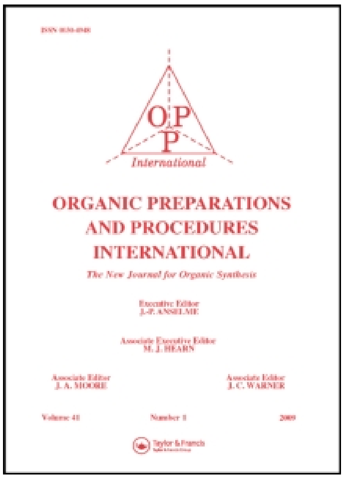

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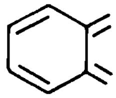
INTRODUCTION AND HISTORICAL PERSPECTIVE

The formation of the very reactive species *o*-quinodimethane 1, also named *o*-xylylene (5,6-bis(methylene)-1,3-cyclohexadiene), was first recognized by Cava and Napier in 1957 when they suggested the formation of α,α′-dibromo-*o*-quinodimethane in the reaction of α,α,α′,α′-tetrabromo-o-xylene with sodium iodide.[1] It was two years later that compound 1 could be generated from sulfone 2 by chelotropic elimination of sulfur dioxide, and trapped in a Diels-Alder cycloaddition by reaction with maleic anhydride.[2]



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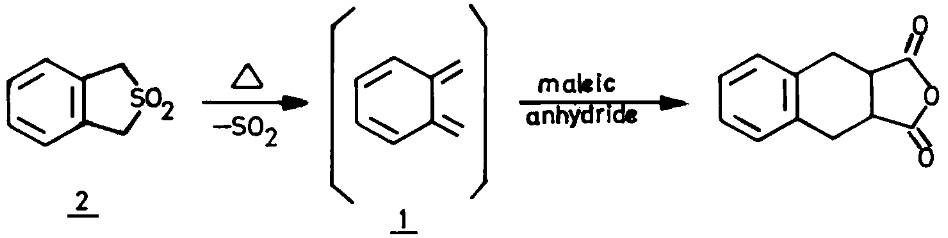
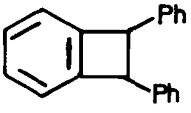


Also at that time, Jensen *et al.* suggested the formation of an *o*-quinodimethane derivative as an intermediate in the thermal additions of 1,2-diphenylbenzocyclobutene (**3**) to dienophiles.[3] A few years later, Errede *et al.* isolated the dimer of the *o*-xylylene (**4**) by a Hofmann elimination at high temperature in conclusive proof of the generation of *o*-xylylene.[4]



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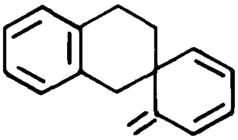


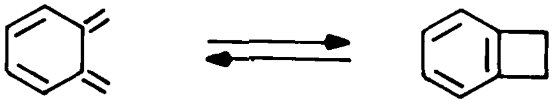
4

Since then, a great variety of methods for the generation of *o*-quinodimethane derivatives have been used in organic synthesis. In fact, the characterization, structure and chemical reactivity of *o*-quinodimethanes have been treated in previous accounts.[5-18] Among them, it is worth mentioning those of Kametani *et al.* devoted to the synthesis of natural products and the somewhat more recent one of Quinkert and Stark,[7] devoted to the stereoselective synthesis of enantiomerically pure natural products. Oppolzer has reviewed[15,16] the application of intramolecular cycloaddition reactions of *o*-quinodimethanes in organic synthesis. Finally, although also included in some of the above mentioned reviews, the photogeneration of *o*-xylylenes as intermediates have been discussed in detail by McCullogh[14] and Sammes.[17]

The more recent review on *o*-quinodimethanes by Charlton and Alauddin[5] shows, in a very attractive systematization, the methods for their generation and their use as dienes in the Diels-Alder reaction as well as the stereochemical implications in the reaction of this elusive intermediate. However, the increasing use of *o*-xylylene in organic synthesis in addition to its theoretical interest suggested the timeliness of an update. Therefore, this review focuses on the recent advances in the structural aspects, the generation of *o*-xylilene from different precursors, its synthesis, its synthetic applications, and also the newly discovered hetero analogues of *o*-quinodimethanes.

I. THEORETICAL AND STRUCTURAL ASPECTS

The thermodynamics and kinetics of the equilibrium gas-phase reaction of o-quinodimethane **1** and benzocyclobutene **5** has already been studied.[19]



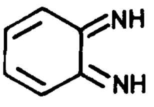
1 **5**

The observed data suggest that **1** can exist together with **5** either in a high temperature equilibrium [equilibrium constants K_{581} =20.8 (measured[19]) and K_{800} ≈4 (estimated[20])] or much more efficiently at low temperatures as an intermediate after the decomposition of a suitable starting compound in a thermal flow reactor [rate constant (**1**→**5**) K_{225} =3.3 s^{-1} ; this corresponds to a half-life $t_{1/2} \approx$ 0.2 s (estimated); reaction time t_R in the reactor, e. g. in combination with a UV photoelectron spectrometer, *c.a.* 0.1 s[21]]. By use of the same strategy, the photoelectron spectrum of **1** was measured for the first time in the gas phase[22] and more recently in acetonitrile solution at room temperature in the UV-visible region.[23]

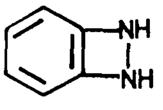
According to MNDO calculations, the standard reaction enthalpy of the reaction **1**→**5** is -82.8 $kJ.mol^{-1}$ (24.2 $kJ.mol^{-1}$ below the experimental value) and the standard reaction entropy is negative (ring closure unfavorable)[20]; compound **1** is thus thermodynamically unfavoured in the equilibrium **1**⇌**5**. Very recently, by trapping experiments with oxygen and by determining the temperature dependence of the equilibrium **1**⇌**5**, the activation parameters for the mutual interconversion of **1** and **5** have been determined and compared with previous literature values.[24]

The existence of *o*-quinodimethanes has been observed by UV-visible spectroscopy and used to study their rates of dimerization.[23] Some *o*-xylylene derivatives are sufficiently long lived for their IR and Raman[25] and ^1H-NMR spectra[26] be determined. However, only very recently has the detection of **1** itself in the presence of of its stable dimers by the technique of flow ^{1}H-NMR been reported.[27] The flow NMR tecnique allows detection of short lived species and usefully complements UV-visible techniques because of its diagnostic capability.

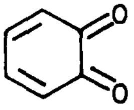
In order to study the relative stabilities of the quinoid forms and the bicyclic forms, the structures of the ground states of the molecules of *o*-quinodimethane (1), o-quinonediimine (6a), o-benzoquinone (6b) and their bicyclic counterparts (5,



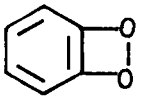
6a



7a



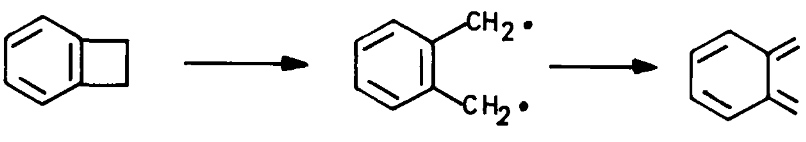
6b



7b

7a and 7b have been studied by *ab initio* SCF calculations using a split-valence basis.[28] Calculated energies indicate that 5 is more stable than 1. For the other pairs, the open quinoid forms are found to be energetically preferred, in good agreement with available experimental data.

Although the reactivity of o-quinodimethane (1) parallels that of a highly reactive diene, it may also be represented as a birradicaloid hydrocarbon (8).[14] In an attempt to determine the reaction mechanism of the Diels-Alder cycloaddition of benzocyclobutene with dienophiles, Kametani *et al*. have calculated

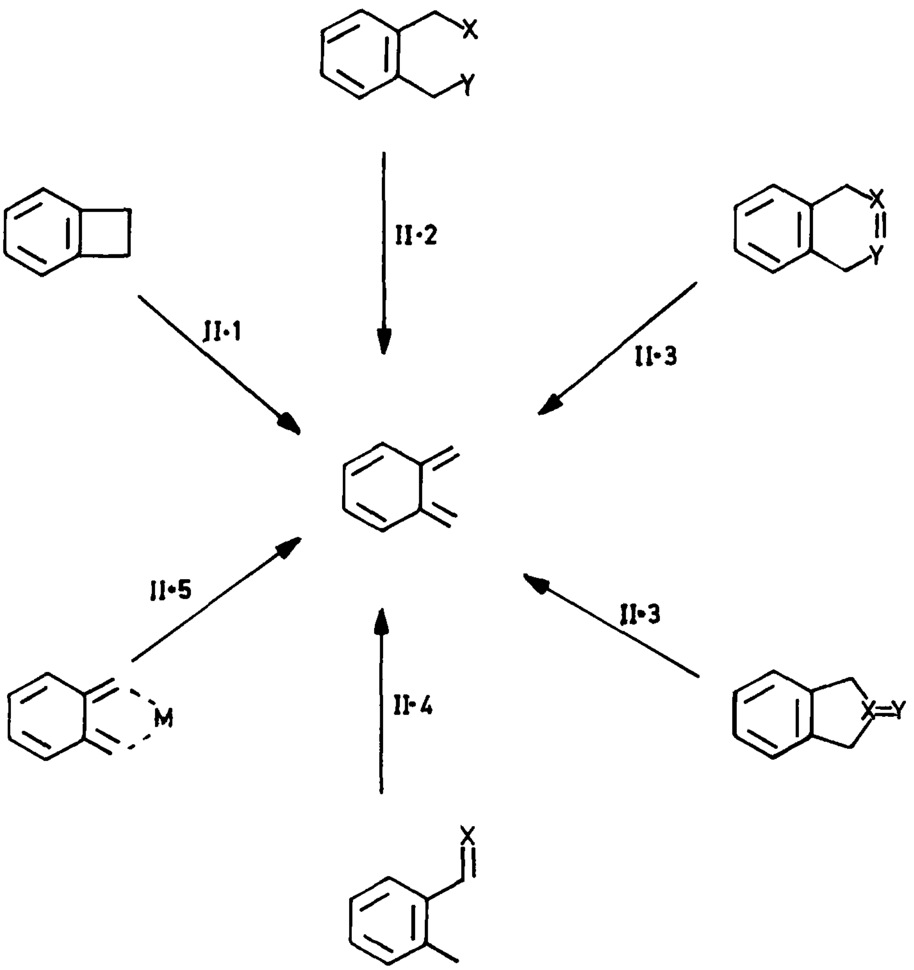


5 8 1

the stabilities for the alternative structures of the intermediate by using MINDO/3, STO-3G, and 4-31G methods. The results led to the conclusion that the Diels-Alder reaction of 5 proceeds via the biradical intermediate (8) by a stepwise cycloaddition.[29] This result is in contrast with previous literature data[14] and the also recent theoretical calculations by Lahti and Berson[30,31] using the INDO/S-CI method for the *ortho*, *meta* and *para* isomers. The latter calculations predict *o*- and *p*-xylylene to be ground-state singlets, whereas "*m*-xylylene" is found to have a ground-state triplet.

Finally, a modification of the Dewar and Dougherty approach allowed the determination of the resonance energy and aromatic character of *o*-quinodimethane more reliably than previous estimates, by taking into account the stabilizing effect of cyclization on all bonding electrons.[32] Very recently Zhou and Parr, by using the principle of chemical hardness and softness, have reported that relative hardness is a particularly good index for identifying aromatic, non-aromatic and anti-aromatic character in organic molecules.[33]

II. POSSIBLE PRECURSORS OF *o*-QUINODIMETHANES

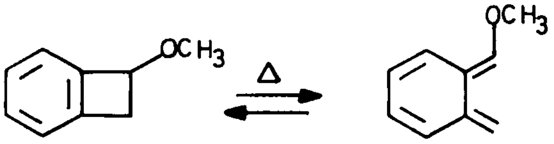


The recent advances in the methodology for the generation of *o*-quinodimethanes have permitted the facile generation of this highly reactive intermediate under mild conditions and with control of the stereochemistry of the cycloaddition reactions with dienophiles. The general procedures to prepare *o*-xylylene can be classified according to the different precursors as illustrated in the scheme below. The numbers on the arrows refer to the appropriate paragraph in which each type of reaction is discussed. It is worth mentioning that although the procedures shown in this scheme may be considered "classical", some very interesting developments concerning these different approaches to *o*-quinodimethanes have recently appeared.

II.1. Thermolysis of Benzocyclobutenes

From the earlier studies on the formation of *o*-xylylenes from from 1,2-diphenylbenzocyclobutenes (**3**)[3] and further kinetic and stereochemical work,[34] a reversible conrotatory opening of the cyclobutene ring was established. This procedure has been widely used for the generation of *o*-quinodimethane derivatives.[35]

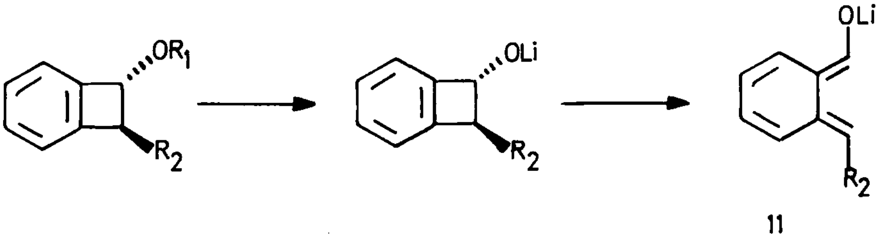
Sammes *et al.*[36] demonstrated that the thermal conversion of α-methoxycyclobutenes (**9**) to α-methoxy-o-xylylene (**10**) occurs with exclusive formation of the *E* isomer. The methoxy group leads to a lowering of *ca.* 9 kcal.mol^{-1} in the activation energy for the ring opening reaction. This lowering of the energy barriers toward *o*-xylylene formation has been observed when other electron-donating substituents are present at sp^3 carbons of the benzocyclobutene ring. Altough the presence of the methoxy group gives place to a lower ring-opening temperature, over 100° must still be reached.



9 **10**

Very recently Choy and Yang[37] have taken advantage of the fact that electron-donating groups at sp^3 carbons of a benzocyclobutenyl ring lower the energy barrier towards *o*-xylylene formation. Thus, the precursor of **11** undergoes ring opening at temperature below 0° to the *o*-xylylene **11**, due to the α-anionic center on the oxygen. Furthermore, the associated metal cation can then behave as a Lewis acid center for a subsequent Diels-Alder reaction at the same temperature. Cations other than Li^+ have been used, but the rate of *o*-xylylene formation and the product distribution in the subsequent Diels-Alder reaction are greatly influenced by the nature of the associated cation.

The use of this procedure led not only to a lowering in the times and temperatures but also to a significant increase of the *endo* selectivity.[38]



11

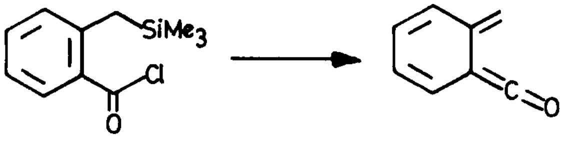
$R_1 = H, Ac;\quad R_2 = H, Ph$

II.2. 1,4-Elimination of α,α′-Substituted *o*-Xylenes

One of the most important methods for the generation of the *o*-quinodimethane intermediate, is the 1,4-elimination from *o*-xylylene derivatives because of the ready availability of the starting materials.

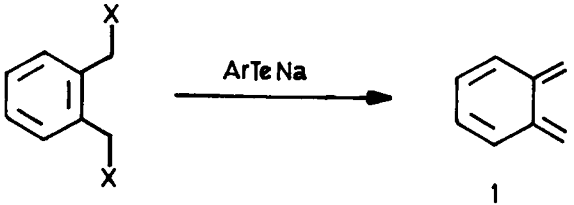
o-Xylene di-, tri, or tetrabromides undergo intramolecular 1,4-dehalogenation by means of sodium iodide,[1] lithium,[39] zinc (the reaction is improved by using ultrasound),[40] copper,[41] iron[42] and chromium.[43] Hoffman elimination of (*o*-methylbenzyl)-trimethylammonium hydroxides,[4] 1,4-elimination of hydrogen halide[44] or methanol,[45] as well as the fluoride-induced 1,4-elimination[46] have been successfully used for the generation of *o*-xylylene (**1**).

By using the fluoride ion catalysed elimination, it has been found that desilylation of *o*-(trimethylsilylmethyl)benzoyl chloride (**12**) provides a convenient route to α-oxo-*o*-quinodimethane (**13**).[47] These compounds are intermediates of considerable interest, which on suitable ⟦2+4⟧ trapping give functionalized bicyclic systems.



12 13

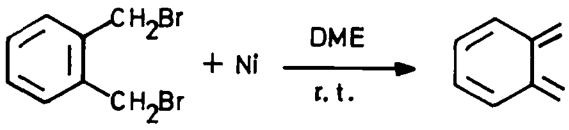
Dehalogenation of α,α′-dihalo-*o*-xylenes to *o*-quinodimethanes with iodide ion was restricted to activated systems having alkoxy substituents on the aryl rings or additional halogen atoms in the benzylic positions. Recently, the first *o*-quinodimethane generation from nonactivated α,α′-dihalo-*o*-xylenes promoted by sodium benzenetellurolate has been described by Sonoda *et al.*[48] It is likely that the reaction proceeds through nucleophilic attack of benzenetellurolate anion at the tellurium atom of α-halo-α′-phenyltelluro-*o*-xylene initially formed *in situ* by the substitution of one of the halogen atoms of the starting α,α′-dihalo-*o*-xylene. When sodium benzeneselenolate was employed, no evidence of *o*-quinodimethane formation was observed.



1

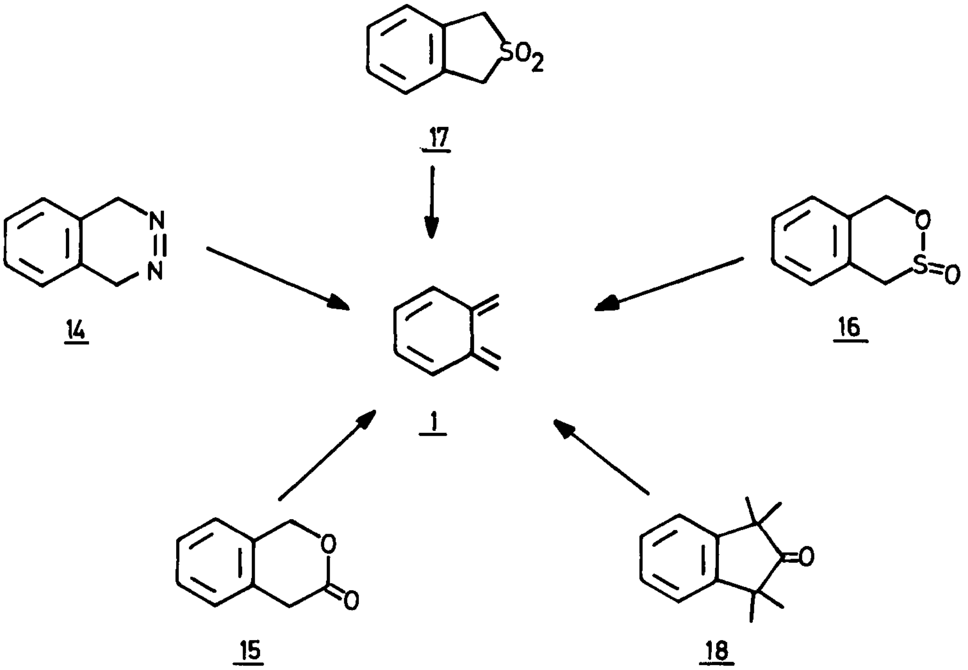
X= Cl, Br, I

Very recently, Rieke *et al.*[49] have reported that 1,4-dihalide eliminations from α,α'-dibromo-*o*-xylene derivatives were induced at room temperature with activated nickel (generated by treatment of nickel(II) iodide with lithium) to give *o*-xylylene intermediates. The presence of methoxy substituents and even electron-withdrawing groups such as bromide and nitrile on the aromatic ring of the starting dibromide were shown to be compatible with the reaction conditions, yielding substituted cycloadducts in good yields.



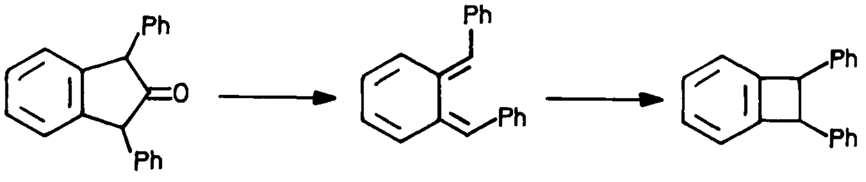
Platz and Haider[50] in a recent communication have reported the matrix isolation of *o*-xylylene **1** by photolysis of α,α'-dichloro-*o*-xylene. This preliminary result indicates that the readily available dihalo compounds may be general precursors under matrix-isolation electron-transfer conditions.

II.3. From Benzofused Heterocyclic Compounds



o-Quinodimethanes have been generated from benzofused heterocyclic compounds by reverse Diels-Alder reaction in which a molecule of nitrogen[51] or carbon dioxide[52] is lost, from **14** and **15** respectively, and by thermal or photochemical chelotropic extrusion of sulfur dioxide from sulfinates (**16**)[15,53] and sulfones (**17**)[15,54] or carbon monoxide from 2-indanones (**18**).[55]

Although the photodecarbonylation of 2-indanones has proved to be a very general route to *o*-xylylenes, Quinkert *et al.*[55] has shown that the loss of carbon monoxide ocurred from the same singlet excited state, which is consistent with a stepwise, nonchelotropic carbon monoxide elimination.

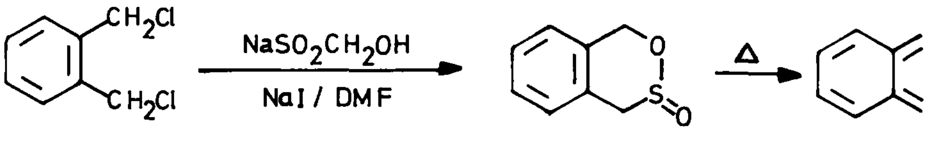


19 **20** **3**

It is also interesting to note that **20** has been reported to be in thermal equilibrium with the cyclized benzocyclobutene (3), in contrast with the parent *o*-xylylene **1** in which cyclization to benzocyclobutene requires irradiation.[14]

Generation of *o*-xylylene **1** from sultine (sulfinate) **16** (4,5-benzo-3,6-dihydro-1,2-oxathiin-2-oxide) has advantages over methods involving metals and the diahalide, which cannot be used in the presence of reducible groups, or the fluoride ion catalyzed decomposition of ⟦*o*-⟦(trimethylsilyl)methyl⟧benzyl⟧-trimethylammonium bromide, because enolization can take place in the quinone adducts.[56] On the other hand, generation of *o*-xylylene **1** by thermal elimination of sulfur dioxide from sultine **16** requires lower temperatures (80°)than the others benzofused cyclic compounds precursors.

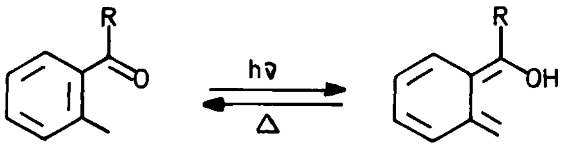
The only inconvenient feature of this method for the generation of **1** involves the synthesis of sultine **16** through a multistep process.[53] However, Dittmer *et al.*[57] have described a one-step synthesis of sultine **16** in good yield by treatment of α,α'-dichloro-*o*-xylene with Rongalite (sodium hydroxymethanesulfinate) and sodium iodide in DMF. This new method for the generation of sultine **16** appears to be more convenient than the multistep processes reported earlier.



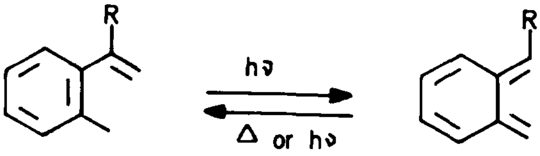
16 1

II.4. From *o*-Methylbenzaldehydes or *o*-Methylstyrenes

The generation of *o*-xylylenes as their α-hydroxy derivatives has been widely studied in two previous reviews.[14,17] *o*-Alkyl substituted aromatic aldehydes or ketones on irradiation undergo the photoenolization by a photochemical 1,5-hydrogen **shift.** Although the flash photolysis results suggest that this is a complex reaction, it seems clear that the hydrogen abstraction occurs in the n-π^* triplet state of the ketone. However, from a synthetic point of view, the photochemical generation of the *o*-xylylene has some drawbacks due to the photochemical isomerization that can occur with some dienophiles and also to the impossibility to produce trappable photoenols on irradiation in other cases.[58]



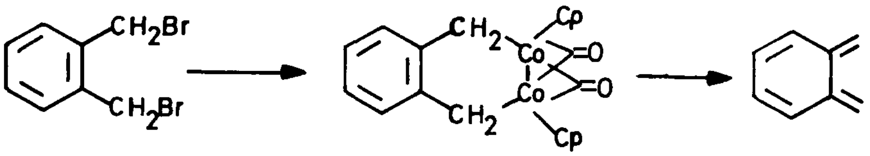
The irradiation of *o*-alkylstyrenes has proved to lead to *o*-quinodimethane derivatives by a 1,5-hydrogen shift. This reaction has been less studied and only a few papers have been published on the subject.[14,17]



II.5. From *o*-Xylylene-Metal Complexes

o-Quinodimethane complexes of a number of different metals have been obtained by different routes.[59] However, the use of these complexes as precursors of *o*-xylylenes has been neglected in the literature.

The only trapping of an *o*-quinodimethane liberated from a metal complex involves the dimetallacyclohexene **21** from which the brigging xylylidene ligand was displaced with phosphines and captured by dienophiles or by dimerization.[60]



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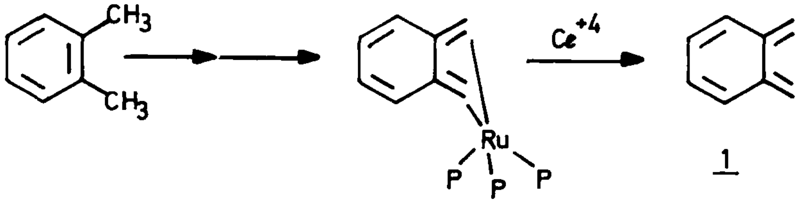
Recently, the first indications of *o*-quinodimethanes being liberated from cromium or rutenium complexes (**22**) by oxydation have been reported.[61] The fact that these complexes can be prepared directly from available starting materials suggests the



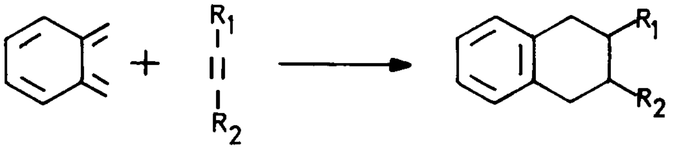
22 1

great potential of this procedure as a route to *o*-xylylene derivatives.

III. SYNYHETIC APPLICATIONS OF o-QUINODIMETHANES

The recent advances in the methodology for generating *o*-quinoduimethanes under mild conditions have lead to its increasing use in the preparation, with high stereochemical control, of a large number of polycyclic compounds, including alkaloids, steroids, terpenoids, antracyclines, lignans and quassinoids.

o-Xylylenes have been mainly used in Diels-Alder cycloadditions by reacting with dienophiles to lead, in a perycyclic process, to the formation of complex polycyclic compounds.



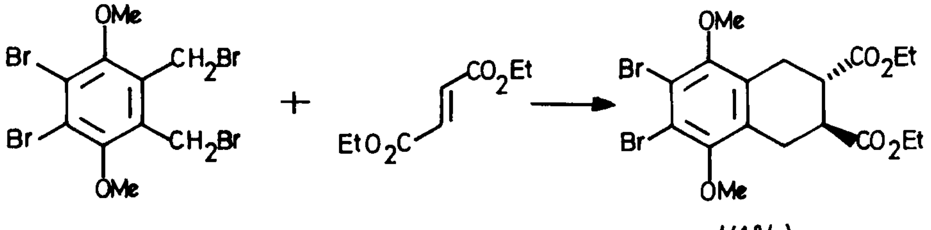
The theoretical aspects on the regio- and stereochemistry of this cycloaddition have been widely treated recently[62] and also in the excellent review by Charlton and Alauddin,[5] to which the reader is referred.

For systematization purposes, the synthetic applications of *o*-quinodimethanes have been divided into two groups: cycloaddition reactions as intermolecular processes and intramolecular cycloadditions. An important aspect also to be included is the role of *o*-xylylenes in the development of Retro-Mass Spectral Synthesis methodology which will complete this topic.

III.1. Cycloaddition Reactions

The large number of papers published on intermolecular cycloadditions involving *o*-quinodimethanes is so vast that to give a full account of this chemistry would be a task for an entire review. Fortunately, many examples can be found in some recente reviews[5,7,10] and especially in the synthesis of lignans and quassinoids. [5,63] A short survey on the more recent advances in intermolecular Diels-Alder reactions of *o*-quinodimethanes is presented below.

In the nickel-mediated cycloadditions of substituted α,α′-dibromide-*o*-xylenes, Rieke *et al.* have demonstrated that the *o*-xylylene intermediates can tolerate electron-withdrawing groups such as nitriles and halogens to yield the corresponding



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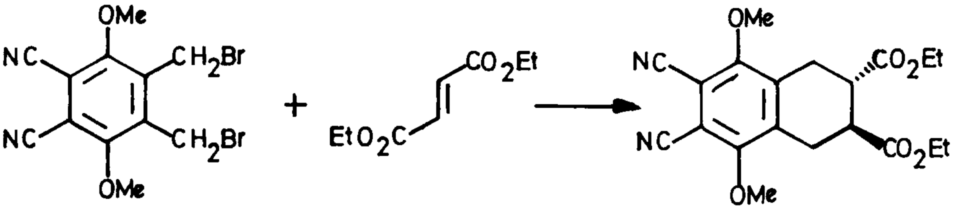
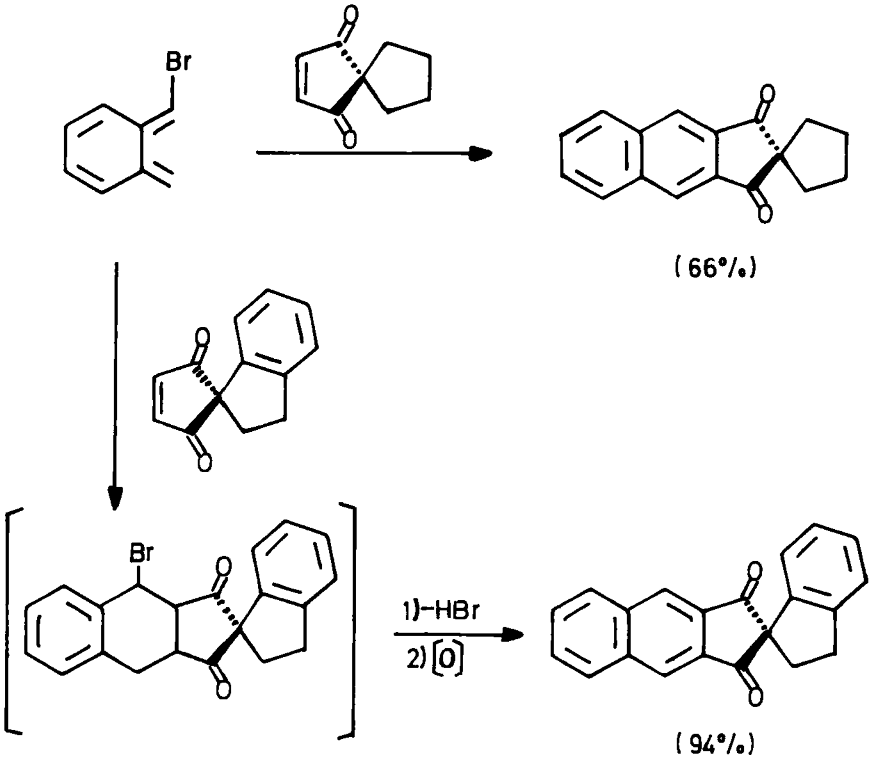


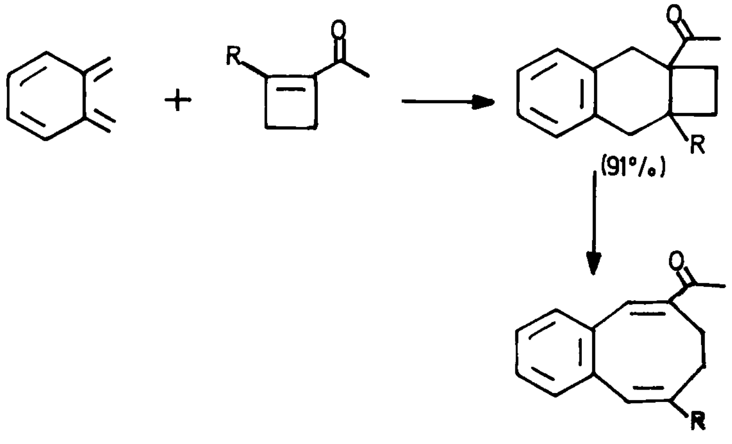
(61%)

cycloadducts in good yields.[49] On the other hand, Bach and Klix[64] have described a simple model compound related to the antitumor and antibiotic compound fredericamycin A which contain the spiro[4,4]nonane moiety. This new synthetic strategy is centered on the concept of constructing the three contiguous rings by Diels-Alder cycloaddition of the highly reactive α-bromo-*o*-quinodimethane intermediate to the corresponding spiro dienophile, followed by spontaneous aromatization.

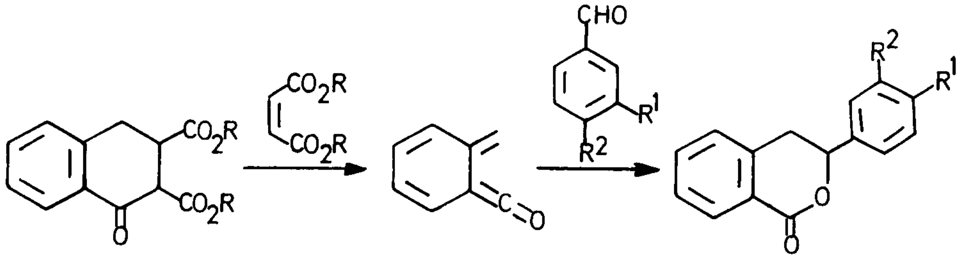
Although functionalized cyclobutene derivatives are promising dienophiles for the preparation of bicyclic compounds, only a few examples have been reported. Recently, Takeda *et al.* have described the first practical method for the preparation of 1-cyclobutenylketones and their cycloaddition reaction with *o*-xylylenes followed by the ring enlargement reaction of the



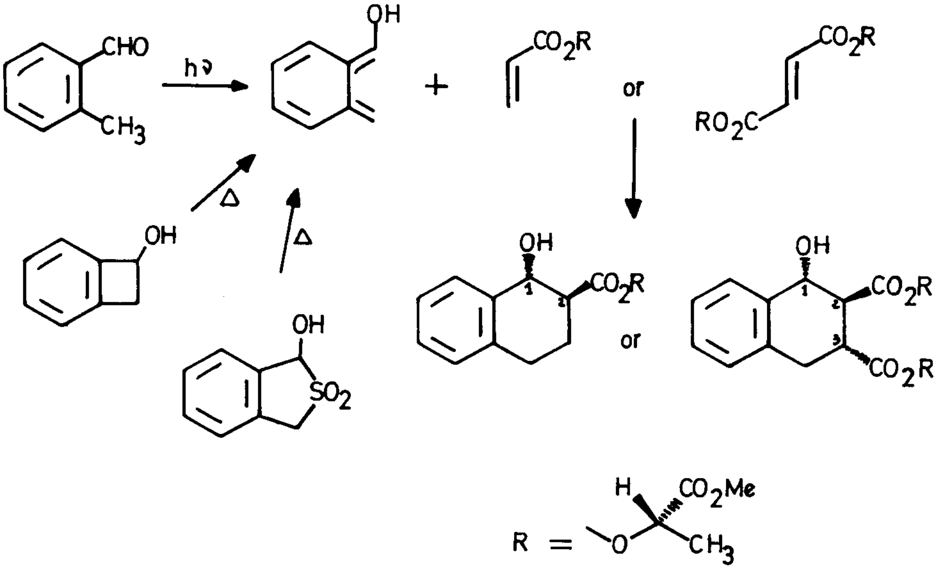
resulting cycloadduct.[66] The *o*-xylylene was so reactive towards the cyclobutene that the reaction was carried out without catalyst at room temperature.



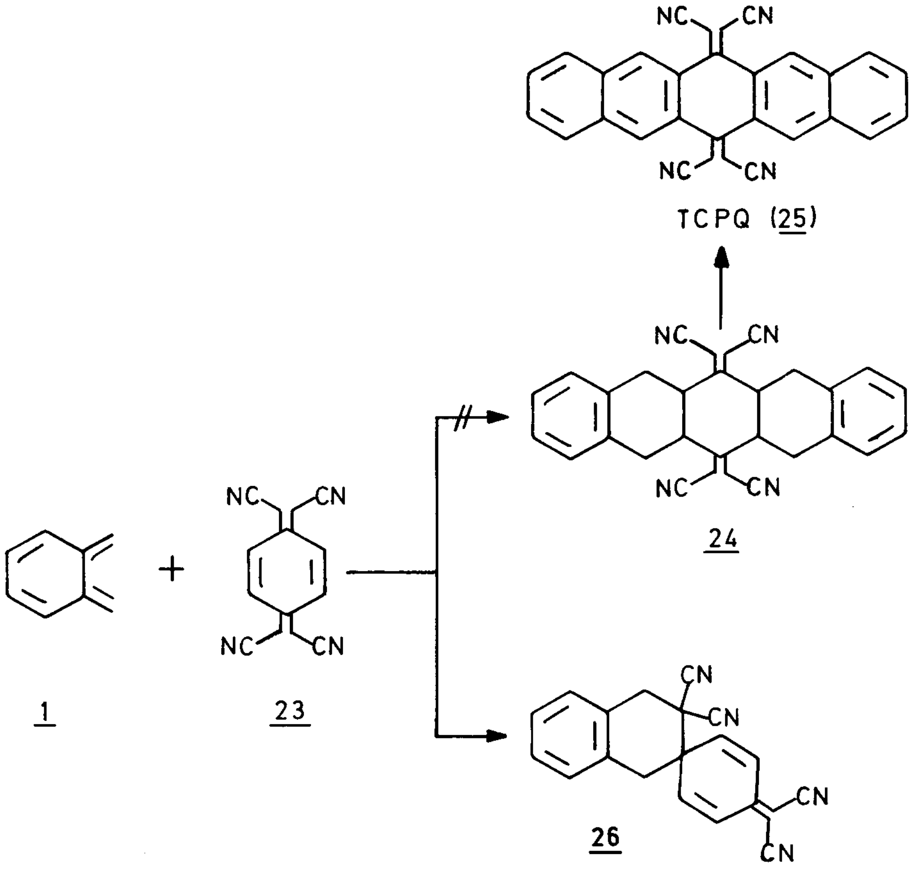
The reaction of α-oxo-*o*-quinodimethane with dienophiles such as olefins and carbonyl groups have been reported to lead to the corresponding α-tetralones and dihydroisocoumarin derivatives respectively.[4 7]



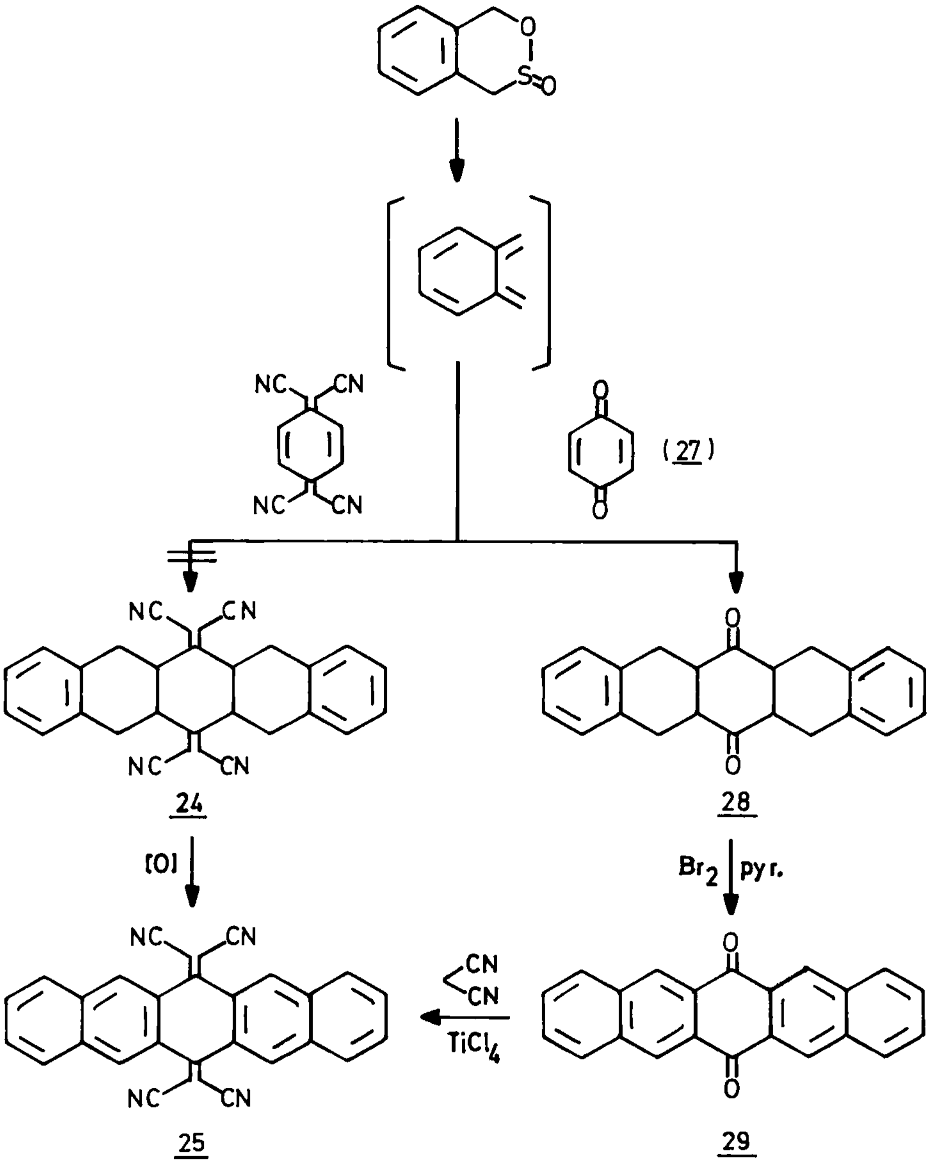
The thermal generation of α-hydroxy-*o*-xylylene from benzocyclobutenol, hydroxysulfone and *o*-tolualdehyde as well as their reactivity with several dienophiles has been studied.[5 8] Although the yields of cycloadducts seem to depend on the procedure followed to generate the *o*-xylylene, the diasteroselectivity of the cycloadditions does not change.



Recently, we have also used *o*-quinodimethanes in the synthesis of new benzo-fused tetracyano-*p*-quinodimethane (TCNQ) derivatives as acceptor molecules to form charge transfer complexes [67] (for a review on this kind of organic conducting materials see ref. 68). Initially, the route followed for the synthesis of tetracyano-6,13-pentacenequinodimethane (TCPQ) (**25**) was a Diels-Alder reaction of TCNQ (**23**) with *o*-quinodimethane (**1**) to form the corresponding bis-adduct **24**. Subsequent dehydrogenation would provide TCPQ (**25**).

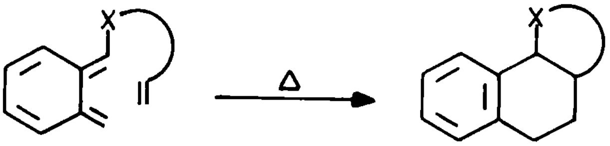


However, the *o*-xylylene generated reacted with the exocyclic double bond to give spiro compound **26**; however, it did react with *p*-benzoquinone (**27**) to give the octahydro-6,13-pentacenedione (**28**) in a one-step reaction. Diketone **28** can be easily oxidized to form 6,13-pentacenedione (**29**) which, upon reaction with malononitrile, yields TCPQ (**25**). Accordingly, we have synthetized a variety of new fused aromatic TCNQ derivatives and their electrochemical properties as acceptors were studied in the aim to form charge transfer complexes.[67]

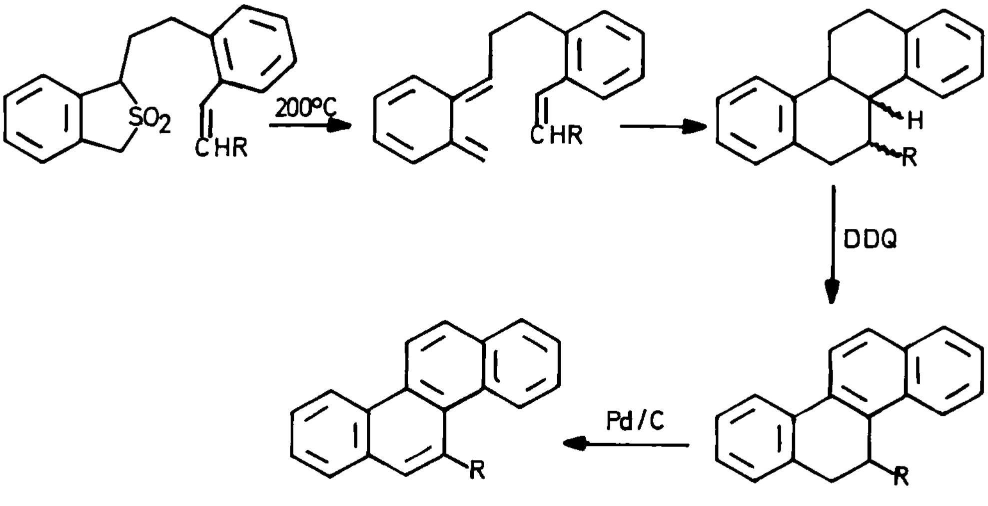


III.2. Intramolecular Cycloadditions

Together with the use of *o*-quinodimethanes in intermolecular reactions with a variety of dienophiles, a great deal of work has been published on intramolecular reactions, in which the *o*-quinodimethane moiety is generated within a complex molecule containing a dienophilic double bond. Important polycyclic compounds have been prepared in this way through highly stereoselective routes. In fact, several reviews have been mainly or exclusively dedicated to this topic. The two reviews by Oppolzer,[15,16] dealing with the scope and limitations of intramolecular cycloaddition reactions, and the reviews by Kametani *et al.*[9-12] on natural products, Fallis[6] and Quinkert[7] as well as the more recent one by Charlton and Alauddin[5] are compulsory reading.

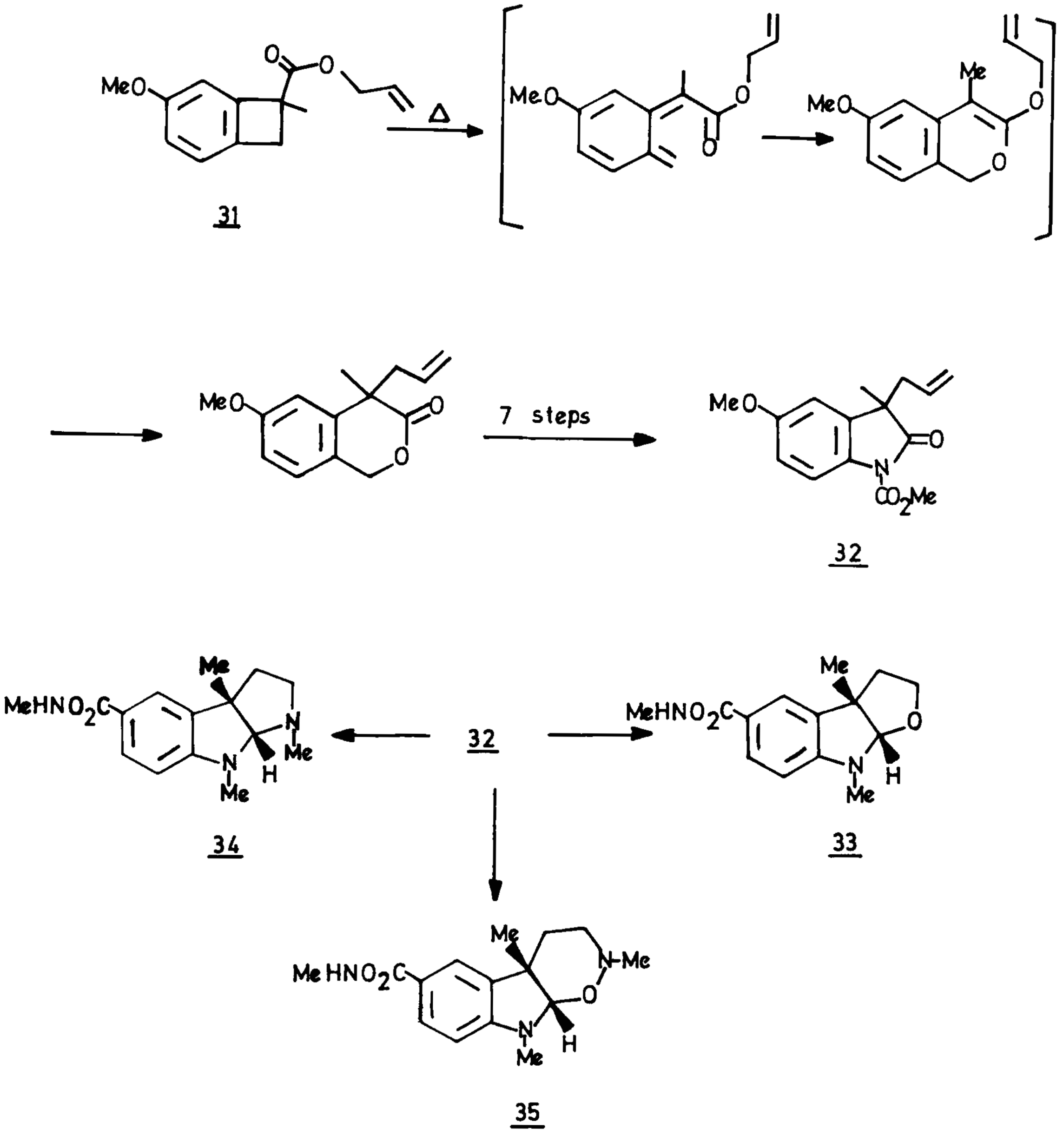


Generally, as a consequence of the steric hindrance, the stereoselectivity of the cycloaddition is often different from the intermolecular process.[6,7] Thus, Levy and Sashikumar have described the synthesis of 5-substituted chrysenes (**30**) *via*

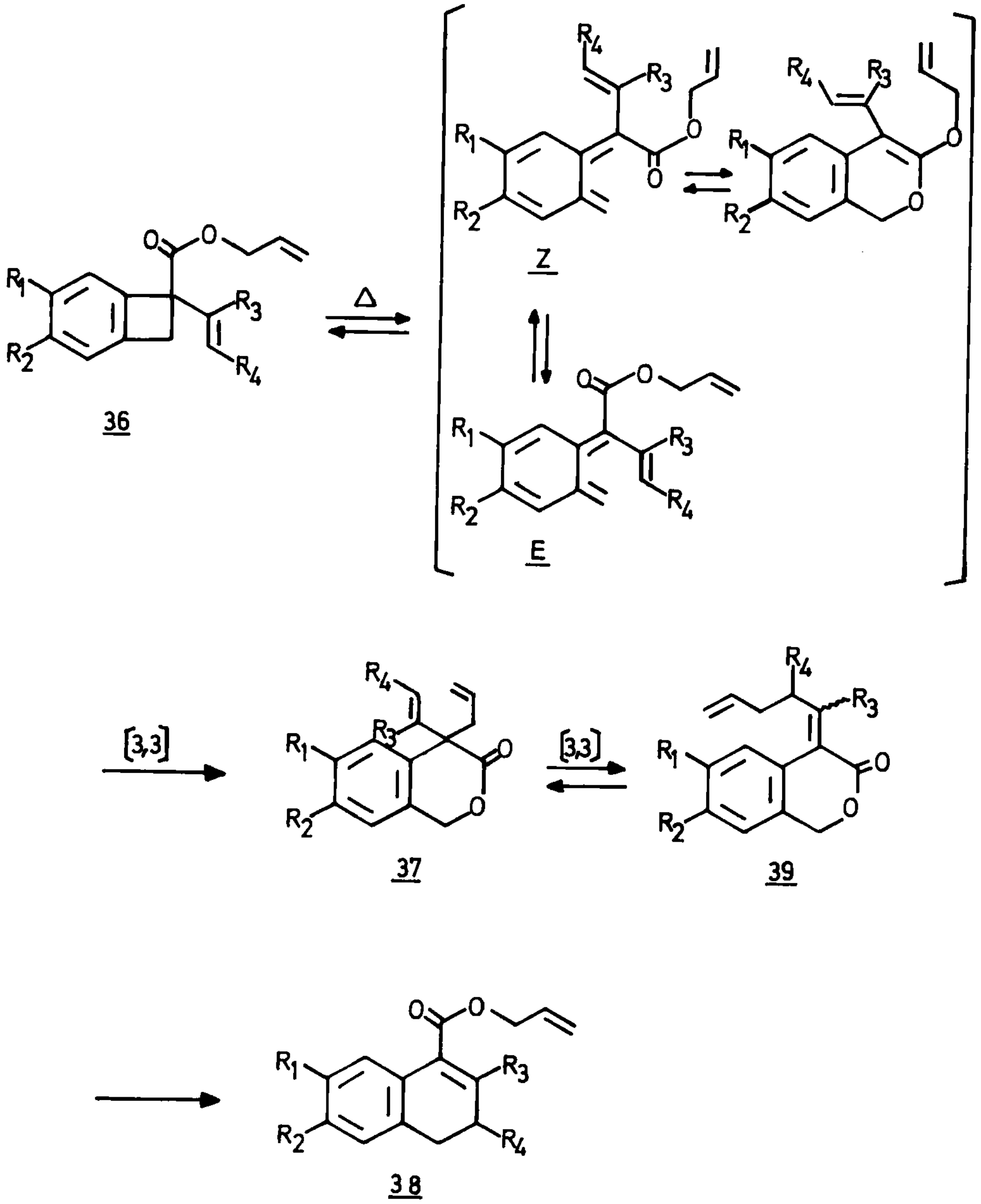


30

intramolecular cycloaddition reactions. While chrysene is itself only weakly biologically active, 5-substituted chrysenes are much more potent in assays for mutagenic and carcinogenic activity,[70] giving rise to a potential pharmacological inte-



rest. In the case of the unsubstituted hexahydrochrysene (R = H), the product was isolated as a 2.1:1 mixture of two isomers corresponding to *trans* and *cis* stereochemistry at the ring junction. This occurs *via* the intervention of both *exo* and *endo* transition states in the cycloaddition, a phenomenon which has been observed in other examples of reactions of this type.[71]



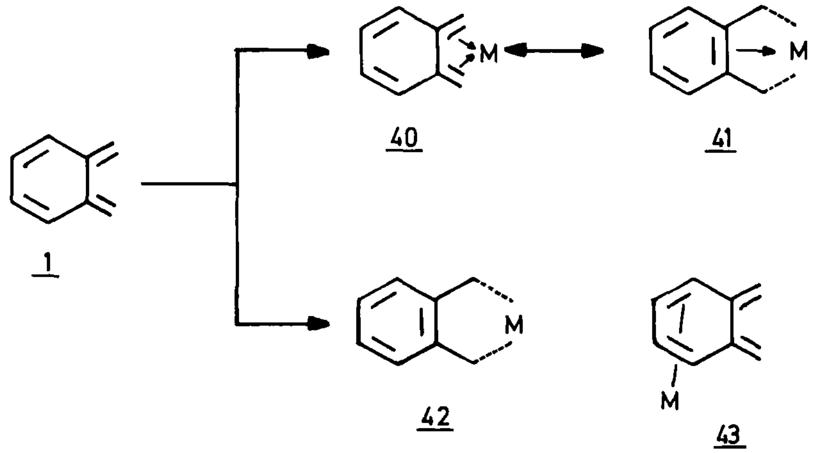
Recently, Fukumoto *et al.*[72] have reported the total synthesis of (±)-physovenine (**33**) and physostigmine (**34**) based on the newly developed electrocyclic ⟦3,3⟧ sigmatropic reactions of *o*-quinodimethane generated *in situ* by thermolysis of the benzocyclobutene (**31**). The oxindole **32** was a common intermediate for both alkaloids.

The application of this strategy has lead to the first total synthesis of the calabar bean alkaloid geneserine (**35**) in a 16 step sequence.[73]

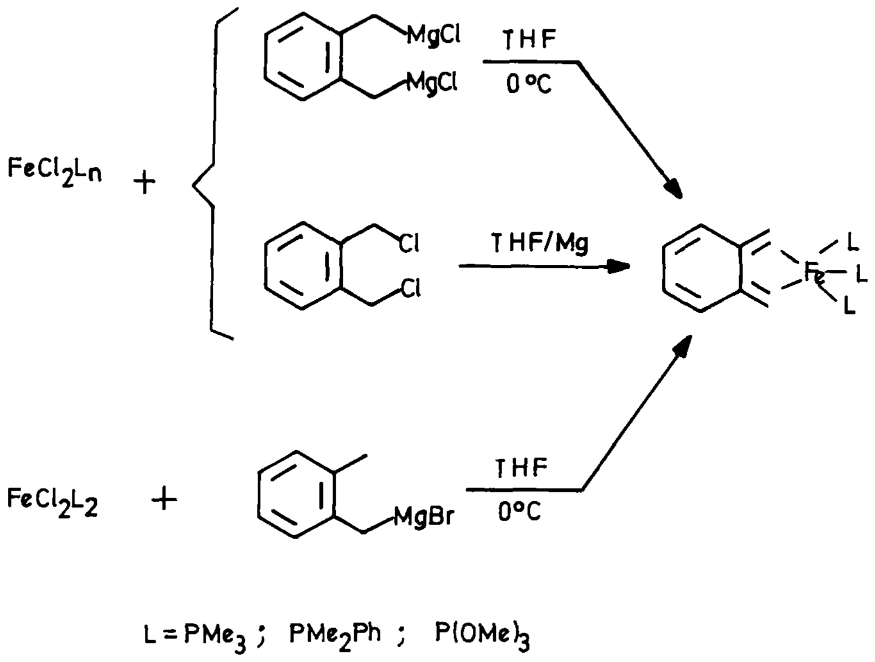
The same researchers have also described the thermolysis of allyl 1-alkenylbenzocyclobutenyl-1-carboxylate (**36**) to produce a mixture of 4,4-disubstituted isochroman-3-ones (**37**),dihydronaftalenes (**38**) and 4-alkylideneisochroman-3-ones (**39**).[74] In this case, two competing electrocyclic reactions during the thermolysis are possible. It proceeded predominantly through *z*-transition state. In addition, this reaction is an unprecedent sequential electrocyclic-double ⟦3,3⟧ sigmatropic reaction of *o*-quinodimethane.

III.3. Other reactions

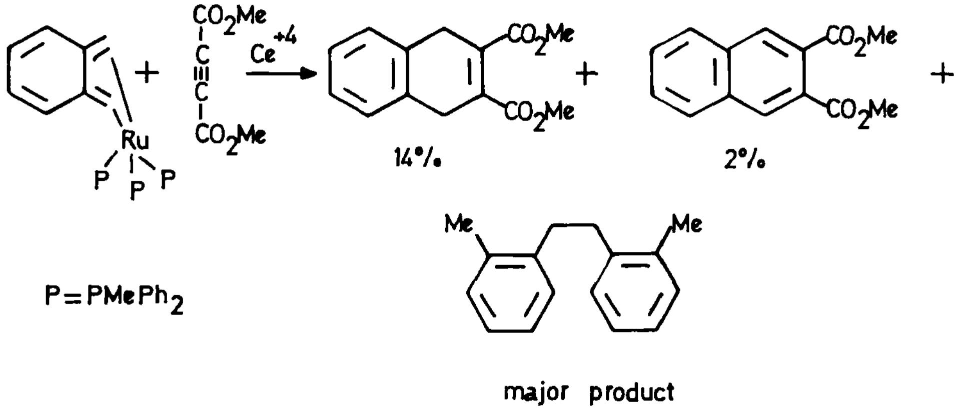
As a ligand, *o*-xylylene also offers a variety of coordination patterns. Thus, it can formally behave as a four-electron biradical ligand as in canonical form **41** but also as a diene ligand as in complexes of type **40**.



Some examples of complexes ⟦**40** ↔ **41**⟧ with *o*-xylylene coordinated to $Fe(CO)_3$[75], $Co(C_5H_5)$[60] or $Ru(PR_3)_3$[59] have been described. *o*-Quinodimethane can also form diene-metal complexes of type **42** and **43**[76]. *o*-Xylylene metal complexes of group 4,5, and 6 metals or platinum (II)[77] and in bimetallic systems[60], have also been reported. Dixneuf *et al.* have more recently reported a simple one-pot reaction leading directly from $FeCl_2$ to the electron-rich iron complexes of *o*-xylylene, by reaction with several precursors.



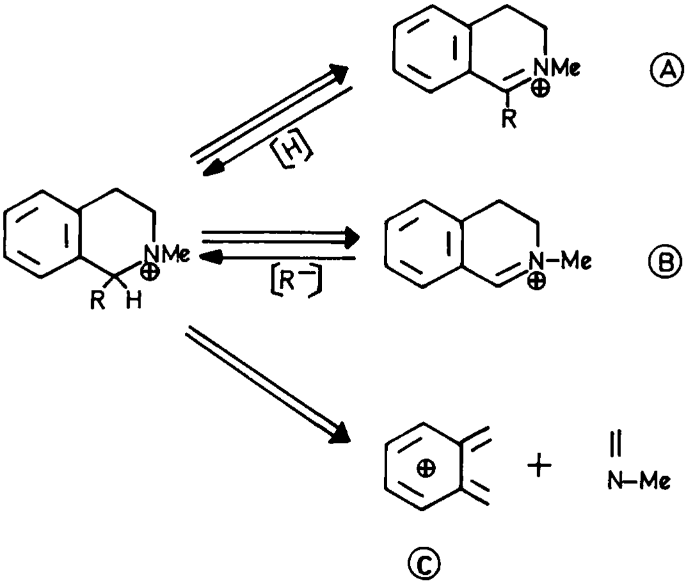
These complexes showed a high tendency to behave as electron-transfer agents to give an unexpectedly stable paramagnetic species. These two characteristics, which are indicative of the electron-rich nature of the complexes, appear to be dependent upon the electron-donor capability of the phosphorus ligand and also by the type of interaction between the hydrocarbon ligand and the metal.[78] Cole-Hamilton *et al.*[61] have described the first indication that *o*-xylylenes can be liberated from ruthenium complexes. The reaction of these complexes with some dienophiles in the presence of cerium (IV) yielded the corresponding cycloadducts in low yields. The yields could probably be optimized by the use of different oxidants and reaction conditions. The use of *o*-xylylene complexes is undergoing an important expansion as a source of *o*-xylylenes and presents a hopeful future for further cycloaddition reactions.



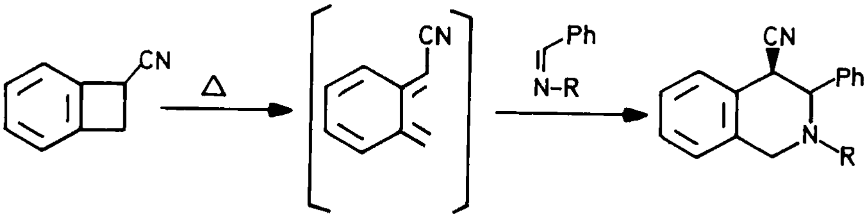
III.4. Retro-Mass Spectral Synthesis Involving *o*-Quinodimethanes

o-Quinodimethanes have played a key role in the development of the so-called Retro-Mass Spectral Synthesis methodology, namely the use of the mass spectrum of a compound as a basis for the design of its synthesis.[79]

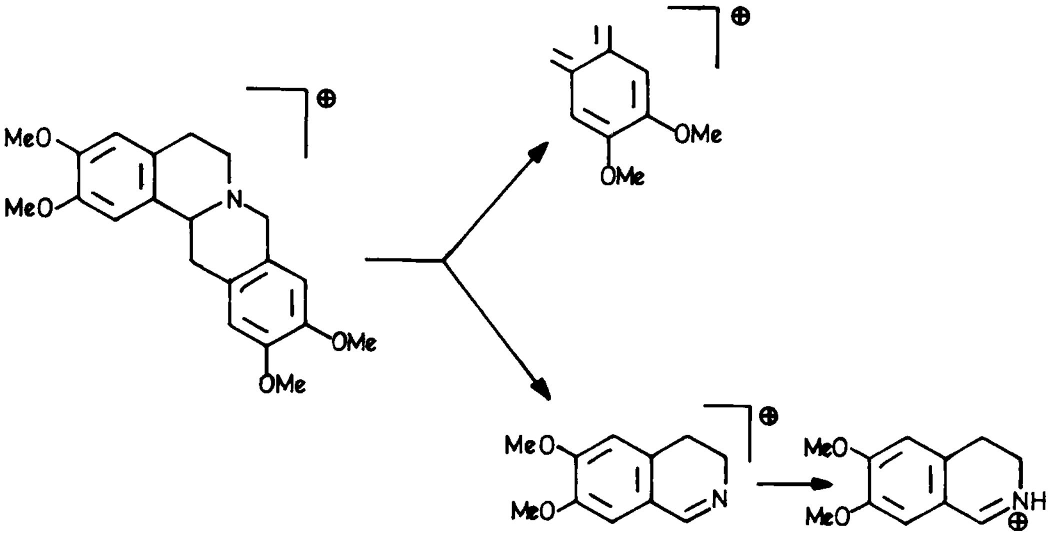
Among the first work in this area, is that of Kametani's group, who realized that the mass spectrum of tetrahydroisoquinoleines showed two fragmentation patterns, leading to ions A and B, together with a third route leading to C. The first two fragmentations are the retro-reactions for two common syntheses of these heterocycles: reduction of dehydrogenated derivatives and alkylation of 3,4-dihydroisoquinoleines. The third route leading to a *o*-quinodimethane and an imine did not correspond to any known synthesis, but suggested the possibility of designing a new one. Thus, a benzocyclobutene was used as a precursor, with a substituent on the four-memebered ring to ensure



the required regioselectivity. The reaction with a Schiff base led to the tetrahydroisoquinoleine, in a new synthesis for this fused ring.[80]

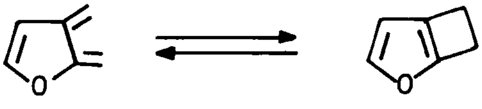


This Retro-Mass Spectral Synthesis approach has been used for the synthesis of complex natural products, mainly alkaloids. In many instances, as for xylopinine, a protoberberine alkaloid, the key intermediate, a *o*-quinodimethane, was again suggested by the mass spectrum. The succesful synthesis can be carried out either with a hydroxy or cyano-substituted benzocyclobutene.[81] Many other natural products have been synthetized by using this methodology.[79]



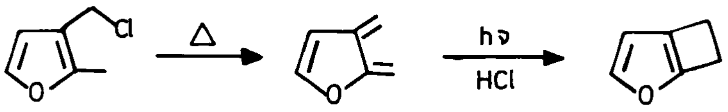
IV. HETERO ANALOGUES OF *o*-QUINODIMETHANES

The theoretical and synthetic interest that presents the chemistry of *o*-quinodimethane has prompted the search of *o*-xylylene heteroanalogues.



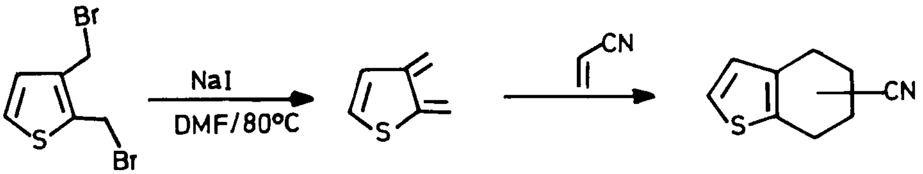
44 45

Thus, although the 2,3-dimethylene-2,3-dihydrofuran (**44**) had been previously detected by trapping reactions, and MS and NMR spectra,[82,83] very recently it has been almost quantitatively generated at pressures of *ca.* 10^{-2} mbar by Münzel and Schweig.[20] They studied the photochemical cyclization to the dihydrocyclobutafuran **45** in a condensed phase (argon matrix). They also carried out some theoretical calculations and the data seems to indicate that structure **45** is thermodynamically unfavored. In consequence, the thermally inaccesible compound **45** can be generated photochemically from its thermodynamically more favorable isomeric form **44**. On the other hand, the



44 45

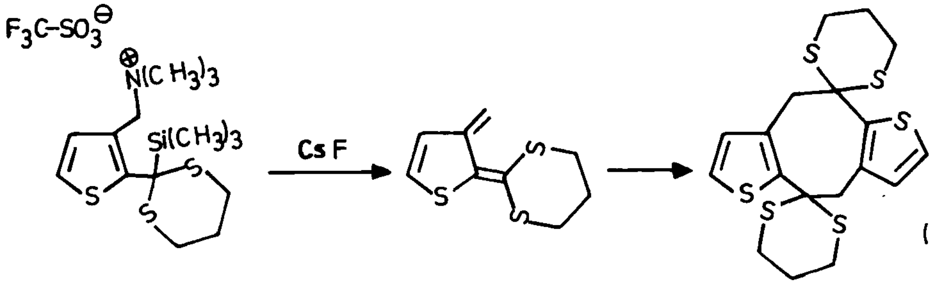
thiophene analogue **47** has been generated by Chadwick and Plant[84] from 2,3-di(bromomethyl)thiophene (**46**) and more recently by an improved procedure by Storr *et al.*[85] Treatment of **46**



46 47 (60%)

at 80° with a dienophile leads to the corresponding Diels-Alder adduct, obtained as a mixture of regioisomers. In the absence of dienophile, only polymeric material was formed.

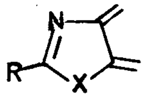
Other thiophene analogues of *o*-xylylene are also known.[84] Similarly, fluoride-induced 1,4-elimination of the triflate salt of thiophene **48** afforded the corresponding cyclooctadiene derivative **50** as a single isomer through the formation of the intermediate **49**.[46]



48 49 50 (51%)

An important generalization is the very recent report by

Storr *et al.*[86] describing the oxazole, thiazole and imidazole analogues of *o*-xylylene (<u>51</u>).



<u>51</u>

CONCLUSIONS AND FURTHER PERSPECTIVES

The theoretical and synthetic interest in *o*-quinodimethanes is now even greater than several years ago because of their utility in highly stereoselective syntheses. Much work has been dedicated to the generation of *o*-xylylenes under milder conditions and, as a consequence, their applications in organic synthesis are growing spectacularly. At the same time, great effort have been put in the search of more readily available precursors for the generation of these useful intermediates. Work in progress on asymmetric synthesis (*inter* and *intra*molecular cycloadditions) from *o*-quinodimethanes as well as the use of its metallocomplexes and heteroanalogues structures will increase the interest in the chemistry of *o*-quinodimethanes.

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