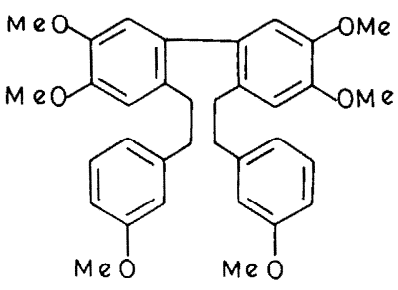
66

A more subtle point, however, concerns the order of events in the coupling process itself. Thus does the conversion **67** → **71** proceed by attack of a radical cation (**68**) upon the other unionized aryl ring, followed by further oxidaton of the product radical cation (**69**),[123] or are a pair of radical cations (**70**) necessary before coupling occurs?[124] The first sequence is an example of an *e.c.e.* reaction (*e*lectron loss, *c*hemical reaction *e*lectron loss) and the second an *e.e.c.* mechanism.

Ronlán *et al.*[120] have shown that in the case of the unsymmetrically substituted bibenzyl **67**; R = H, n = 2 the dimethoxylated ring is oxidised at +1.2 V, whereas the monomethoxylated nucleus is not ionized until the anode potential is raised to +1.6 V.

In a preparative experiment at the lower potential the major product was the dehydro dimer (**72**) but at the higher voltage, when presumably both rings may exist as radical cations, the intramolecular coupled product (**71**) was formed. These observations provide very strong evidence that two radical cations are necessary for aryl–aryl bond formation, but in extending this study to substrates with varying length alkyl bridges between the two aryl nuclei these same authors *et al.*[121] found it necessary to propose that both *e.c.e* and *e.e.c.* mechanisms may operate depending upon the substrate. Not surprisingly, successful intramolecular coupling depends not only upon electronic factors, but also upon the adoption of geometrically favourable transition states. Thus intramolecular cyclisation occurs with symmetrically substituted biarylalkanes (**67**) when n < 4, but if n > 6 dehydrodimers (**73**) are obtained. In the specific case of the diarylalkane **67** (R = OMe) where n = 5, the benzocycloheptane (**74**) is produced.





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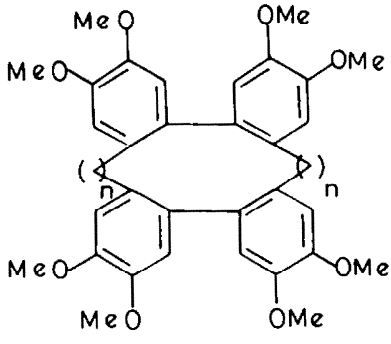

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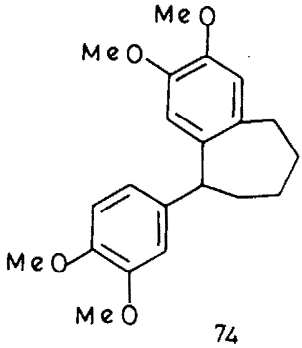
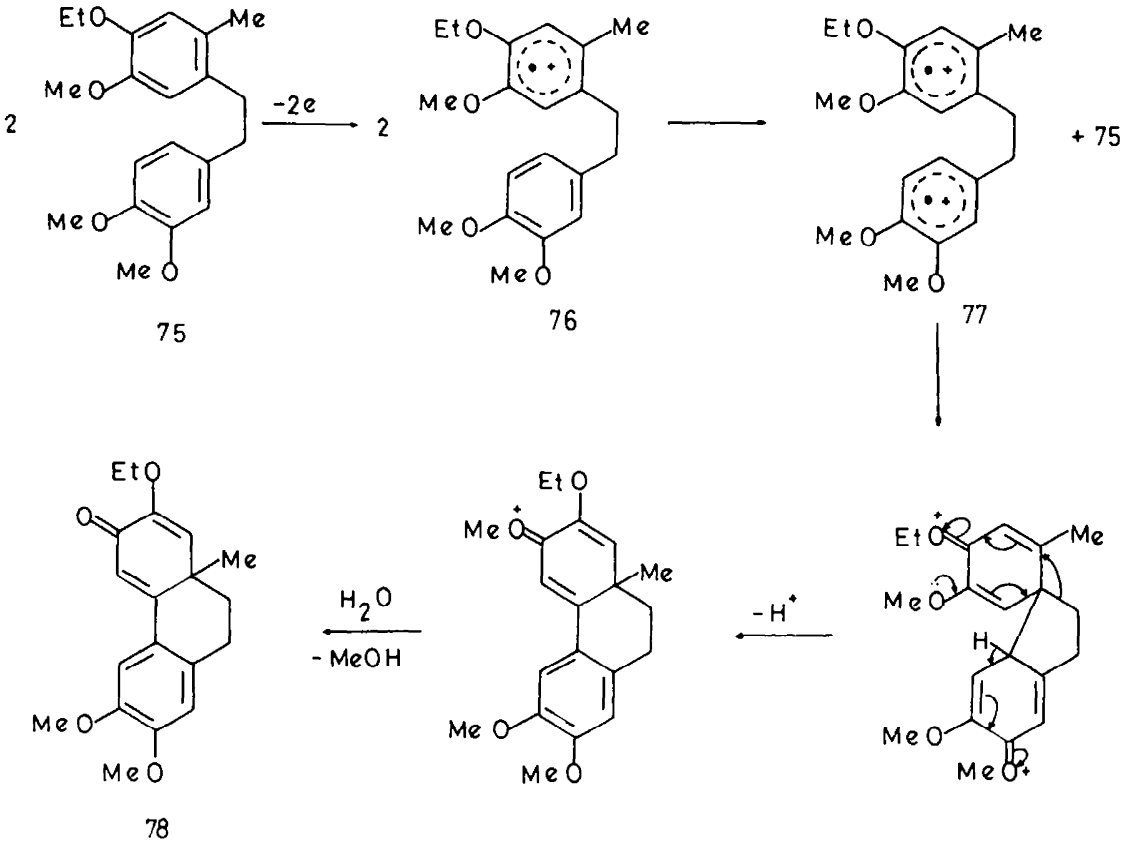


74

The description *e.e.c.* implies consecutive loss of two electrons rather than simultaneous ionization of both aryl nuclei, but even this summary is probably an over-simplification since Miller *et al.*,[125] working with the bibenzyl (**75**) have analysed the kinetics of the intramolecular coupling reaction which leads ultimately to the dienone **78**. They conclude that the radical cation **76**, formed from the most highly substituted ring, undergoes electronic disproportionation into the dicationic species **77** and unionised starting material. The latter reaction, which is second order in terms of the radical cation, is especially probable near the electrode where there is a locally high concentration. Both the formation of the cation radical and its subsequent disproportionation are fast reversible reactions, but the rate

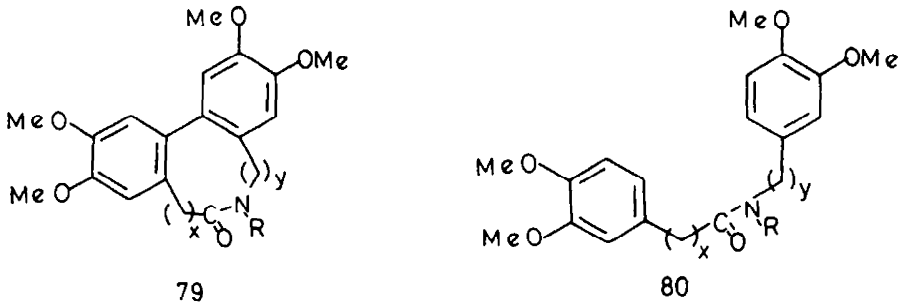
determining step is cyclisation of the dication. In the case of this particular substrate the rate determining step is followed by deprotonation and rearrangement (not necessarily in that order) to give the stable cation.

Finally, work-up effects demethylation of this cation releasing the dienone **78**.



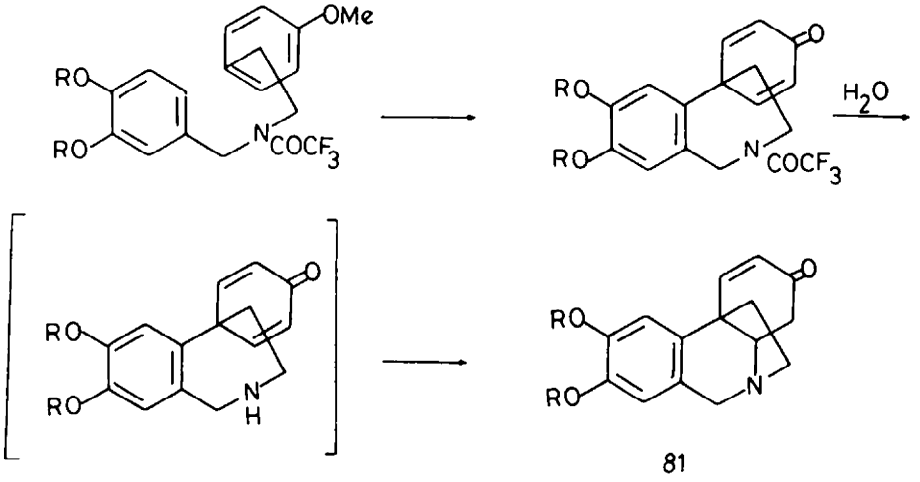
It seems likely that this composite mechanism may have wide application, but it is probable that the disproportionation step may only occur in diarylalkanes where the ionization potentials of the two aryl nuclei are similar, and that substituents replacing methylene groups and appropriately positioned in the bridging chain may strongly influence the mechanism.

Sainsbury and Wyatt[126] sought to apply anodic cyclisation to the synthesis of nitrogen heterocycles **79** utilising amides **80** as starting materials, but whereas intramolecular coupling occurred with the tertiary amides **80** (R = Me) only intermolecularly bonded products were formed by the oxidation of the secondary amides **80** (R = H). This result is easily understood in terms of the preferred stereochemistry of the amides: secondary amides existing almost exclusively in the *Z*-form, whereas the tertiary derivatives are a mixture of *E*- and *Z*-forms. Interestingly the yields of intramolecularly cyclised products **79** correspond closely with the proportion of the *E*-form in the mixture suggesting that $E \rightleftharpoons Z$ inter-conversion is slow relative to either intra- or inter-molecular coupling.



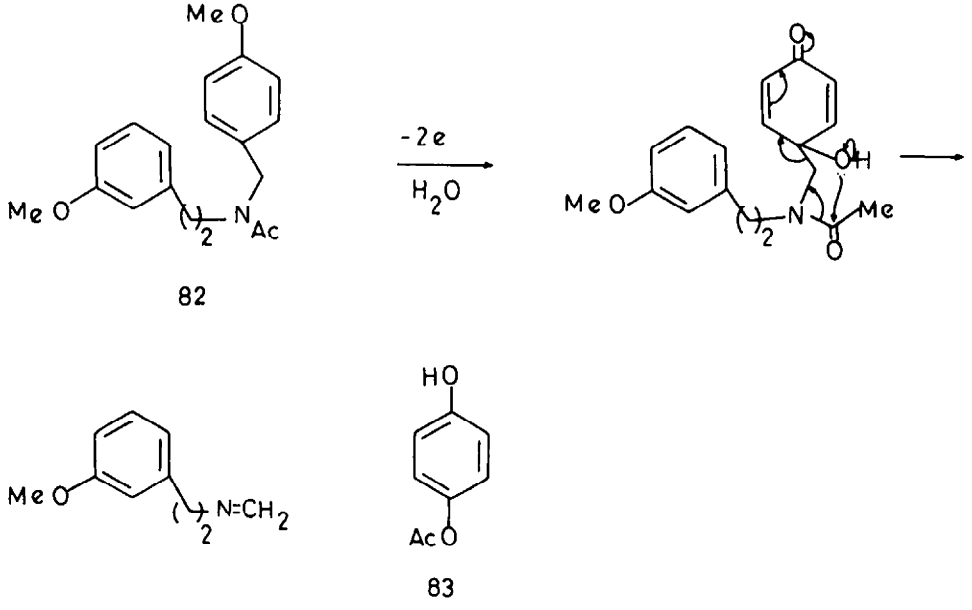
79 80

The cyclisation of amides has been employed very successfully by Kotani and his colleagues[127] in the synthesis of (±)-oxocrinine **81** (R,R = OCH_2O) and (±)-oxomartidine **81** (R = MeO) from the N-trifluoroacetyl derivatives of N-(4-methoxyphenylethyl)-3,4-methylenedioxy- and N-(4-methoxyphenylethyl)-3,4-dimethoxy-benzylamines respectively.



81

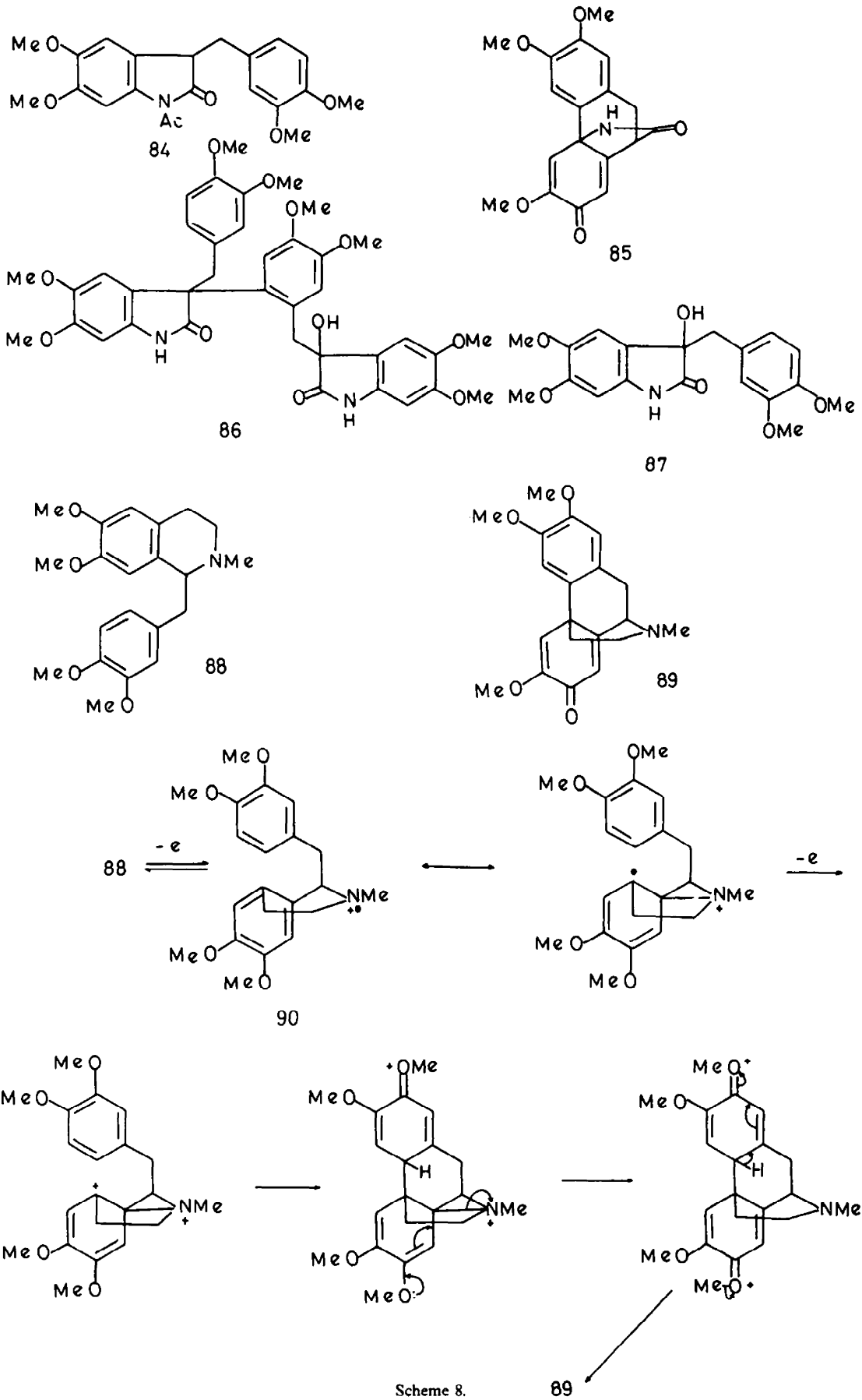
Yields in these electrochemical cyclisations are good ~60% despite the fact that the aryl rings have different oxidation potentials. However, in a related experiment Sainsbury and Wyatt[128] observed that the amide **82** failed to ring-close on anodic oxidation, decomposing instead to 4-hydroxyphenylacetate (**83**) and other "low" molecular weight products. A possible rationalization for this reaction is as follows:



82

83

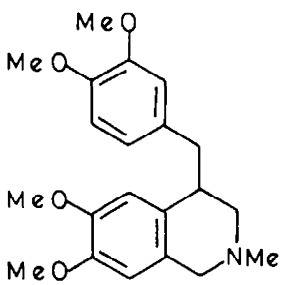
This "mechanism" implies that hydration occurs early in the electrolysis reaction, seemingly a fairly common event in many other oxidations conducted in acetonitrile for this solvent is difficult to obtain free from water. Interestingly, however, a repetition of the reaction in anhydrous dichloromethane/trifluorocetic acid also gave some 4-hydroxyphenylacetate. In both cases water was added during the work-up procedure. A further illustration of hydration is provided by the oxindole derivative **84**, which on anodic oxidation in acetonitrile gave both the intra- and inter-molecularly coupled products **85** and **86** respectively as well as the 3-hydroxyoxindole **87**.[128] Unfortunately repetition of this experiment in dichloromethane-trifluoroacetic acid led to complex mixtures.



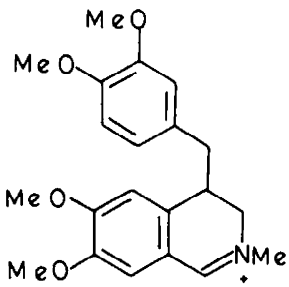
Scheme 8.

Most interest in the natural product area has focussed upon the electrochemistry of isoquinoline derivatives, initiated by the report[12,130] that (±)-laudanosine (**88**) can be converted into (±)-flavinanthine (**89**) in high yield using an anode potential of +1.1 V. Originally this synthesis was conducted in such a way that the amino function was protonated and the mechanism then follows a course similar to that of the cyclisation of bibenzyls, but it was noted later[131,132] that (±)-flavinanthine is also formed from the free base, now at an anode potential of only +0.55 V. At such a voltage the aryl rings cannot be ionized directly so it has been suggested[10] that initial electron transfer involves the amine lone pair; the coupling reaction may then involve electrophilic attack by the aminium ion **90** or homoconjugation between the amine function and the benzene ring fused to the heterocycle. The latter course seems very attractive since the geometry of the system is virtually identical with that of the appropriate homoallylic and 2-phenylallyl cations where homoconjugation is well characterised. These arguments are summarised by Scheme 8.

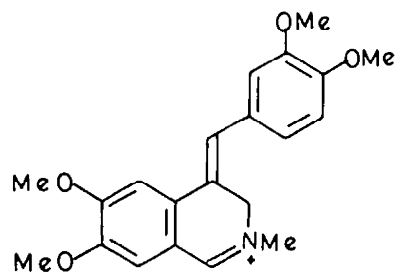
Circumstantial evidence in favour of this type of anchimeric assistance is provided by the fact that the corresponding 4-benzyltetrahydroisoquinoline **91** fails to undergo intramolecular coupling at potentials near to +0.6 V.[133] Here homoconjugation does not provide a situation which favours intramolecular coupling to an isomorphinandienone derivative. Interestingly, however, oxidation of the hydrochloride salt at higher potentials leads to the 3,4-dihydroisoquinolinium salts **92** and **93**, rather than any intramolecular product.



91

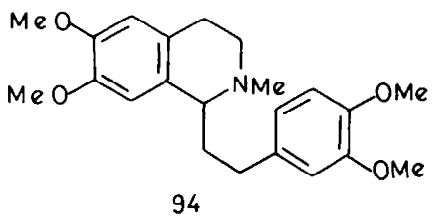


92

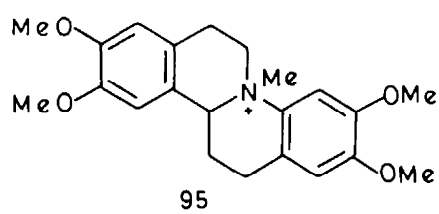


93

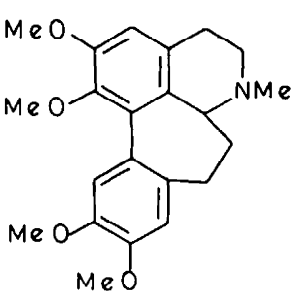
Where the N-atom of isoquinoline derivatives is not protected, either by protonation or acylation, premature ionisation of the lone pair electrons may lead to N–C coupled products. Thus anodic oxidation of the 1-phenethyltetrahydroisoquinoline **94** in acetonitrile containing sodium perchlorate affords the tetracyclic salt **95**,[134] but in trifluoroacetic acid solution the homoaporphine **96** is obtained.[135] Oxidation of the methiodide of **94** gives the intermolecularly coupled product **97**.[134]



94



95



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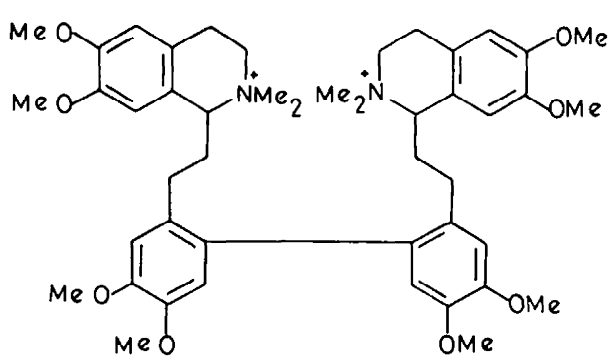

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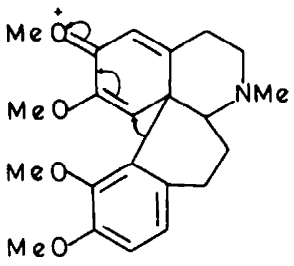

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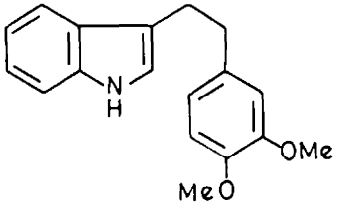
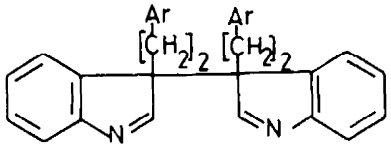
98

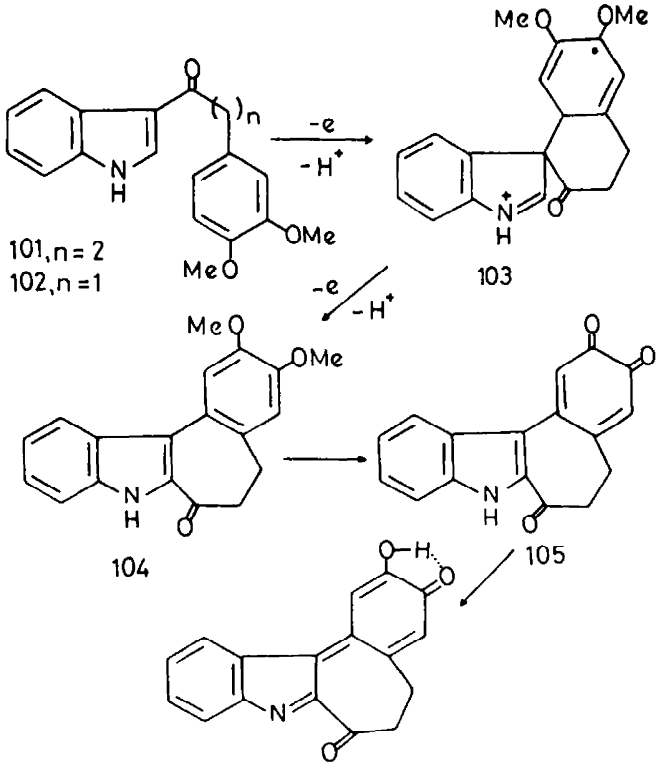


99



100

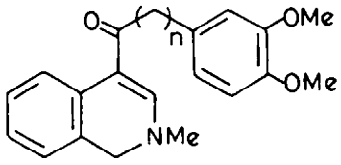
Ar = 3,4-(Me O)$_2$C$_6$H$_3$-



The formation of the homoaporphine **96** appears at first sight to result from an *ortho–para* coupling reaction, but it most probably originates by rearrangement of the *para–para* coupled intermediate **98** as shown below (see also Section 8).

Attempts to extend anodic coupling reactions to indole derivatives are rendered difficult by the ease with which the heterocycle is oxidised. For example, the 3-phenethylindole **99** fails to cyclise but at an anode potential of ~0.8 V yields intermolecular products such as the bisindolenine **100**.[128] However, the enamido ketone **101** is more resistant to ionisation and here the heterocyclic system is not oxidised below an anode potential of ~1.6 V. A preparative experiment conducted at +1.1 V affords the hydroxyquinone **106** and so it is possible that the radical cation formed from the dimethoxylated aryl ring reacts at the indole 3-position giving a spiro-intermediate (**103**) which undergoes oxidation and selective bond breaking and rearrangement to yield the tetracycle **104**. Further oxidation leads on to the quinone **105**, which finally tautomerises to the indolenine **106**.

When this experiment is extended to the lower homologue **102** no intramolecularly coupled products are isolated. This result has been analysed in terms of a geometrically unfavoured transition state,[136] but it is perhaps significant that the enamido ketone **107** analogous to **102** also fails to undergo intramolecular anodic cyclisation and is recovered unchanged.[137] Further experiments with the homologue **108** are in progress in the author's laboratory.



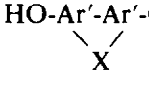
107, n = 1
108 n = 2

8. VANADIUM, THALLIUM AND MANGANESE OXIDANTS

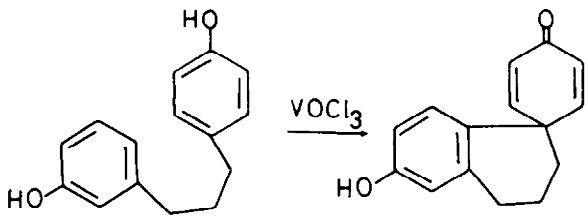
Many of the experiments described in the previous section have been also conducted using reagents such as the vanadium oxytrihalides, thallium trifluoroacetate and manganic tri-sacetylacetonate. Since these oxidants are considered to effect electron transfer and form radical cations with electron rich substrates[138–140] a direct comparison between the results of anodic and chemically induced oxidative coupling is often possible.

The application of this type of reagent to aryl–aryl coupling reactions has its origins in the observation[141] that vanadium oxytrichloride forms phenoxyvanadium(V) complexes with phenols. These complexes may be isolated and it occurred to Schwartz *et al.*[100] that this reagent might be used as an "internal oxidizing agent". Thus by binding to the substrate in a stoichiometric ratio prior to oxidation the reaction itself could be carried out avoiding excesses of reagent which in more traditional procedures (see Section 6) are commonly responsible for over oxidation and consequent poor yields. A summary of this approach is then as follows (where X = a bridging unit between two hydroxylated aromatic nuclei and M is the reagent).

$$\mathrm{HOAr\,x\,ArOH} \xrightarrow{\mathrm{M}} \mathrm{MOAr\,X\,ArOM} \longrightarrow [\mathrm{.OAr\,X\,ArO.}]$$

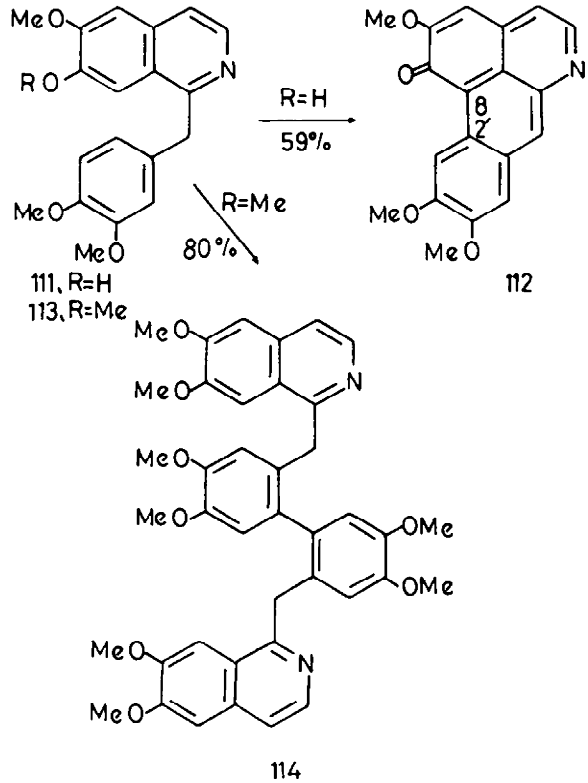


Realisation of this concept was achieved by the oxidation of the 1,3-bis(hydroxyphenyl)alkane **109** to the dienone **110** in 76% yield, which is 15–20 times greater than the yield obtained using potassium hexacyanoferrate(III). However, it is noted that hydroxy and peroxy radicals are stabilized by complex formation with oxyvanadium (V) ions[142] so that this increase in product yield may, in part, be due to stabilization of radical intermediates during the coupling process.



109 110

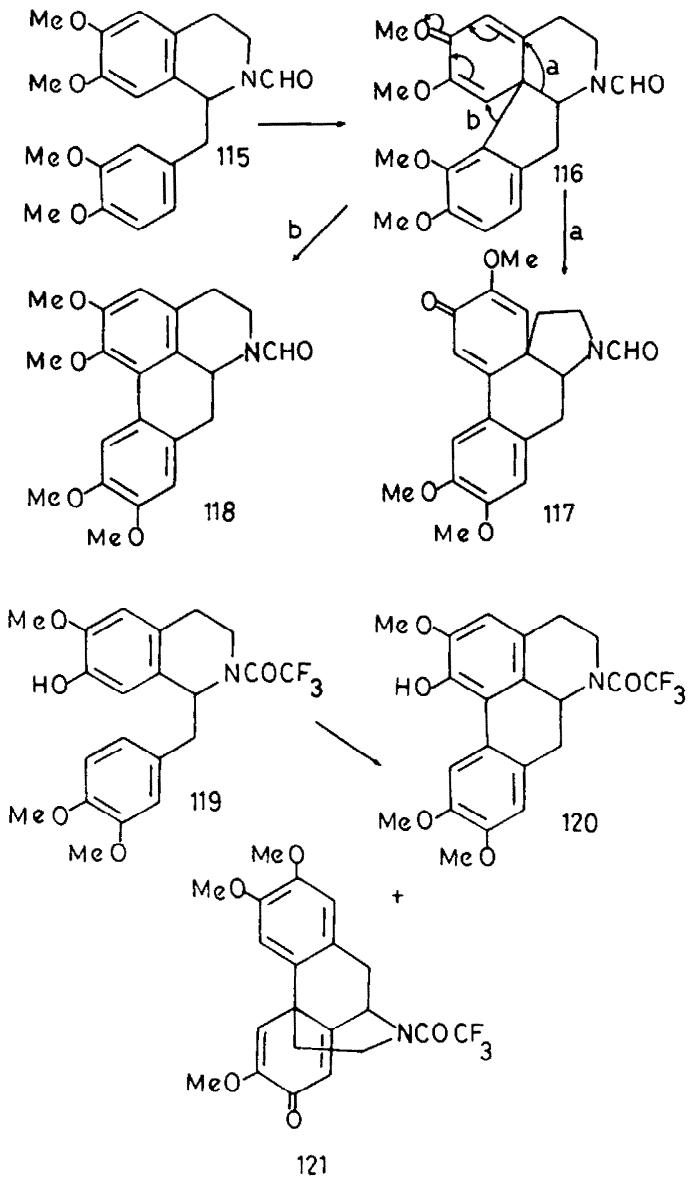
Vanadium oxytrifluoride has largely replaced vanadium oxytrichloride nowadays. The reagent, first introduced by Kupchan in 1973,[143] is frequently used with both phenols and phenolic ethers. Thus 7-O-demethylpapaverine(III) is converted by this reagent in trifluoroacetic acid solution into the oxoaporphine **112** in 59% yield. The yields with some other oxidising agents are: manganese dioxide in trifluoroacetic acid 30%; cerium (IV) sulphate in dilute sulphuric acid 25%; chromium (VI) oxide in a mixture of aqueous sulphuric acid and acetic acid 25%; and lead (IV) oxide in trifluoroacetic acid 22%.



When papaverine (**113**) is the substrate intramolecular does not occur, instead the dehydrodimer **114** is formed. Metal complexation with the phenolic OH group is probably involved in the formation of the oxoaporphine **112**, but the formation of the C-2', C8 bond in this product is unlikely to be the result of direct coupling (see p. 3328). More typically (±)-N-formylnorlaudanosine **115** gives the spirodiene **117** in 55% yield and (±)-N-formylnorglaucine **118** in 6% yield—presumbaly through alternative rearrangements of the initial cation intermediate **116** (or an equivalent).[144]

Similarly (±)-N-trifluoroacetylnorcodamine (**119**) affords (±)-N-trifluoroacetylwilsonirene (**120**) in 70% yield, together with 8% of the dienone (**121**).[135]

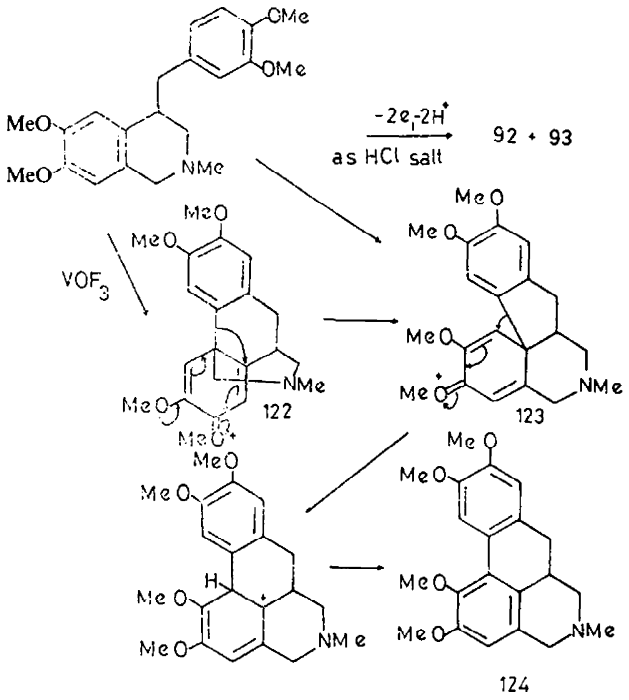
In the case of the 4-benzyltetrahydroisoquinoline **91** (p. 3345), for example, we have seen that anodic oxidation leads to dehydrogenation rather than intramolecular cyclisation, but Dyke and Warren[146] record that with vanadium oxytrifluoride in ethylacetate/trifluoroacetic acid/trifluoroacetic anhydride solution isoaporphine formation occurs. These authors propose that



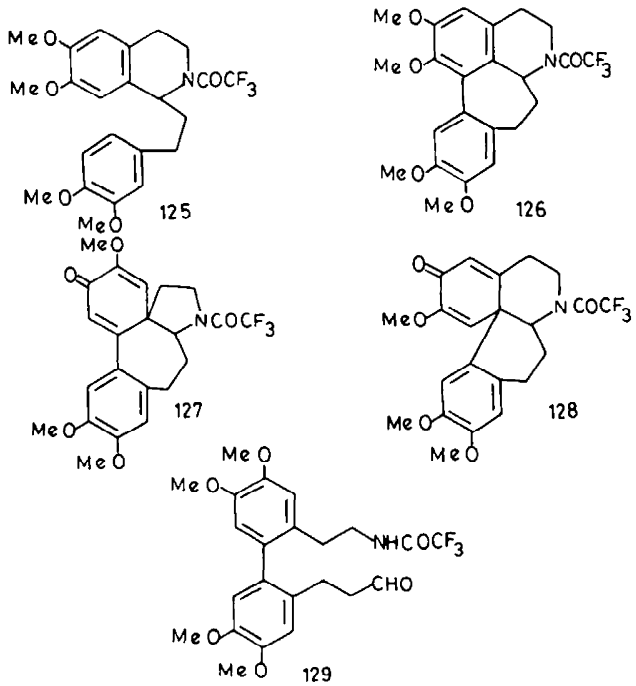
the cation **122** is the initial product and that this then undergoes two consecutive sigmatropic rearrangements. Such a scheme seems rather elaborate since the alternative *para–para* union may give the appropriate precursor **123** for the isoaporphine (**124**) directly. Indeed, anchimeric assistance via the N-atom (see p. 3345) also favours the more expeditious initial coupling.

It is also surprising that no intermolecular products were isolated from this reaction with an "unprotected" amine—although the isolated products only accounted for ~50% of the starting material. Kupchan *et al.*[135] have stressed that optimum yields of intramolecularly coupled products are obtained only when complete protonation of the nitrogen lone pair is achieved, and working with 1-phenethyltetrahydroisoquinolines in TFA/TFAA these authors found it necessary to add fluorosulphonic acid in order to repress the formation of dehydropolymers. Even so the productivity of the reaction was not high.

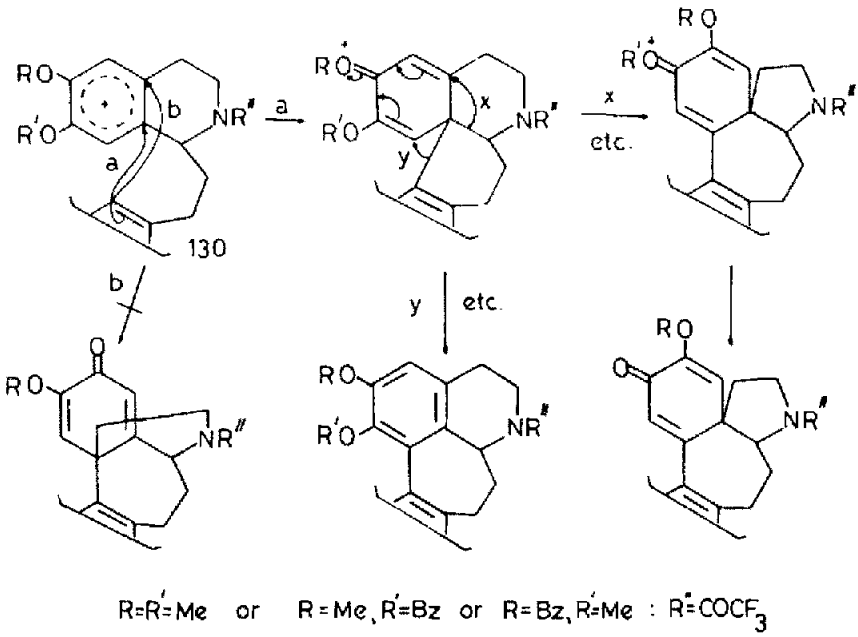
Far better results are obtained when the N-trifluoroacetyl analogues are prepared first and then oxidised in a separate step. Fluorosulphonic acid is then no longer necessary and in the case of (±)-N-trifluoroacetylhomonorlaudanosine (**125**) a vanadium oxytrifluoride oxidation afforded a series of cyclised products, namely homoaporphine **126** (2%), homoneospirenedione **127** (64%), homoproerythrinadienone **128** (5%) and aldehyde-amide **129** (22%) which together represent a near quantitative conversion.


CMe
OMe
MeO
MeO
NMe
-2e,-2H+
as HCl salt
92 + 93
VOF3
122
123
124

Scheme 9.

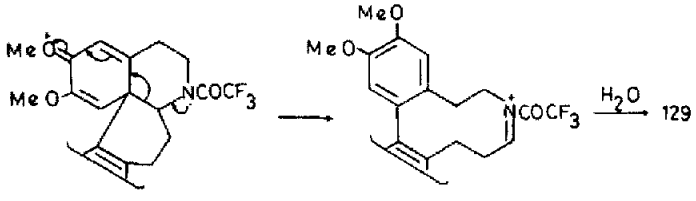

NCOCF3
125
126
127
128
NHCOCF3
CHO
129

Obviously these products cannot arise from the tetramethoxy-1-phenethyltetrahydroisoquinoline directly, but may be generated by rearrangement of one of the two intermediates resulting from alternative "*para–para*" pathways **a** or **b** shown in the part formula **130**. By analysing the products from the oxidation of 6- and 7-benzyloxytrimethoxy-1-phenethyltetrahydroisoquinolines Kupchan *et al.* conclude that the reaction follows path **a** and that route **b** leading to a homomorphinandienone is of no significance.



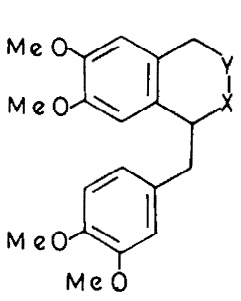
Scheme 10.

The iminourethane **129** is also considered to arise from the intermediate cation **131** via the iminium species **132** as shown below. Indeed when the N-trifluoroacetyl function was replaced by an N-carbonylethoxy substituent, so that the N atom retains a higher electron density, the yield of the corresponding aldehyde-amide increased to 62%.

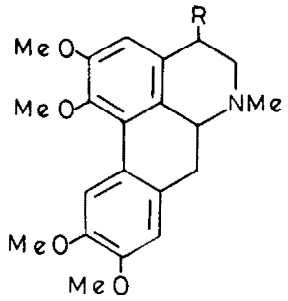


131 132

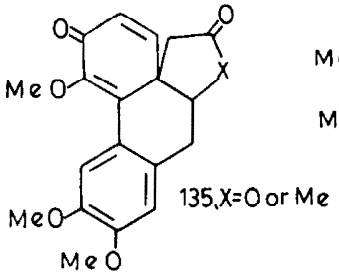
In one instance at least benzylic hydroxylation has been noted[147] using vanadium oxytrifluoride in trifluoroacetic acid, thus oxidation of (±)-laudanosine **133** (X = NMe; Y = CH_2) gave (±)-cataline **134** (R = OH), together with a small amount of (±)-glaucine **134** (R = H). On the other hand Elliott has reported[148] that oxidation of the 1-benzylisochromanone **133** (X = O, Y = CO) and the 1-benzylisoquinoline **133** (X = NMe, Y = CO) does not yield aporphine-like structures, but gives instead spirodienones **135**, and in the case of the isochromanone, the bridged lactone **136** as well. As recorded above aporphines are probably derived from the same intermediate as the spirodienones so that minor differences in reaction conditions may favour one product rather than the other. However, the bridged lactone is a novel addition to the range of cyclised products, for it is related to the isopavine **137**[149] and this may prove to be useful in synthesis of similar structures.



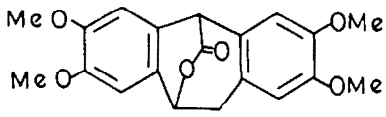
133



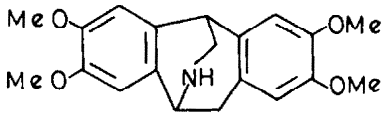
134



135, X=O or Me



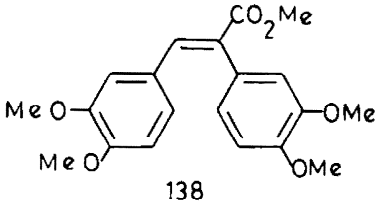
136



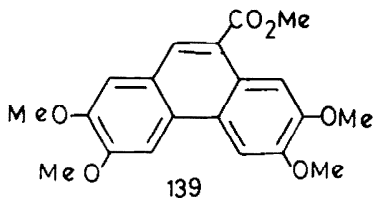
137

The use of vanadium oxytrifluoride is not restricted to heterocyclic systems and, for example, the stilbene **138** has been oxidised to the phenanthrene **139** in 69% yield.[150] This compares very favourably with a photochemical cyclisation which only gives a 31% conversion. Similarly Kende and Liebskind[151] have used this reagent to cyclise the diester **140** to the dibenzocyclooctadiene **141**—a key step in their synthesis of the antileukaemic lignan steganacin (*cf.* p. 3330).

An alternative reagent to vanadium oxytrifluoride is thallium(III) tristrifluoroacetate (TTFA) and pioneering studies with this oxidant by McKillop *et al.*[152] led Schwartz[153] to experiment with the phenol **142** which can be ring-closed to the spirodienone **143** in 87% yield. It was proposed that a phenoxonium ion or its equivalent is involved, but in this and similar reactions with phenols intermolecularly coupled products are not encountered, and Palmquist *et al.*[154] suggest that thallium



138



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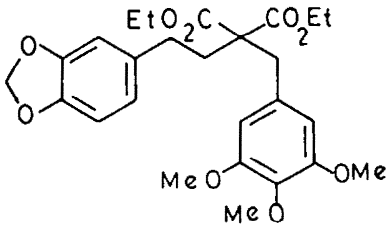
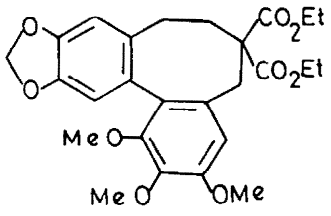
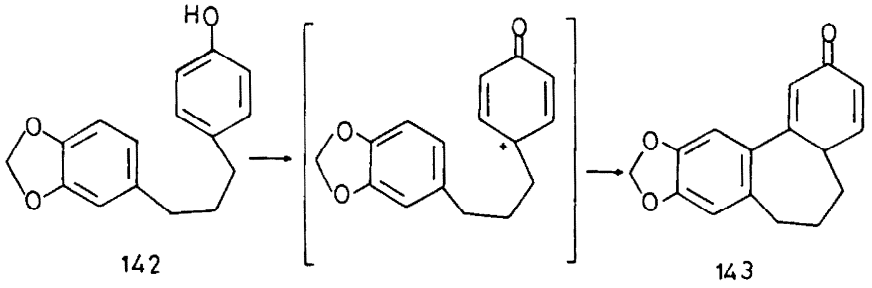


140



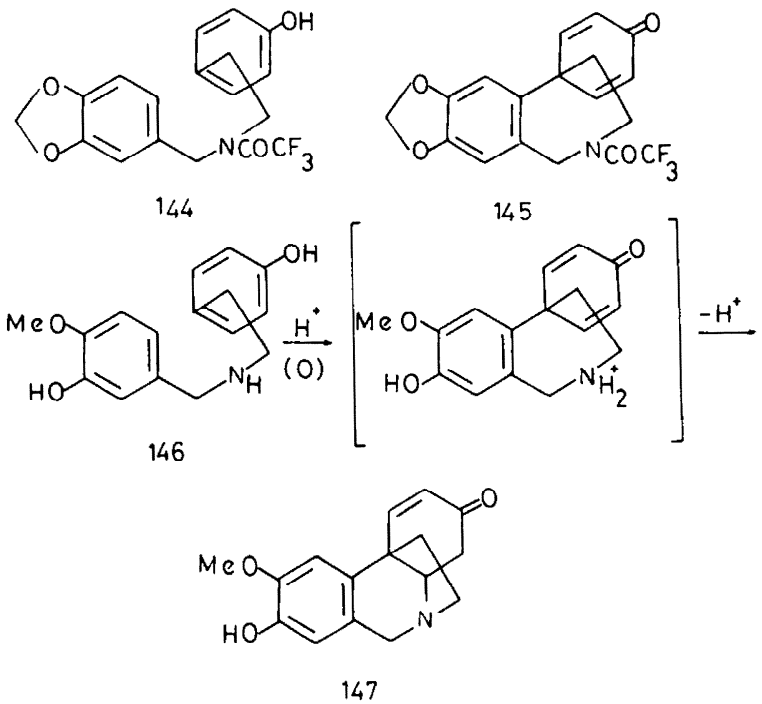
141

phenolates are the primary intermediates. Geometric considerations seem to be critical, however, since phenolic diaryl-ethanes and -butanes do not cyclise. These last authors conclude that in such cases the reaction stops at the thallium phenolate stage, since after hydrolytic work-up, the starting phenol is recovered unchanged.



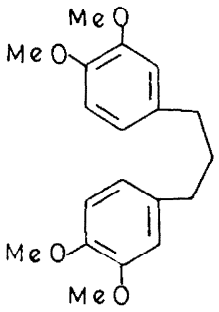
142 143

Thallium tristrifluoroacetate has also been employed with nitrogenous substrates.For example, the N-trifluoroacetylphenylethylamine **144** gave the enone **145**.[155] The yield, however, was only 19% compared to a 88% conversion when vanadium oxytrifluoride was used.[22] With basic substrates it is usual to protect the N- atom. The trifluoroacetyl group has just been mentioned, other protecting groups include ethoxycarbonyl[156] or formyl,[157] and borane complexes have also been used.[158] Tomioka *et al.*[159] on the other hand rely on quaternization in trifluoroacetic acid solution and, in what they describe as, a biogenetic-type synthesis, they obtained oxomartidine **147** in a remarkably high 66.5%-yield from O-methylnorbelladine **146**. Compared with phenolic oxidative experiments conducted with older reagents, for example iron(III) chloride-dimethylformamide[160] this is a considerable improvement.

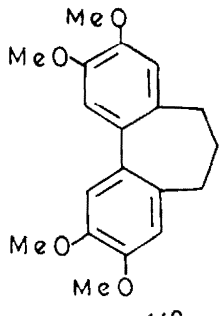


144 145 146 147

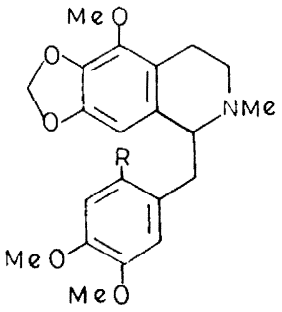
Although thallium tristrifluoroacetate is most frequently used with phenolic substrates it may also be employed with phenolic ethers, thus the bis(dimethoxyphenyl) propane **148** is converted into the dibenzocycloheptadiene **149** in 81% yield.[161]



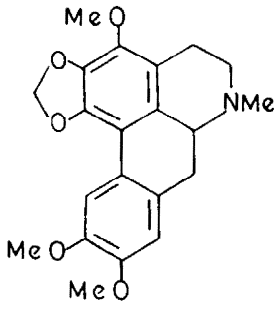
148



149



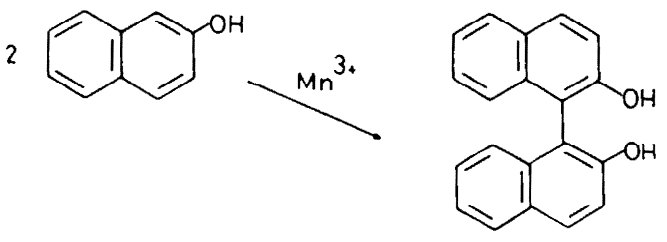
150, R = H
151, R = NH_2



152

Similarly (±)-ocoteine (**152**) can be prepared by the oxidation of the tetrahydroisoquinoline **150**.[162] The yield is a considerable advance upon that obtained by Pschorr cyclisation of the more inaccessible amine **151** (46 vs 11%).[163] Clearly phenoxonium ions or thallium phenolates cannot be involved here and now it is assumed that the reaction resembles anodic oxidation and requires the participation of arene radical cations.[164]

Manganese(III) acetonylacetate is another reagent which has been used to couple phenols and phenolic ethers. First introduced by Dewar and Nakaya,[165] it oxidises 2-naphthol into 2,2′-dihydroxy-1,1′-binaphthyl (**153**) in 69% yield and has the advantage that, provided oxygen is excluded from the reaction mixture, over oxidation to the quinone is avoided.

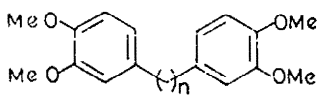


153

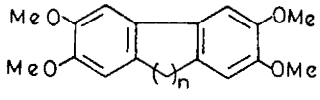
Scheme 11.

The reagent has not found much application with non-phenolic substrates probably because yields tend to be lower than, say, when anodic oxidation is used. For example, bis(3,4-dimethoxyphenyl) alkanes of general structure **154** can be cyclised to the corresponding tricycles

155 [166] The % conversions for anodic and manganese(III)acetonylacetate ring closures are respectively: n = 1,95 and 45%; n = 2,95 and 45%; n = 3,94 and 60%; n = 4,93 and 90%. In the case of n = 5 the benzocycloheptane **74** is formed and the conversions are 38 and 25% respectively (see p. 3340).



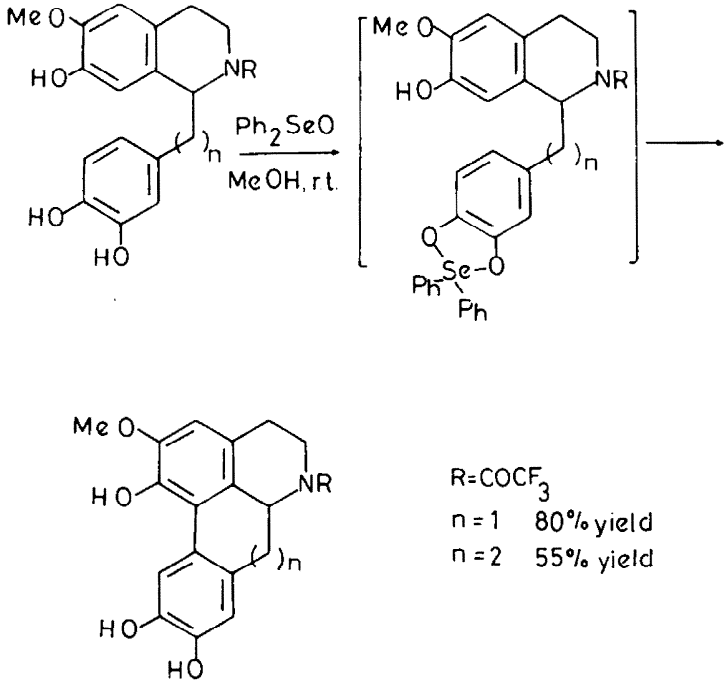
154



155

9. SELENIUM AND TELLERIUM OXIDANTS[167]

Diphenyl selenoxide is recommended as a mild and selective oxidant for the synthesis of phenolic substrates.[168] Where catechol units are present, as in the following example, selenurane derivatives are possible intermediates.



Scheme 12.

Bergman[169] has shown that arenes react with tellurium(IV) chloride at 60-80° to give aryl tellurium trichlorides and/or bis(aryl)tellurium dichlorides. Both types of product are converted into biaryls by heating with degassed Raney Ni. Yields are in the range 40-75% and the method has been exemplified by the synthesis of biphenyl, 2,2'-dinaphthyl, and various halogeno, aminoalkyl- and alkoxy-biphenyls. Diaryltellurides are probable intermediates in this reaction and somewhat better

yields are obtained if the reaction is controlled to give bis(aryl)tellurium dichlorides which are reduced with hydrazine, prior to treatment with Raney Ni:

$$ArH + TeCl_4 \xrightarrow{60-80^\circ} ArTeCl_3 + HCl$$

$$ArTeCl_3 + ArH \xrightarrow{160} (Ar)_2TeCl_2$$

$$(Ar)_2TeCl_2 \xrightarrow{NH_2NH_2} (Ar\,Te\,Ar) \xrightarrow[200^\circ]{Ni} Ar\text{-}Ar + Te$$

10. MISCELLANEOUS ROUTES TO BIARYLS

Inevitably there are a large number of biaryl coupling procedures, some efficient, some less so, which have not been widely adopted for various reasons. A limited selection of these miscellaneous techniques is summarised below:

(i) Diaryliodinium bromides yield biaryls when reacted with methylmagnesium iodide and anhydrous nickel(II) chloride in diethyl ether solution.[170] A variety of alkyl-, alkoxy- or halogeno-substituted substrates may be employed but if the two rings in the bromide are unsymmetrically substituted mixtures of biaryls result. Yields are typically ~55%.

$$Ar\text{-}\overset{+}{I}\text{-}Ar'\ Br^- \xrightarrow[NiCl_2]{MeMgI} Ar\text{-}Ar + Ar'\text{-}Ar' + Ar\text{-}Ar'$$

(ii) The reaction of arylmagnesium halides or aryllithium reagents[171-178] with a salt of thallium, uranium or a first group transition metal has been found to be useful in the synthesis of biaryls. Thus Taylor *et al.*,[179] showed that thallium(I) bromide with arylmagnesium halides unsubstituted in the *ortho*-positions affords symmetrical biaryls in yields ranging from 65–95%, depending upon the substrate. Metallic thallium is deposited, but the reaction is not governed by simple stoichiometric relationships and a sequence of redox reactions among the three thallium valence states is involved.

Thallium(III) trifluoroacetate has also been used,[178] but here the arylmagnesium bromide is converted by this reagent into the corresponding diarylthallium(III) bromide. Anion exchange affords the diarylthallium(III) trifluoroacetate which when photolysed in benzene yields the appropriate arylbenzene.

(iii) Biaryls can be synthesised by the decomposition of arylboranes with methanolic potassium hydroxide and silver nitrate.[180] The arylborane is formed from the corresponding arylbromide and magnesium in the presence of diborane; tetrahydrofuran is the solvent. However, whereas bromobenzene gives biphenyl in 59% yield, 2-bromotoluene affords 2,2'dimethylbiphenyl in only 17% yield.

(iv) Symmetrical biaryls are available via the rhodium-catalysed dimerization of aryl mercuric salts in the presence of lithium chloride.[181] Near quantitative conversions of simple aryl salts are claimed. This reaction appears to be very similar to the decomposition of aryl mercuric salts with catalytic amounts of palladium(II) chloride which has already been discussed (p. 3334).

(v) In perhaps the most simple biaryl synthesis so far described Bamfield and Quan[182] have reacted aryl chlorides or bromides with sodium hydroxide, sodium formate and palladium on charcoal in an aqueous suspension containing a surfactant such as cetyltrimethyl ammonium bromide. The productivity varies with the surfactant and, of course, the substrate, but may be as high as 65%.

SUMMARY

There are so many techniques which may be used to generate an aryl–aryl bond that it is almost impossible to predict which will give the optimum yield from any particular substrate. The Pschorr synthesis is rarely used nowadays although modified Ullmann procedures, particularly using nickel (0) reagents seem attractive. The intramolecular photochemical cyclisation of aryl halides can be very productive, but such reactions cannot be scaled up easily since few laboratories have large photochemical reactors.

Traditional phenolic oxidative coupling reactions using such reagents as potassium hexacyanoferrate(III) are still reported in the chemical literature. However, thallium tristrifluoroacetate seems to be a more rewarding oxidant but it remains to be seen if diphenyl selenoxide turns out to be an even better choice. In the case of non phenolic substrates, the author prefers anodic

oxidation particularly where the rings to be joined have similar oxidation potentials. This method has the considerable advantage that using simple analytical procedures beforehand the precise voltage for oxidation can be selected. Chemical oxidants do not offer this selectivity and they are expensive.

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REFERENCES

[1]R. Pschorr, *Ber. Dtsch. Chem. Ger.* **29**, 496 (1896).
[2]J. I. G. Cadogan, *Chem. Soc. Special Publication* **24**, 71 (1970).
[3]J. I. G. Cadogan, R. G. M. Landells and J. T. Sharp, *Chem. Comm.* 85 (1976).
[4]R. M. Elofson and F. F. Gadallah, *J. Org. Chem.* **36**, 1769 (1971).
[5]J. K. Kochi, *J. Am. Chem. Soc.* **77**, 3208 (1955).
[6]R. M. Elofson and F. F. Gadallah, *J. Org. Chem.* **34**, 3335 (1969).
[7]J. I. G. Cadogan, *Accounts Chem. Res.* **4**, 186 (1971).
[8]E. M. Kosower, *Ibid.* p. 193.
[9]R. M. Elofson, F. F. Gadallah and K. F. Schulz, *J. Org. Chem.* **36**, 1526 (1971).
[10]N. A. Porter, G. R. Dubay and J. G. Green, *J. Am. Chem. Soc.* **100**, 920 (1978).
[11]C. Rüchardt, E. Merz, B. Freudenberg, H.-J. Opgenorth, C. C. Tan and R. Werner, *Chem. Soc. Special Publication* **24**, 51 (1970).
[12]J. F. Bunnett and C. Yijima, *J. Org. Chem.* **42**, 639 (1977).
[13]T. J. Broxton, J. F. Bunnett and C. H. Paik, *Ibid.* p. 643.
[14]A. H. Lewin, N. C. Peterson and R. J. Michl, *Ibid.* **39**, 2747 (1974).
[15]T. Cohen, K. W. Smith and M. D. Swerdloff, *J. Am. Chem. Soc.* **93**, 4303 (1971).
[16]P. J. Leake, *Chem. Revs* **56**, 27 (1956).
[17]D. F. de Tar, *Org. Reactions* **9**, 409 (1957).
[18]A. J. Floyd, S. F. Dyke and S. E. Ward, *Chem. Revs* **76**, 509 (1976).
[19]M. Sainsbury, *Chemistry of Carbon Compounds* 2nd Edn, Vol. III, p. 104. Elsevier, Amsterdam (1979).
[20]J. L. Huppatz, *Austral. J. Chem.* **26**, 1307 (1973).
[21]S. M. Kupchan, V. Kameswaran and J. W. A. Finlay, *J. Org. Chem.* **38**, 405 (1973).
[22]M. P. Cava, I. Noguchi and K. T. Buck, *Ibid.* **38**, 2394 (1973).
[23]D. R. Dalton and A. A. Abraham, *Syn. Commun.* **2**, 72 (1972).
[24]T. Kametani, T. Sugahara and K. Fukumoto, *Tetrahedron* **27**, 5367 (1971).
[25]M. Julliard, C. Siv, G. Vernin and J. Metzger, *Helv. Chim. Acta* **61**, 2941 (1978).
[26]F. F. Gadallah, A. A. Cantu and R. M. Elofson, *J. Org. Chem.* **38**, 2386 (1973).
[27]T. Caronna, F. Ferrarro and S. Servi, *Tetrahedron Letters* 657 (1979).
[28]W. E. Bachmann and R. A. Hoffman, *Organic Reactions* **2**, 224 (1944).
[29]O. C. Dermer and M. T. Edmison, *Chem. Revs.* **57**, 77 (1957).
[30]D. H. Hey, *Quarterly Revs* **25**, 483 (1971).
[31]M. G. Bartle, R. K. Mackie and J. M. Tedder, *Chem. Comm.* 271 (1974)
[32]S. H. Korzeniowski, L. Blum and G. W. Gokel, *Tetrahedron Letters* 1871 (1977).
[33]P. E. Fanta, *Chem. Revs* **38**, 139 (1946); **64**, 613 (1964); *Synthesis* **9** (1974).
[34]M. Nilsson, *Sv. Kem. Tidskr.* **73**, 447 (1961); **80**, 192 (1968).
[35]R. G. R. Bacon and H. A. O. Hill, *Quart. Revs* **19**, 95 (1965).
[36]M. Goshaev, O. S. Otroshchenko and A. A. Sadykov, *Russian Chem. Revs* **41**, 12 (1972).
[37]J. F. Normant, *Synthesis* 63 (1972).
[38]M. Goshaev, O. S. Otroshchenko, A. A. Sadykov, *Zh. Khim.* **7Zh**, 354 (1970).
[39]A. E. Jukes, *Adv. Organomet. Chem.* **12**, 215 (1974).
[40]T. Cohnen and I. Cristea, *J. Org. Chem.* **40**, 3649 (1975); *J. Am. Chem. Soc.* **98**, 748 (1976).
[41]G. van Koten, J. T. B. H. Jastrebski and J. G. Noltes, *Chem. Comm.* 203 (1977).
[42]F. E. Ziegler, I. Chliwner, J. N. Fowler, S. J. Kanfer, S. J. Kno and N. D. Sinha, *J. Am. Chem. Soc.* **102**, 790 (1980).
[43]G. van Koten and J. G. Noltes, *J. Organomet. Chem.* **104**, 127 (1976); G. van Koten, J. T. B. H. Jastrzebski and J. G. Noltes, *J. Org. Chem.* **42**, 2047 (1977).
[44]A. C. Cope and R. N. Gourley, *J. Organomet. Chem.* **8**, 527 (1967).
[45]A. C. Cope and E. C. Friedrich, *J. Am. Chem. Soc.* **90**, 909 (1968).
[46]A. J. Lensink, G. van Koten and J. G. Noltes, *J. Organomet. Chem.* **56**, 379 (1973).
[47]R. D. Ricke and L. D. Rhyne, *J. Org. Chem.* **44**, 3447 (1979).
[48]J. M. Birchal, R. Hazard, R. N. Hazeldine and W. Wakalski, *J. Chem. Soc.* (C), 47 (1967).
[49]M. F. Semmelhack, P. M. Helquist and L. D. Jones, *J. Am. Chem. Soc.* **93**, 5908 (1971).
[50]A. S. Kende, L. S. Liebeskind and D. M. Braitsch, *Tetrahedron Letters* 3375 (1975).
[51]M. Meri, Y. Hashimoto and Y. Ban, *Ibid.* 631 (1980).
[52]M. Zembayashi, K. Tamao, J. Yoshida and M. Kumada, *Ibid.* 4089 (1977).
[53]K. Takagi, N. Hayama and S. Inokawa, *Chem. Letters* 917 (1979).
[54]M. F. Semmelhack and L. S. Rono, *J. Am. Chem. Soc.* **97**, 3873 (1975).
[55]T. T. Tsou and J. K. Kochi, *Ibid.* **101**, 6319, 7547 (1979).
[56]J. Grimshaw, R. J. Haslett and J. T. Grimshaw, *J. Chem. Soc.* Perkin Trans. 1 2448 (1977).
[57]J. Grimshaw and D. Mannus, *Ibid.* Perkin Trans. 1 2456 (1977).
[58]J. Grimshaw and R. J. Haslett, *Ibid.* Perkin Trans. 1 657 (1980).
[59]P. M. Maitlis, *The Organic Chemistry of Palladium* Vol. II, Catalytic Reactions pp. 60 71. Academic Press, New York (1971).
[60]R. van Helden and G. Verberg, *Rec. Trav. Chim. Pays-Bas* **84**, 1263 (1965).
[61]F. R. S. Clark, R. O. C. Norman, C. B. Thomas and J. S. Wilson, *J. Chem. Soc.* Perkin Trans. 1 1289 (1974).

[62]G. G. Arzoumanidis and F. C. Rauch, *Chemtech.* 700 (1973).
[63]M. K. Starchovskii, M. N. Vargaftikand and I. I. Monseev, *Ivz. Akad. Nauk. S.S.R. Ser. Khim.* 215 (1979).
[64]J. Davidson and C. Triggs, *Chem. Ind.* 457 (1966).
[65]C. H. Bushweller, *Tetrahedron Letters* 6123 (1968).
[66]T. Sakakibara, J. Kotobuki and Y. Dogomori, *Chem. Letters* 25 (1977).
[67]T. Itahara, *Chem. Comm.* 49 (1980).
[68]I. V. Kozhevnikov, S. A. Tuzovskaya, V. P. Lopatinskii, V. M. Sutyagin, O. V. Rotar and K. I. Matveev, *React. Kinet. Catal. Letters* **9**, 287 (1978).
[69]B. Akermark, L. Eberson, E. Jonsson and E. Pettersson, *J. Org. Chem.* **40**, 1365 (1975).
[70]T. Itahara and T. Sakakibara, *Synthesis* 607 (1978).
[71]H. Itatani and H. Yoshimoto, *Chem. Ind.* 674 (1971).
[72]P. M. Osipov, L. P. Metlova and T. I. Emel'yanova, *Ukr. Khim. Zh.* **44**, 660 (1978).
[73]M. O. Unger and R. A. Fouty, *J. Org. Chem.* **34**, 18 (1969).
[74]R. A. Kretchmer and R. Glowivè, *Ibid.* **41**, 2661 (1976).
[75]Ch. O. Parker and P. E. Spoerri, *Nature* **166**, 603 (1950).
[76]G. B. Gill, *Quart. Revs.* **22**, 358 (1968); and refs cited.
[77]F. R. Stermitz, *Organic Photochem.* (Edited by O. L. Chapman), Vol. 1, p. 247. Marcel Dekker, New York (1967).
[78]E. V. Blackburn and C. J. Timmons, *Quart Revs.* **23**, 482 (1969).
[79]J. Bendig, M. Beyermann and D. Kreysig, *Tetrahedron Letters* 3659 (1977).
[80]W. H. Laarhoven, *Tetrahedron* **26**, 4865 (1970).
[81]E. V. Blackburn and C. J. Timmons, *J. Chem. Soc.* C 172 (1970).
[82]R. Srinivasan and J. N. C. Hsu, *J. Am. Chem. Soc.* **93**, 2816 (1971).
[83]I. Ninomiya, H. Takasugi and T. Naito, *Chem. Comm.* 732 (1973).
[84]G. Lenz, *Synthesis* 489 (1978).
[85]H. Hara, O. Hoshino, B. Umezawa, *Tetrahedron Letters* 5031 (1972).
[86]M. Kihara and S. Kobayashi, *Chem. Pharm. Bull.* **26**, 155 (1978).
[87]B. R. Pai, H. Suguna, S. Rajeswari and G. Manikumar, *Ind. J. Chem.* **16B**, 421 (1978).
[88]D. A. Whiting and A. F. Wood, *J. Chem. Soc.* Perkin Trans. 1 623 (1980).
[89]K. E. Malternd, T. Anthousen and J. Hjortas, *Tetrahedron Letters* 3069 (1976).
[90]M. Nagain, M. Kubo, M. Fujita, T. Inone and M. Matsuo, *Chem. Comm.* 338 (1976).
[91]D. H. R. Barton and T. Cohen, *Festschrift, Arthur stoll*, p. 117. Birkhauser, Basel (1957).
[92]C. H. Hassall and A. I. Scott, *Chemistry of Natural Phenolic Compounds* (Edited by W. D. Ollis) p. 119. Pergamon, Oxford (1961).
[93]W. I. Taylor and A. R. Battersby, *Oxidative Coupling of Phenols.* Marcel Dekker, New York (1967).
[94]K. Mothes and H. R. Schutte, *Biosynthese der Alkaloide.* B.V.E.B., Deutsche Verlag der Wissenschaften, Berlin (1969).
[95]T. Kametani, *Lect. Heterocycl. Chem.* **2**, 57 (1974).
[96]R. D. Bracho, Ph.D Thesis, University of London 1974 (quoted in Ref. 97).
[97]A. G. M. Barrett, D. H. R. Barton, G. Frankowiak, D. Papaioannon and D. A. Widdowson, *J. Chem. Soc.* Perkin Trans. 1 662 (1979).
[98]S. Tobinaga, *Bioorg. Chem.* **4**, 110 (1975).
[99]B. Franck, G. Dunkelmann and H. J. Lubs, *Angew. Chem.* Int. Ed. **6**, 1075 (1967).
[100]M. A. Schwartz, R. A. Holton and S. W. Scott, *J. Am. Chem. Soc.* **91**, 2800 (1969).
[101]W. A. Water, *J. Chem. Soc.* (B), 2026 (1971).
[102]F. R. Hewgill and G. B. Howie, *Austral. J. Chem.* **31**, 1061 (1978).
[103]F. R. Hewgill and G. B. Howie, *Ibid.* p. 1069.
[104]W. W. Kaeding, *J. Org. Chem.* **28**, 1063 (1963).
[105]V. V. Karpov and M. L. Khidekel, *Zh. Org. Khim.* **4**, 861 (1968).
[106]F. R. Hewgill and G. B. Howie, *Austral. J. Chem.* **31**, 907 (1978).
[107]A. Tkac, R. Prikryl and L. Malik, *J. Elastoplast.* **5**, 20 (1973).
[108]J. Kreska, A. Tkac, R. Prikryl and L. Malik, *Makromol. Chem.* **176**, 157 (1975).
[109]N. Minami and S. Kijima, *Yakugaku Zasshi* **98**, 433 (1978); *Chem. Absts.* **89**, 75337m.
[110a]T. F. Rutledge, *U.S. Pat.* 4,097,460 (1978); [b]4,098,830 (1977); [c]4,100,205 (1978); [d]4,100,202 (1978); [e]4,139,544 (1979).
[111]T. Kametani, T. Satoh, M. Takemura, Y. Ohta, M. Ihara and K. Fukumoto, *Heterocycles* 175 (1976); T. Kametani, Y. Satoh, H. Terasawa, Y. Ohta, K. Fukumoto and K. Takahashi, *J. Am. Chem. Soc.* **99**, 3805.
[112]J. Tsuji and H. Takayanagi, *Ibid.* **96**, 7349 (1974).
[113]T. Kametani and M. Ihara, *J. Chem. Soc.* Perkin Trans. 1 629 (1980).
[114]F. Fitcher and E. Bruner, *Bull. Soc. Chim. Fr.* **19**, 281 (1916).
[115]F. Fitcher and W. Deitrich, *Helv. Chim. Acta.* **7**, 131 (1924).
[116]F. J. Vermillion Jr. and I. A. Pearl, *J. Electrochem. Soc.* **111**, 1992 (1964).
[117]J. M. Bobbitt, H. Yagi, S. Shibuya and J. F. Stock, *J. Org. Chem.* **36**, 3006 (1971).
[118]K. Dimroth, W. Umbach and H. Thomas, *Chem. Ber.* **100**, 132 (1967).
[119]A. Ronlán and V. D. Parker, *J. Chem. Soc.* **(D)**, 1643 (1971).
[120]A. Ronlán, O. Hammerich and V. D. Parker, *J. Am. Chem. Soc.* **95**, 7132 (1973).
[121]A. Ronlán and V. D. Parker, *J. Org. Chem.* **39**, 1014 (1974); A. Nilsson, U. Palmquist, A. Ronlán and V. D. Parker, *J. Am. Chem. Soc.* **97**, 3540 (1975); U. Palmquist, A. Nilsson, V. D. Parker and A. Ronlán, *Ibid.* **98**, 2571 (1976).
[122]A. Zweig, H. G. Hodgson and W. H. Jura, *Ibid.* **85**, 4124 (1963); A. Zweig, J. E. Lehson and M. A. Murray, *Ibid.* p. 3933.
[123]K. Nyberg, *Acta. Chem. Scand.* **25**, 2499 (1971).
[124]V. D. Parker, U. Palmquist and A. Ronlán, *Ibid.* **28B**, 1241 (1974).
[125]J. B. Kerr, T. C. Jempty and L. Miller, *J. Am. Chem. Soc.* **101**, 7338 (1979).
[126]M. Sainsbury and J. Wyatt, *J. Chem. Soc.* Perkin Trans. 1 1750 (1977).
[127]E. Kotani, N. Tekeuchi and S. Tobinaga, *Chem. Comm.* 550 (1973).
[128]M. Sainsbury and J. Wyatt, *J. Chem. Soc.* Perkin 1 108 (1979).
[129]L. L. Miller, F. R. Stermitz and J. R. Falck, *J. Am. Chem. Soc.* **95**, 2651.
[130]J. R. Falck, L. L. Miller and F. R. Stermitz, *Tetrahedron* **30**, 931 (1974).

[131]L. L. Miller, F. R. Stermitz, J. Y. Becker and V. Ramachandran, *J. Am. Chem. Soc.* **97**, 2922 (1975).
[132]J. Y. Becker, L. L. Miller and F. R. Stermitz, *J. Electroanal. Chem. Interfacial Electrochem.* **68**, 18 (1976).
[133]M. Carmody and M. Sainsbury, *J. Chem. Soc.* Perkin Trans. 1 (1980); in press.
[134]A. Najafi and M. Sainsbury, *Heterocycles* **6**, 459 (1977).
[135]S. M. Kupchan, O. P. Dhingra, C.-K. Kim and V. Kameswaran, *J. Org. Chem.* **43**, 2521 (1978).
[136]M. Sainsbury, *Heterocycles* **9**, 1349 (1978).
[137]M. Powell and M. Sainsbury, *157th Meet. Electrochem. Soc.* St. Louis (1980).
[138]S. D. Ibekwe and J. Myatt, *J. Organomet. Chem.* **31**, C65 (1971).
[139]W. Mowat, A. Shortland, G. Yagupsky, N. J. Hill, M. Yagupsky and G. Wilkinson, *J. Chem. Soc.* Dalton Trans. 533 (1972).
[140]L. E. Manzer, R. C. Gearhart, L. J. Guggenberger and J. F. Whitney, *Chem. Comm.* 942 (1976).
[141]H. Funk, W. Weiss and M. Zeisung, *Z. Anorg. Allg. Chem.* **296**, 36 (1958).
[142]M. S. Bains, J. C. Arthur Jr. and O. Hinojosa, *J. Am. Chem. Soc.* **91**, 4673 (1969).
[143]S. M. Kupchan and A. J. Liepa, *Ibid.* **95**, 4062 (1973).
[144]S. M. Kupchan, A. J. Liepa, V. Kameswaran and R. F. Bryan, *Ibid.* **95**, 6861 (1973).
[145]S. M. Kupchan, O. P. Dhringra and C-K Kim, *J. Org. Chem.* **41**, 4049 (1976).
[146]S. F. Dyke and P. Warren, *Tetrahedron* **35**, 2555 (1979).
[147]J. Hartenstein and G. Salzinger, *Angew. Chem.* **89**, 739 (1977).
[148]I. W. Elliott, *J. Org. Chem.* **42**, 1090 (1977); *Ibid.* **44**, 1162 (1979) [see also U. Palmquist, A. Nilsson, T. Petterson, A. Ronlán and V. D. Parker, *J. Org. Chem.* **44**, 196 (1979)].
[149]A. R. Battersby and D. A. Yeowell, *J. Chem. Soc.* 1988 (1958).
[150]A. J. Liepa and R. E. Summons, *Chem. Comm.* 826 (1977).
[151]A. S. Kende and L. S. Liebskind, *J. Am. Chem. Soc.* **98**, 267 (1976).
[152]A. McKillop, B. P. Swan and E. C. Taylor, *Tetrahedron* **26**, 4031 (1970).
[153]M. A. Schwartz, B. F. Rose and B. Vishnuvajjala, *J. Am. Chem. Soc.* **95**, 612 (1973).
[154]U. Palmquist, A. Nilsson, V. D. Parker and A. Ronlán, *Ibid.* **98**, 2571 (1976).
[155]M. A. Schwartz and I. S. Mani, *Ibid.* **97**, 1239 (1975).
[156]S. M. Kupchan, J. A. Liepa, V. Kameswaran and R. F. Bryan, *Ibid.* **95**, 6861 (1973).
[157]M. A. Schwartz, B. F. Bose, B. Vishnuvajjala, *Ibid.* **95**, 612 (1973).
[158]S. M. Kupchan, O. P. Dhingra and C-K Kim, *J. Org. Chem.* **43**, 4076 (1978).
[159]K. Tomioka, K. Koga and S. Yamada, *Chem. Pharm. Bull.* **25**, 2681 (1977).
[160]E. Kotani, N. Takeuchi and S. Tobinaga, *Tetrahedron Letters* (1973).
[161]A. McKillop, A. G. Turrell and E. C. Taylor, *J. Org. Chem.* **42**, 764 (1977).
[162]E. C. Taylor, J. G. Andrade and A. McKillop, *Chem. Comm.* 538 (1977).
[163]T. R. Govinachari, B. Pai and G. Shanmugasundaraman, *Tetrahedron* **20**, 2895 (1964).
[164]I. H. Elson and J. K. Kochi, *J. Am. Chem. Soc.* **95**, 5060 (1973).
[165]M. J. S. Dewar and T. Nakaya, *Ibid.* **90**, 7134 (1968).
[166]A. Ronlán and V. D. Parker, *J. Org. Chem.* **39**, 1014 (1974); see also V. D. Parker and A. Ronlán, *J. Am. Chem. Soc.* **97**, 4714 (1975).
[167]H. J. Reich, *Oxidation in Organic Chemistry*, (Edited by W. S. Trahanovsky), Part C. Academic Press, New York (1978).
[168]J. P. Marino and A. Schwartz, *Tetrahedron Letters* 3253 (1979).
[169]J. Bergman, *Tetrahedron* **28**, 3323 (1972); J. Bergman, R. Carlsson and B. Sjoberg, *Org. Syn.* **57**, 18 (1977).
[170]Y. Tamura, M. W. Inoue and J. Minamikawa, *Synthesis* 822 (1978).
[171]M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Non-metallic Elements.* Prentice Hall, New York (1954).
[172]A. McKillop, L. F. Elsom and E. C. Taylor, *Tetrahedron* **26**, 4041 (1970).
[173]W. B. Smith, *J. Org. Chem.* **26**, 4206 (1961).
[174]J. P. Morizur and R. Palland, *C.R. Acad. Sci. Paris.* **C, 252**, 3074 (1961).
[175]R. Palland and J. L. Zenou, *Ibid.* **266**, 1608 (1968).
[176]G. Adda and R. Palland, *Ibid.* **266**, 35 (1968).
[177]R. Palland and J. M. Pleau, *Ibid.* **267**, 507 (1969).
[178]B. Sarry and W. Hanke, *Z. Anorg. Allg. Chem.* **296**, 229 (1958).
[179]E. C. Taylor, H. W. Altland and A. McKillop, *J. Org. Chem.* **40**, 2351 (1975).
[180]S. W. Breuer and F. S. Broster, *Tetrahedron Letters* 2193 (1972).
[181]R. C. Larock, *U.S. Pat.* 4,026,957 (1978).
[182]P. Bamfield and P. M. Quan, *Synthesis* 537 (1978).