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o-Quinone methides: intermediates underdeveloped and underutilized in organic synthesis

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1. Introduction to *o*-quinone methides

o-Methylene cyclohexadienones such as **1** and their β-substituted counterparts (R^2 or $R^3 \neq H$, Fig. 1), which are collectively referred to as *ortho*-quinone methides (*o*-QMs), are highly reactive and ephemeral intermediates that have been extensively harnessed by nature. A variety of plants, animals and insects capitalize upon these species as a means of defense. Moreover, the therapeutic benefits of vitamins E and K as well as the anti-cancer properties of natural products such as the anthracycline antibiotics result

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Keywords: *o*-quinone methides; organic synthesis; chromans; *o*-alkylated phenols; benzopyrans.

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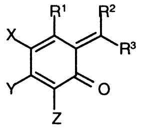


1

R^1, X, Y, Z = anything

R^2 and R^3 must display **no** heteroatom electron lone pair in conjugation with o-QM

Figure 1.

from the capacity of these compounds to form an *o*-quinone methide species in vivo. Enzymes associated with various maladies, such as β-glucuronidase[1] and β-glucusidase,[2] have been targeted with phenol glycoside prodrugs that are transformed by the targeted enzyme into an *o*-QM intermediate which subsequently inactivates the deleterious target enzyme. However, despite general knowledge of *o*-QMs for a century these intermediates still lie outside the synthetic mainstream. Although their assorted functional groups suggest abundant synthetic potential, surprisingly few *o*-QMs have been utilized as intermediates in total syntheses. We speculate that this omission is a consequence of *o*-QM reactivity, which mandates their in situ generation and consumption, thereby severely limiting their range of potential reactions. In this review we describe the methods by which *o*-QMs are prepared, the benefits and limitations associated with each method as well as current applications in total synthesis.

1.1. Scope of this review

Because of the transient nature of *o*-QMs, preparing a comprehensive review proved to be more difficult than we first imagined. Conventional structure searching methods failed to produce a comprehensive overview of their chemistry as these intermediates are usually deduced rather than isolated. Therefore, we have relied upon a combination of a word search for '*ortho*-quinone methide' using the *Scifinder*® and the *Web of Science*® databases along with substructure searches using *Scifinder*® for each of the precursors found. To limit the scope of the discussion, however, we have focused on *o*-QMs of similar reactivity. Therefore, systems that contain a heteroatom in the core six-membered ring or α to the methide portion (R^2 or R^3) and thus in conjugation with the carbonyl have been excluded (cf. **1**, Fig. 1). These structural elements drastically alter the electrophilicity of the *o*-QM. Hits fulfilling these criteria were then re-examined through the *Citation Index*® along with any subsequent references that emerged from these activities. Literature searches ceased in March of 2002.

1.2. Evidence for the existence of *o*-QMs

When describing the chemistry of an entity that is difficult to isolate and identify, its mere existence may be questioned. However, there is abundant indirect evidence for the in situ formation of *o*-QMs. Most indirect evidence comes from the structural identification of the products that result from dimerizations, trimerizations, intramolecular and intermolecular [4+2] cycloadditions, as well as the nucleophilic trapping of *o*-QMs. In 1907, Fries was the first to suggest that an *o*-quinone methide intermediate explained the formation of dimers and trimers for a particular reaction.[3] Over the next 50 years, the hypothetical structure was used to justify numerous observations. The first direct evidence for its structure came in 1963, when Gardner collected and spectroscopically analyzed an *o*-quinone methide at −100°C to provide the first tangible proof of the structure.[4b] There was a subsequent flurry of examples where structural elements such as an electron donating heteroatom or extended conjugation enabled isolation and characterization of 'stabilized' *o*-QMs. These activities culminate in a recent report by Amouri, who constructed several organometallic π-complexes that contain the ring diene of various *o*-quinone methides as an η^4 donor with osmium, rhodium and iridium metal atoms.[5]

An *o*-QM behaves as a combination of the charged zwitterion (**3**) and the biradical (**4**) (Fig. 2). The contribution of these canonical forms leads to the conclusion that (*E*/*Z*) geometries in *o*-QMs are fluxional; far more so than in traditional olefins. The distribution among these geometric isomers is believed to result from the difference between the non-bonded interactions shown in Fig. 2. If from a steric standpoint the R^1 substituent is smaller than oxygen, then the *E*-configuration is preferred (cf. **2**). However, increasing the size of the R^1 substituent can cause the *Z*-configuration to predominate (cf. **5**). The (*E*/*Z*) ratio proves important in governing the diastereoselective outcome for some reactions such as Diels–Alder cycloadditions. Moreover, the olefin geometry can change the course of a reaction altogether; a *Z*-configured *o*-QM (cf. **5**) can undergo a 1,5-sigmatropic rearrangement or an electrocyclization, while an *E*-configured *o*-QM (cf. **2**) cannot. In addition to circumstantial evidence for the equilibrium between E and Z isomers of an *o*-QM, direct evidence is suggested by a deuterium isotope study devised by Moore.[6e]

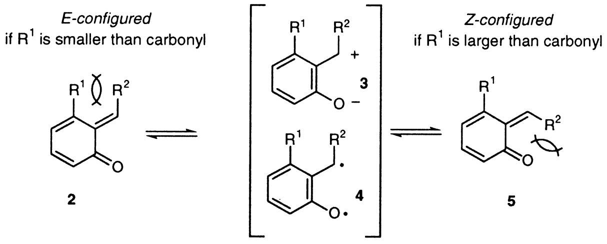


Figure 2.

1.3. Theoretical considerations regarding reactivity

Several computational studies aimed at deciphering the reactivities of *o*-QMs have been carried out. A series of *o*-QMs have been computationally investigated by the HMO method in order to predict their reactivity.[7a] Modifications to stabilize and destabilize the hypothetical charged ground-state contributors shown in Fig. 2 have, for the most part, exhibited the expected changes. However, care must be exercised when attempting to apply a frontier molecular orbital (FMO) approach to predict the outcome of reactions involving *o*-QMs. The FMO model does not account for the gain in resonance energy that results upon restoration of aromaticity upon addition of a nucleophile.[8] For example, when the *o*-QM **6** and butadiene are theoretically combined from a FMO perspective, the spirocycle **7** is predicted because of a better match among the respective orbital coefficients in the two components. Thus, a FMO analysis does not predict formation of the chroman **8**, which is experimentally observed (Fig. 3). To improve the correlation between experiment and theory, *o*-QMs have been the focus of more sophisticated calculations. Lanteri showed the regiochemistry of Diels–Alder reactions of *o*-QMs could be predicted by CNDO/2 theoretical analyses.[9] More recently, the role of H-bonding and other solvent effects have been investigated through DFT computational studies to determine their effects on the reactivity of *o*-QMs.[10a]

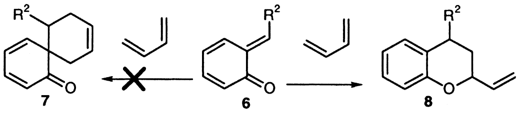


Figure 3.

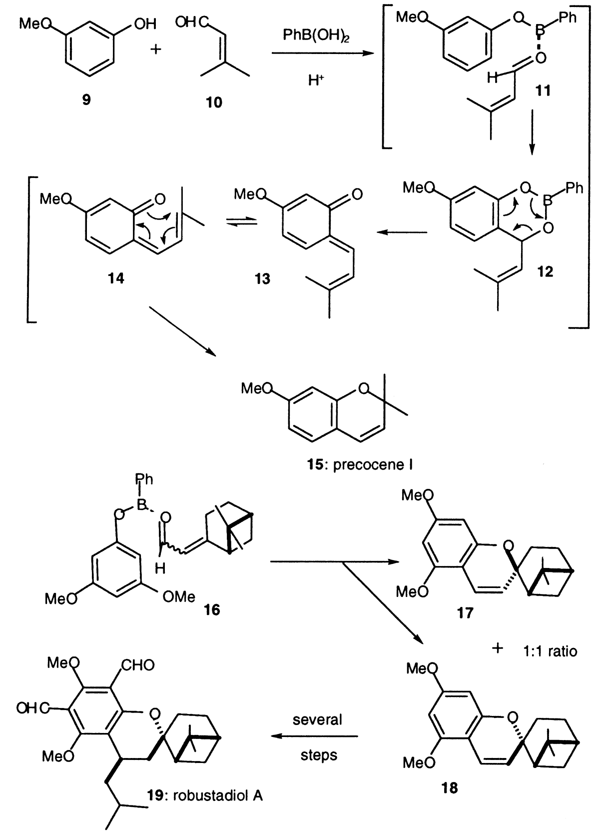
1.4. Earlier reviews and discussions

In spite of several significant literature reviews detailing the unusual reactivity of *o*-QMs, the picture of the potential synthetic utility for these highly reactive species has been slow to emerge. Turner reviewed the literature regarding *o*-QMs through 1964. Their predilection to dimerize and trimerize, as well as a few examples of *o*-QM trapping by nucleophiles and electron rich olefins were discussed.[11] Schleigh reviewed the synthetic applications of *o*-QMs through 1971.[12] Desimoni discussed their use as heterodienes in Diels–Alder applications through 1975.[13] Wakselman reviewed their biological applications through 1983, focusing on their potential as agents for selective enzyme inhibition and for modification of specific amino acids in proteins including their use as protecting groups for amino and hydroxyl functionalities.[14] Boger and Weinreb reviewed methods for preparing *o*-QMs and their applications in inverse demand Diels–Alder reactions in 1987.[15] In 1996, Wan reviewed photolytic methods for initiating *o*-QM chemistry.[16] In our review we have included many of the works cited in previous reviews to better support the premise that *o*-QMs are a synthetic enigma, whose potential has only recently begun to be realized.

1.5. Past synthetic applications employing *o*-QMs

An *o*-QM embodies a minimum of seven carbon atoms. In principle, it can be appended with any number of functional groups. Despite its potential in the synthesis of a diverse range of natural products, particularly coumarins and *o*-functionalized phenols that are prevalent in natural sources throughout the terrestrial and oceanic kingdoms, relatively few syntheses have employed *o*-QMs. To the best of our knowledge, all of these are shown in Figs. 4–13. The most common use has been in intramolecular [4+2] cycloaddition, dimerization, and electrocyclization formats. Excluding dimerization processes, only a scattering of intermolecular applications have been demonstrated.

The mobility between *E* and *Z* isomers of *o*-QMs was cleverly exploited by Lau and Dufresne in a one-pot synthesis of precocene I (**15**) from the phenol **9** and aldehyde **10** (Fig. 4). Heating these together with $PhB(OH)_2$ results in a chelation controlled regioselective addition of



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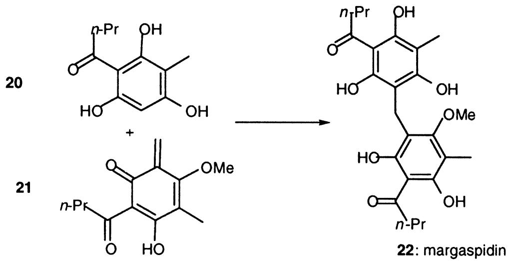

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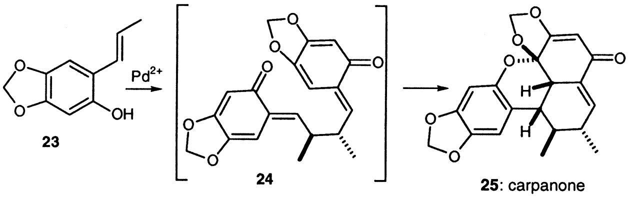

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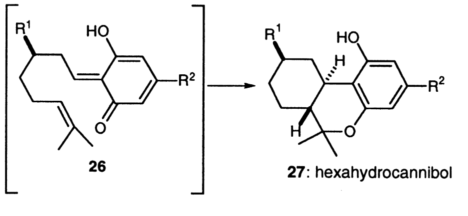

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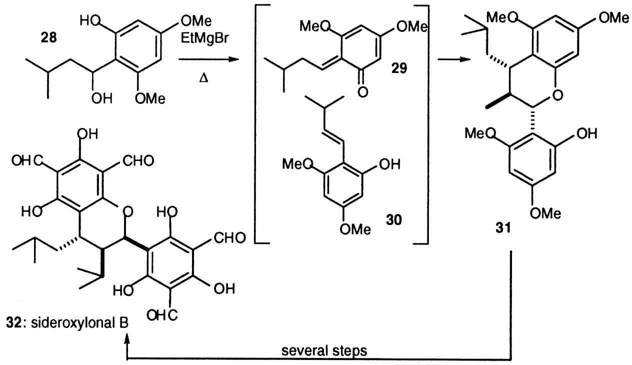

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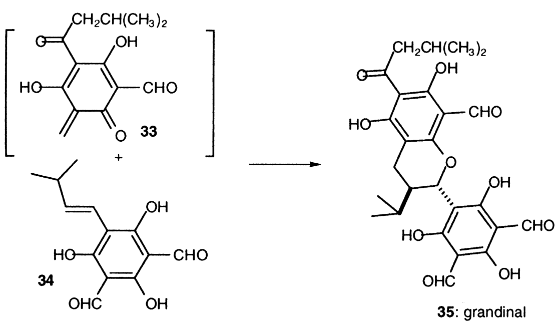

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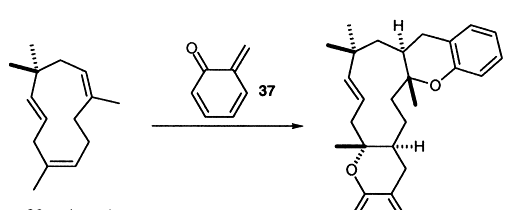

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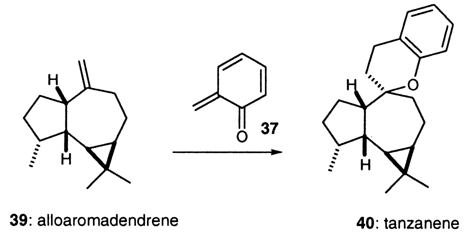
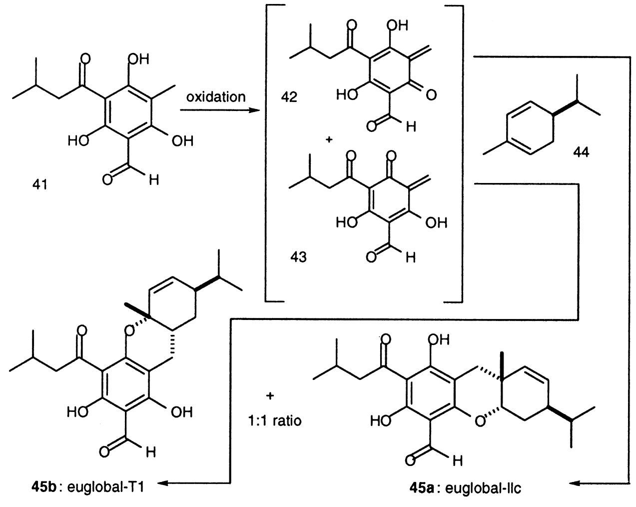


Figure 11.



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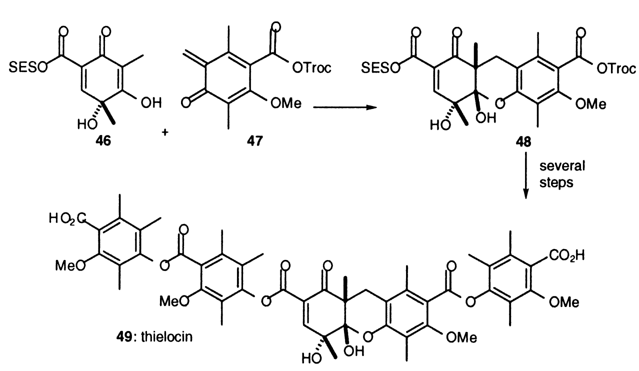


Figure 13.

the aldehyde *ortho* to the phenol (cf. **11**). The resulting benzoborin **12** collapses to give the *E o*-QM which is in equilibrium with its *Z* isomer. An electrocyclization ensues with the *Z* isomer resulting in precocene I. Lau and Dufresne used a similar electrocyclization strategy from complex **16**, to produce **17** and **18**; the latter was employed in a synthesis of robustadiol A (**19**).[17d]

In vivo feeding experiments with an isotopically labeled monomer demonstrated that Margaspidin (**22**)[18] emerges from C-alkylation of a phenol (**20**) with its corresponding *o*-QM (**21**) (Fig. 5). A similar sequence has often been utilized to assemble calix[*n*]arenes.[19]

The dimer carpanone (**25**) was first assembled by Chapman[20c] and then later constructed by Trivedi (Fig. 6).[21] Both processes involved a one step oxidative coupling of the monomer **23**. The bis-quinone methide **24**, which is produced when the monomer is exposed to either palladium diacetate or silver(I) oxide, undergoes an intramolecular [4+2]-cycloaddition with itself. Maeda reports a similar strategy for other lignans.[22]

Hexahydrocannibol (HHC; **27**) has been a frequent target for *o*-QM chemistry (Fig. 7). Marino,[23] Casiraghi,[24h] Tius,[25] Murphy,[26c,d] Sato,[27e] Inoue,[28a] Lau and Dufresne,[17c] and Wang[29] have all fashioned a HHC core with various attendant functional groups using an intramolecular [4+2] of **26**, which has been generated by a number of methods.

Tatsuta finds that treatment of the phenol **28**, that contains an *o*-benzyl alcohol, with EtMgBr affords a mixture of the *o*-QM **29** and the styrene **30** (Fig. 8). These compounds undergo a [4+2] cycloaddition with one another and the resulting adduct **31** can subsequently be converted into sideroxylonal B (**32**).[30]

Etoh generated the *o*-QM **33** by oxidation of grandiol and found that it underwent cycloaddition with the styrene **34** resulting in the formation of grandinal (**35**) (Fig. 9).[31]

Baldwin recently reported a biomimetic route to lucidene (**38**) that involves bis-addition of the thermally generated parent *o*-QM **37** to α-humulene **36** (Fig. 10).[32]

Paknikar generated the parent *o*-QM **37** by oxidation of 2-methyl phenol and found that it underwent a diastereoselective cycloaddition with the exocyclic olefin of alloaromadendrene (**39**) resulting in tanzanene (**40**) (Fig. 11).[33]

Chiba has completed several isomers of the euglobal family by electrochemical oxidation of the phenol **41** (Fig. 12). The regioisomeric *o*-QMs **42** and **43** are generated which then undergo a reaction with α-phellandrene to produce the euglobals **13a** and **b**.[34b]

Young generated the *o*-QM **47** and found that it underwent a regioselective and diastereoselective cycloaddition with the cyclohexadienone **46** to produce **48** (Fig. 13). This material was converted to the group II phospholipase A_2 (PLA_2) inhibitor, thielocin (**49**).[35]

1.6. Biochemical ramifications of *o*-QMs

Despite being little used from a synthetic standpoint, *o*-QMs are often invoked as the species that is responsible for the bioactivity of a particular natural product (Fig. 14).[36] Many of the pathways for bio-activation illuminate the methods by which *o*-QMs can be generated and utilized in synthesis.

Moore proposed that the anticancer efficacy of several quinone natural products results from their ability to form an *o*-QM species in vivo upon bio-reductive activation.[6a] The benzoquinone mitomycin C (**50**) undergoes reduction to produce the *o*-QM **51**,[37] while the napthaquinone kalafungin (**52**) forms the *o*-QM **53** following bio-reduction.[38] The anthracyclic anthraquinones, daunomycin (**54**),[39a,b] adriamycin (**55**),[39a,b] steffimycin (**56**),[40] nogalamycin (**57**),[41] menogaril (**58**),[39c,d] and aclacinomycin A (**57**),[42] are all believed to eradicate hypoxic cells of solid tumors by undergoing bio-reductive activation in oxygen poor regions to form analogs of the *o*-quinone methide **60** that subsequently alkylate DNA or enzymes associated with cell division.[43]

The efficacy of the anti-bacterial agent totarol (**61**)[44] is thought to be the result of its ability to oxidize to the *o*-quinone methide **62** in vivo (Fig. 15).

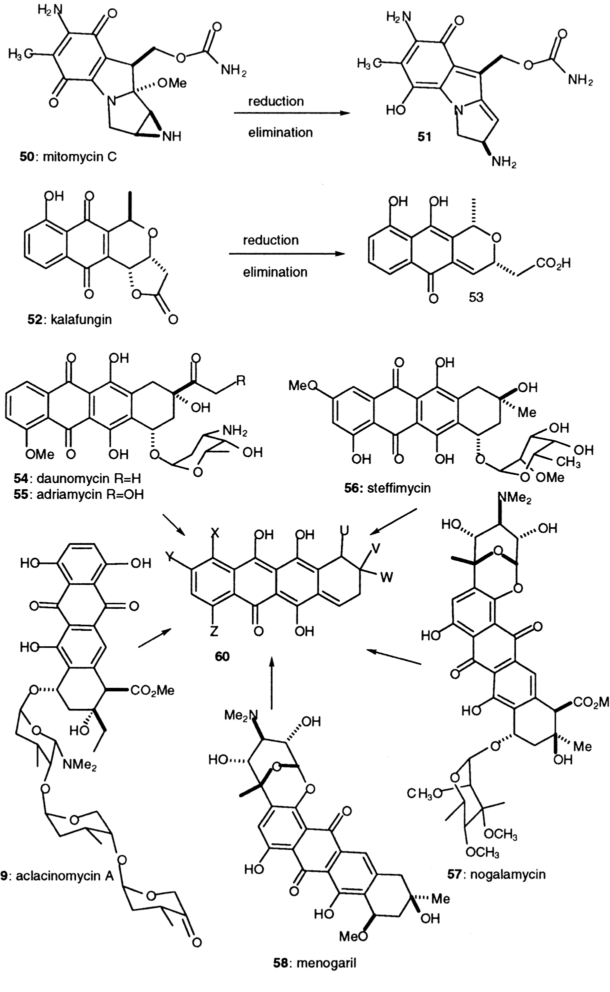


Figure 14.

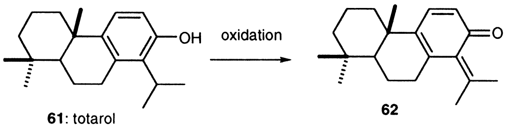


Figure 15.

Similarly, the efficacy of the anti-diabetic troglitazone (**63**) is linked to the compounds predilection to form the *o*-QM **64** upon oxidation with P450 (Fig. 16).[45]

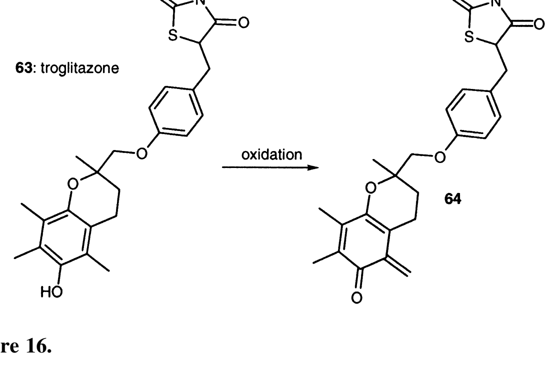


Figure 16.

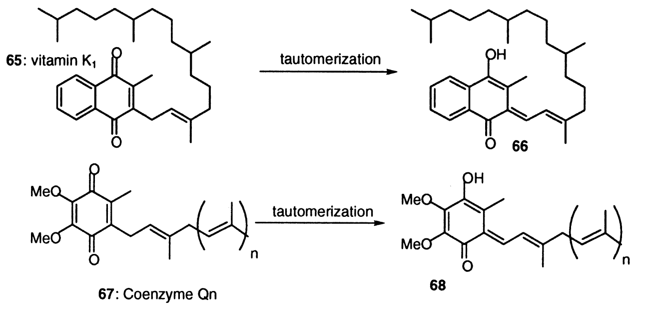


Figure 17.

Vitamin K (**65**)[46] and Coenzyme Q_n (**67**) play critical roles in electron transfer and energy transport via their respective *o*-QM tautomers **66** and **68** (Fig. 17).

The anti-oxidant vitamin E (**69**),[47,52a] undergoes selective oxidation of a single methyl residue to form an *o*-QM (**70**) that then dimerizes to yield **71** (Fig. 18). Interestingly upon the addition of vitamin C, the *o*-QM dimer of vitamin E undergoes reductive retro-dimerization leading to speculation that it serves as a molecular switch in order to inhibit free-radical oxidation of polyunsaturated fatty esters in vivo.

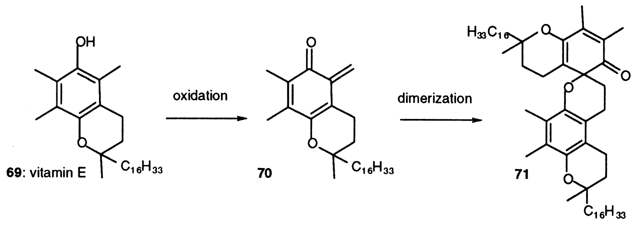


Figure 18.

The phenol glycoside salicortin (**72**)[2] undergoes β-glucosidase activation to generate the *o*-QM **37** that irreversibly inactivates the enzyme (Fig. 19). Salicortin is used by several plants as a defensive weapon to prevent infestation by gypsy moths and tent caterpillars. Clearly such a diverse and eclectic range of biological applications implies that *o*-QMs possess a tremendous potential as synthetic intermediates.

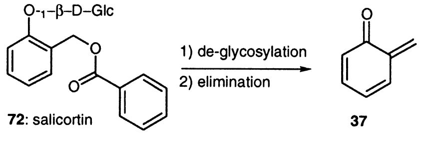


Figure 19.

2. Synthetic methods used to generate *o*-QMs

Many of the synthetic techniques for producing *o*-QMs, which include: (a) tautomerization, (b) oxidation, (c) thermolysis, (d) photolysis, (e) acid promotion (f) base facilitation and (g) the olefination of quinones, mirror biochemical sequences used by nature. However, most biochemical operations are well timed, delivering a *pro*-reactive species to the target site and then generating the highly reactive *o*-QM at low concentrations in close proximity to the intended nucleophile. Laboratory methods, being far less specific, are plagued by unwanted dimerizations. Moreover, the conditions associated with the generation of *o*-QMs have a profound influence on the type of reactions that these species are able to undergo.

2.1. Initiation by tautomerization

An α-substituted *p*-quinone with an allylic proton adjacent to the quinonic ring can form an *o*-QM upon tautomerization (Fig. 17). The classic biological example of this type of generation method is vitamin K_1 (**65**), which plays an important role in promoting blood coagulation via its redox cycle that involves the *o*-QM tautomer **66** (Fig. 17).[48] In a laboratory setting Jurd was among the first to demonstrate that tautomerization to an *o*-QM could initiate a subsequent reaction.[49b–f] He reports that warming the benzoquinone **73**, results in the formation of the hemiketal **75** along with minor amounts of the spirocycle dimer **76** and the cyclic ether dimer **77** (Fig. 20). The *o*-QM **74** is speculated to be an intermediate for all of these products.

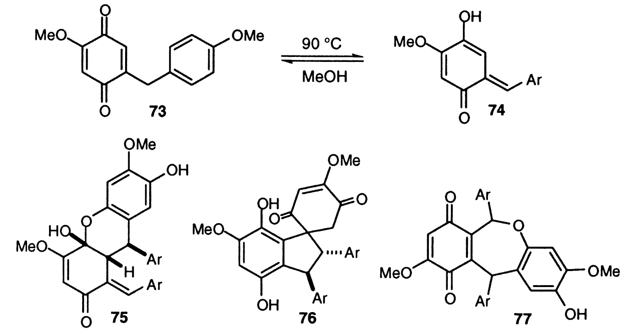


Figure 20.

2.2. Oxidative initiation

Although a variety of chemical oxidants can be used to generate an *o*-QM, the method is restricted from a structural perspective. Because *para*-quinone methides (*p*-QMs) are less polarized and more stable than their corresponding *o*-QMs, *p*-QMs are formed more readily than *o*-QMs. Hence, generation of an *o*-QM by an oxidation method is viable only if the *para*-position is unsubstituted or substituted with a functional group that contains no α-protons. Although this limits the synthetic potential, the oxidative generation method has found abundant use, particularly for initiating a variety of intramolecular reactions.

The bio-activation of vitamin E (**69**) best epitomizes the oxidation generation process in a biological setting. Vitamin E (**69**) acts as a *pro*-cellular anti-oxidant (Fig. 18). It undergoes oxidation to the corresponding *o*-QM with most types of active oxygen species. Interestingly the oxidant dictates the course that the reaction follows. For example, alkoxyl radicals lead to the dimer **71**, which can be reduced by vitamin C to regenerate compound **69**. Thus, vitamin C and E are participants in a complete redox cycle. On the other hand, when a peroxyl radical undergoes reaction with vitamin E (**69**), either the 5-alkoxymethyl derivative **80** or the epoxide **79** is formed (Fig. 21).[50] However, even more interesting is that the oxidation of vitamin E (**69**) proves to be entirely regioselective. An easy explanation for this type of selectivity among various aromatic compounds was offered by Mills and Nixon.[51] It is believed to be a consequence of bond angles about an sp^2 carbon atom and the relative ease with which these can be compressed relative to one another. For example, when a large ring is appended on an aromatic nucleus the outside bond angle (a) at the ring junction is smaller than the inside bond angle (b). Because of the obvious 1,2-non-bonded interactions, it is easier to compress $\angle ABC$ rather than the $\angle ABD$ or $\angle CBD$ in an isolated olefin such as **81**. Therefore the *o*-QM isomer **70** is preferred to **78** because angle $(a)<(b)$ and $\angle ABC$ is more readily compressed than $\angle ABD$ or $\angle CBD$.

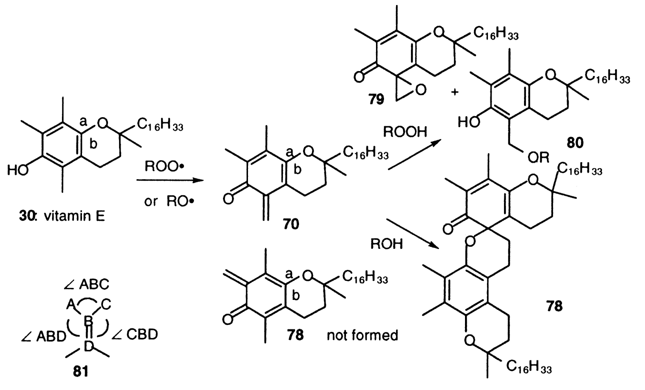
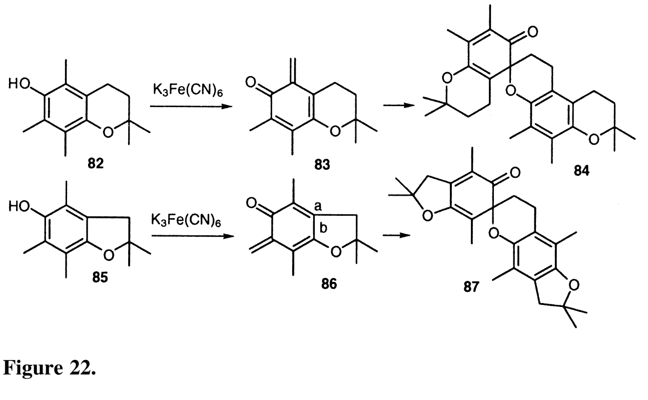


Figure 21.

Dean has further explored the subtle difference between oxidation at two different *ortho* positions (Fig. 22).[52c] He finds that the chroman **82**, an analog of vitamin E (**69**), undergoes a $K_3Fe(CN)_6$ mediated oxidation as expected to produce **83** which subsequently dimerizes to **84.** The benzofuran nucleus **85**, however, undergoes oxidation at a different methyl substituent to form the *o*-QM **86**, which subsequently dimerizes in analogous fashion to form **84**. In this instance, since a small ring is appended to the aromatic nucleus, the outside bond angle (a) at the ring junction is larger than the inside bond angle (b). Hence, the *o*-QM **86** is the isomer that is formed since the (b) angle is more readily compressed than the (a) angle.

Waters was among the first to investigate the generation of *o*-QMs using chemical oxidants for a synthetic purpose. He found that a combination of silver(I) oxide with **88** generates the *o*-QM **89** that undergoes immediate self-condensation to form the spirodimer **90** (Fig. 23).[53] Bolon subsequently concluded that Ag_2O was a superior oxidant for generating *o*-QMs for subsequent self-condensation as well as for intramolecular and intermolecular reactions.[54] Indeed, Ag_2O remains the oxidant of choice. However, several other oxidative methods can be employed. Butler demonstrated that $K_3Fe(CN)_6$ and PbO_2 were effective reagents.[55] Kasturi documented that DDQ oxidized naphthols to *o*-QM intermediates.[56b,d,h] Habicher established that bromine could be used as an oxidant.[57a] More recently, Chiba reported that an electrochemical oxidative method results in the formation of synthetically useful *o*-QM intermediates.[34a–c]



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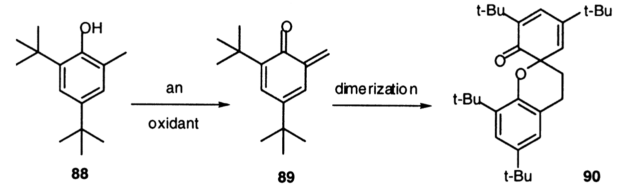


Figure 23.

In addition to the oxidants described previously, which are used in conjunction with *o*-alkylated phenols, several other oxidants are applicable to specific classes of aromatic compounds (Fig. 24). Adam reported that the epoxidation of various benzofurans such as **91**, with DMDO, leads to an equilibrium between the *o*-quinone methide **93** and the epoxide **92**.[58] Suzuki found that exposure of 2-methoxy-1-(2-methoxy-vinyl)-naphthalenes and benzenes (**94**) to $[O_2{}^1]$ leads to an *o*-quinone methide such as **96** by way of a peroxy intermediate (**95**).[59] It should be noted that the Adam procedure leads to a rather unusual structure where the *o*-QM is disubstituted at the β-position.

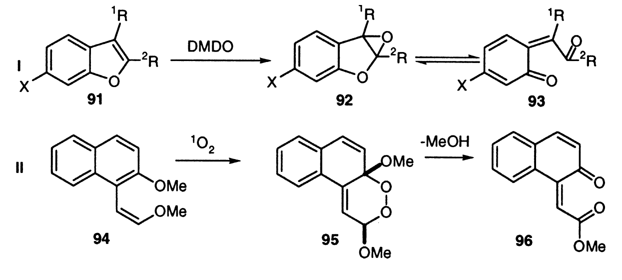


Figure 24.

2.3. Thermal initiation

Despite the absence of the equivalent biological process, thermolysis has been the method of choice among synthetic chemists for generating *o*-QMs. Fig. 25 shows the precursors that have been utilized. It should be noted that all thermal generation techniques preclude the application of nucleophiles that are thermally unstable. Moreover, most can result in corruption of stereochemistry in reactions that can lead to diastereomeric mixtures. With any given precursor, there is a substantial temperature range for

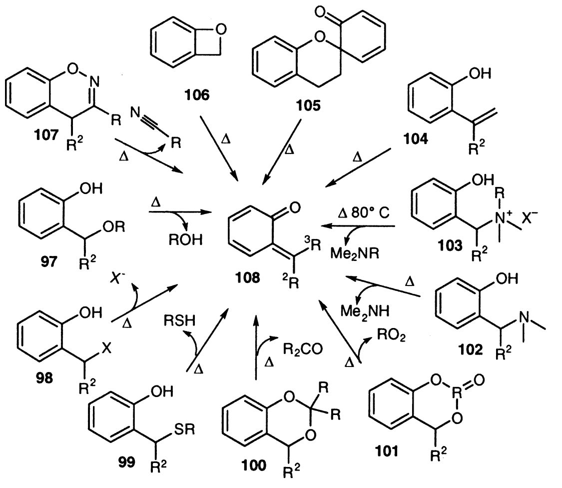


Figure 25.

initiation that depends upon the substituents. In general, if the process involves significant non-bonded interactions, then the temperature requirements are higher, while extended conjugation or other stabilizing factors lowers the overall temperature requirements. All of these precursors (**97–107**) prove highly successful when the *o*-QM is consumed in a subsequent intramolecular reaction. Application of each towards intermolecular reactions, however, is significantly more challenging because of the tendency toward dimerization.

The technique of flash vacuum pyrolysis (FVP) overcomes this problem to some degree, because the reactive *o*-QM intermediate is generated at low-pressure and therefore low concentration. However, implementation of FVP for large-scale preparation of starting materials is problematic. Moreover, many of the *o*-QM precursors shown in Fig. 25 are either unstable or relatively inaccessible. For example, most *o*-hydroxyl benzyl alcohols, ethers, halides, and thioethers (**97–99**) prove unstable toward chromatography. Additional substitution at the benzylic position complicates their preparation. Their cyclic derivatives **100–101** afford some additional stability, but again preparing derivatives with benzylic substitution is problematic.

Although Mannich bases such as **102** are more robust, the Mannich reaction is complicated by multiple additions of the phenol to methyl-iminium. Moreover, only the unsubstituted iminium ($H_2C{=}N^+R_2$) generated from formaldehyde is typically used leading to *o*-QMs which are unsubstituted at the β-position ($R^2{=}R^3{=}H$). While quaternization of the amine can lower the thermal requirement for *o*-QM generation, **103** is limited by the restrictions placed on its precursor **102**.

Compounds **104–107** all lead to *o*-QMs upon heating in a relatively nucleophile free environment. Styrenes such as **104** and the benzooxetane **106** require extremely high temperatures. Because these precursors have only been used for dimerization reactions they are of little synthetic value. The heat requirements for thermally cracking spirodimers such as **105** are more moderate (120–150°C). Furthermore, these spirodimers are readily constructed by treatment of the corresponding *o*-alkyl phenols with Ag_2O. The 3-alkylated-4*H*-benzo[*e*][1,2]oxazine **107** affords *o*-QMs at much lower temperatures (60–80°C).

Hultzsch,[60] Schmidt,[61a,c] Mulder,[62b,c] and Sprengling[63] have independently examined pyrolysis of *o*-hydroxy-benzylalcohols such as **97**. Wakselman,[64] Gardner,[4] Mulder[62c] and Britt[65] have investigated the pyrolysis of the corresponding *o*-hydroxy-benzylethers (R≠H). Schmidt[61a,b] and Habicher[57] have examined *o*-hydroxy-benzylhalides of type **98**. Chiba reports that heating an *o*-hydroxy-benzylthioether such as **99** results in an *o*-QM. Moreover, it appears that larger thioether substituents require lower temperatures for activation.[34a,c] Lhomme investigated benzodioxins such as **100**.[66] Sheppard reported the pyrolysis of a sulfonate such as **101** (R=S).[67] Von Strandtmann[68] and Bilgic[69] have investigated the pyrolysis of Mannich bases such as **102**. Gardner[4a] and Breuer[70] have independently harnessed *o*-hydroxybenzyltrimethyl-ammonium iodides, such as **103**, as precursor to *o*-QMs. Hansen utilized a 1,5-sigmatropic rearrangement of 2-vinyl phenols such as **104** to generate *o*-QMs.[71] Mulder,[62a,b] Gajewski,[72] Dean,[52a,b] and Yamato[73] utilized a retro Diels–Alder reactions of chromans, such as the dimer **105**, and additional benzopyrans. Heaney[74] and Adam[58d,g] showed that a thermal [$\pi 2_s$+p2s+n2s] valence isomerization of the 2H-benzooxetanes such as **106** leads to the corresponding *o*-QM. Shudo[75] and Goldschmidt[76] have investigated thermolysis of 1,2-benzooxazines such as **107**.

In addition to the traditional methods shown in Fig. 25, there are other thermal procedures for specific structural ensembles (Fig. 26). Moore reported that addition of a vinyl anion of an allene to squaric acid derivatives results in **109**, which leads to an *o*-QM intermediate **110** upon heating.[6e] However, the synthesis of the appropriate precursors for this procedure can be lengthy. Zanirato reports a generation method from the 1-azobenzofuran **111**. Heating expels N_2 forming an intermediate nitrene, which undergoes further rearrangement to afford the nitrile *o*-QM **112**.[77]

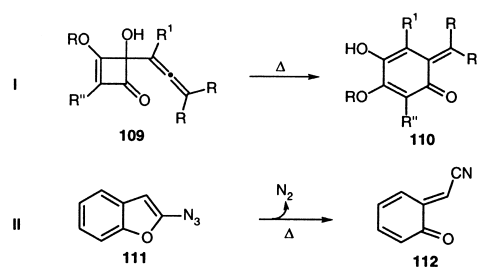


Figure 26.

Fig. 27 shows what we believe to be the most synthetically valuable of all the thermal protocols. The benefit of these metal mediated sequences is that each allows a variety of type **6** *o*-QMs (R^2≠H) to be constructed rapidly by *o*-functionalization of the phenol **113**, prior to generation of the *o*-QM. Lau and Dufresne pioneered the development of the dioxaborins **115** as *o*-QM precursors.[17] The dioxamagnesium predecessor, **114**, was developed independently by Casnati,[24] Pochini,[78] and Murphy.[26] Exposure of either of these 'aldol like' adducts to heat results in the formation of an *o*-QM. In the case of the Mg^{II} mediated reaction,

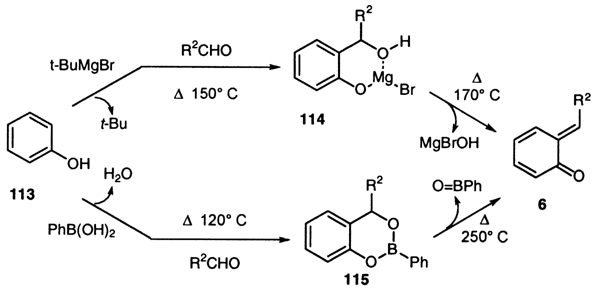


Figure 27.

however, the temperature for the initial addition and the subsequent *o*-QM formation are similar, making the protocol primarily useful for intramolecular reactions or reactions which result in a net bis-addition of the phenoxide to the aldehyde. The dioxaborin procedure, on the other hand, displays a significant temperature difference for each transformation; the initial addition to the aldehyde proceeds at a much lower temperature. Moreover, unlike an *o*-hydroxybenzyl alcohol, the intermediate dioxaborin **115** proves stable and can be isolated and purified; this is not the case for **114**. Therefore, the Lau–Dufresne procedure proves quite useful for both intramolecular and intermolecular applications. However, it has two limitations: (1) the reactants must withstand acidic reaction media, and (2) the high temperature and acidic byproducts can corrupt the diastereoselectivity in some types of reactions.

2.4. Photochemical facilitation

Photochemical excitation drastically reduces the temperatures required for *o*-QM generation for many of the precursors shown in Fig. 25. In many cases, excitation with light can induce the *o*-QM to form at ambient or even lower temperatures. Thus, in principle, photochemical initiation heralds the development of new diastereoselective reactions for *o*-QMs. In practice, however, photochemical generation is rarely used synthetically due to two problems. First, many of the precursors remain unstable and difficult to purify. Second, most of the precursors require high energy (short λ) to facilitate formation of the *o*-QM. With high energy light many other functional groups as well as nucleophilic partners can be excited into a reactive state as well as the *o*-QM precursor, thereby resulting in unwanted side reactions. Hence, photolysis cannot tolerate a wide range of substituents and solvents.

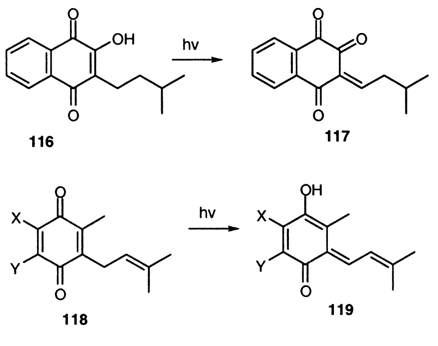


Figure 28.

Most of the early investigations examined the application of UV light to facilitate quinone tautomerization (Fig. 28). The interest in this process stemmed from recognition that quinones, such as vitamin K_1 (**65**) and its benzoquinone analog coenzyme Q_n, (**67**) which resembles **116** and **118** play essential roles in the plant and animal kingdoms through electron transport. Ettlinger,[79] Creed,[80] and Leary[46a] independently investigated the photochemistry of tocoquinone-1 and related napthaquinones to gain insight into the role that these compounds play in photobiology. They demonstrated that **116** and **118**, when irradiated with UV light produce the corresponding *o*-QM **117** and **119**, species which in turn undergo further reactions such as oxidation with oxygen.

Perhaps the best-studied photochemical *o*-QM precursors from a mechanistic perspective are *o*-hydroxybenzyl alcohols and ethers such as **97** (Fig. 29). Padwa,[81a,b] Kresge[82] and Wan[83] have independently shown that these compounds (R^2=–H or –Ph) readily form the corresponding *o*-QMs **6** at room temperature upon photolysis at 254 nm (R^2=–H).

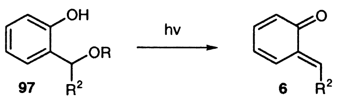


Figure 29.

Saito has investigated the photochemical irradiation of phenolic Mannich bases such as **102** (Fig. 30).[84] The reaction, as a consequence of the lone pair of electron on the nitrogen, proceeds to the *o*-QM **6** with a much lower energy of light (>300 nm) and higher quantum yield (Φ=0.98 compared to Φ<0.25 for *o*-hydroxyl benzyl ethers and alcohols) than its *o*-hydroxy benzyl alcohol predecessor shown in Fig. 29. Moreover, Mannich bases such as **102** are more easily handled than their ether or alcohol counter-parts. Unfortunately, the method in which the Mannich base is prepared limits the procedure to the formation of *o*-QMs such as **6** without β-substituents (R^2=–H).

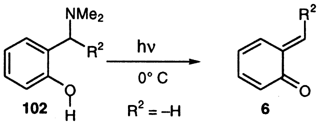


Figure 30.

Freccero has investigated the laser flash photolysis of the benzyl ammonium salt **103** in water (Fig. 31).[10b] Because **103** is derived from **102**, it too is limited to the generation of *o*-QMs such as **6** without β-substituents (R^2=–H). However, the reaction proceeds at 254 nm (Φ=0.98) more efficiently than the dimethylamine precursor utilized in the preceding Saito procedure (Fig. 30). Because precursor **103**

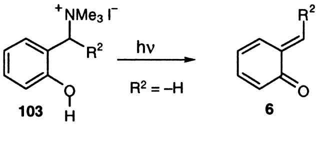


Figure 31.

is less nucleophilic then its mannich base counterpart **102**, it is less likely to undergo alkyation with the *o*-QM **6** than precursor **102** in the Saito protocol.

Gutsche,[85] Yates,[86] and Wan[83f,g,h] have shown that *o*-hydroxystyrenes such as **104** undergo an excited state intramolecular proton transfer (ESIPT) at 254 nm resulting in appreciable amounts of the *o*-QM **6** (Fig. 32, $\Phi=0.13$, $R^2=Ph$). The product undergoes a rapid 1,5-sigmatropic shift that results in reformation of the starting material **104**. These studies confirmed that the isomerization barrier for the conversion of **120**(*E*) into **120**(*Z*) is further reduced by photolytic conditions. However, the only synthetic application for this technique is the 1,4-addition of alcohols or water across the *o*-QM.

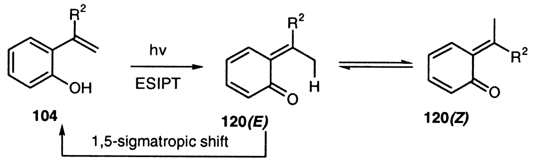


Figure 32.

Chapman,[20b] Padwa,[81a,b] and Gutsche[85] have examined irradiation of benzofuran-2-one **121** ($R^2=Ph$) and found that it undergoes rapid decarbonylation to produce the *o*-QM **6** (Fig. 33). In most instances, the corresponding *o*-hydroxybenzyl ether or alcohol (**97**) emerged as the product because the reaction is conducted in a protic or aqueous solvent system. The reaction is difficult to control for synthetic purposes because its success is highly dependent on the tautomeric composition of the lactone **121**, which generally requires a protic, and therefore, nucleophilic solvent.

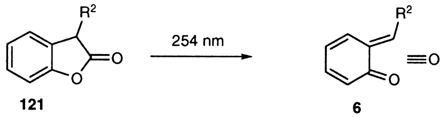


Figure 33.

Solomon reported that the photochemical valence isomerization of the *o*-quinone methide **37** to the benzooxetane **106** occurs at 350 nm and that the reverse reaction occurs at 254 nm (Fig. 34).[87] Tomioka has developed a means to procure the benzooxetane **106** from *o*-hydroxyphenyldiazomethane **123**, which in turn is available from the masked diazo compound **122**. Photolysis of **122** at 10 K results in the hydroxyphenylcarbene **124**, which undergoes an expected O–H insertion.[88]

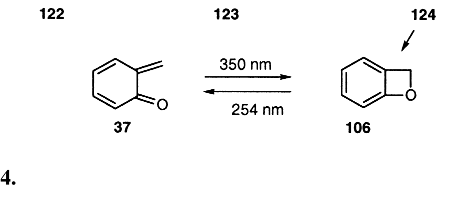


Figure 34.

Sheridan reported that photolysis of the diazo compound **125** at 433 nm and 10 K results in the benzofuranyl chlorocarbene **126**, which under the influence of light at 313 nm undergoes ring opening to produce the *o*-QM **127** (Fig. 35).[89]

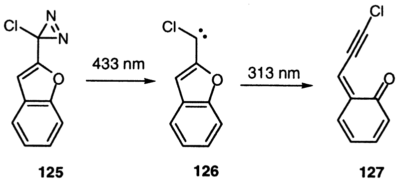


Figure 35.

2.5. Acid facilitation and triggers

Many of the thermal and tautomerization processes can be induced to occur at lower temperatures by the addition of acid. Indeed, many of the *o*-hydroxybenzyl alcohols and ethers (cf. **97**, Fig. 25) are unstable towards chromatography on silica gel for this very reason. Acidic silica gel promotes formation of the *o*-QM, which in turn undergoes dimerization and trimerization. In addition to acid facilitating the generation of an *o*-QM from a phenol, acids can be used to trigger *o*-QM formation from more stable precursors. The common theme among these procedures is protection of the phenol with an acid labile protecting group, thereby affording some temporary stability to the *o*-QM precursor. Treatment with acid cleaves this stabilizing group to reveal the free phenol and residual acid facilitates formation of the *o*-QM. Although enhancing reactivity, acid facilitation often leads to a decrease in the diastereoselectivity of subsequent transformations, especially in the case of [4+2] cycloadditions, which become more ionic in nature. In some cases, acid results in unexpected rearrangement products. Moreover, acidic conditions reduce the range of nucleophiles that can be deployed in the reaction mixture.

Chiba reported that a combination of wet montmorillonite in $LiClO_4/CH_3NO_2$ facilitates the formation of **6** from either **97** or **99** at room temperature (Fig. 36).[34d] However, subsequent [4+2] reactions appear to be entirely ionic exhibiting very little diastereoselectivity. Sato[27] reported that $BF_3{\cdot}Et_2O$ assists in the formation of **6** from **99**, but found that the diastereoselectivity in subsequent cycloadditions approaches (1:1); he previously found that several of the *o*-(1-(alkylthio)alkyl)phenols when treated with silver oxide and an electron-rich alkene exhibited >20:1 diastereoselectivity in the cycloaddition.

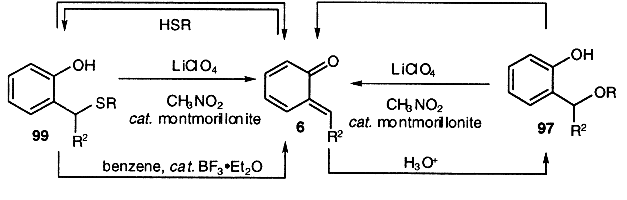


Figure 36.

Lau and Dufresne reported that acids greatly enhance the ability of 2-phenyl-4H-1,3,2-benzodioxaborins **115** to form *o*-QMs such as **6**. Acid decreases the temperature requirements for initiation by as much as 200°C (Fig. 37).[17b] Although this modification expands the range of nucleophiles to encompasses those that are thermally unstable, it significantly decreases the diastereoselectivity for some types of reactions.

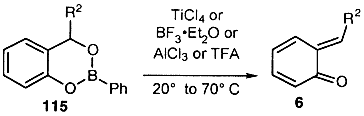


Figure 37.

To the best of our knowledge, there have been only four accounts of using acid to facilitate both deprotection and the subsequent generation of an *o*-QM from a relatively stable precursor (Fig. 38). All involve protection of the phenol moiety prior to the creation of the benzylic leaving group. Kasturi[56c,e,f] develop a triggering sequence, where the THP protected phenol **128**, which displays an *o*-methyl residue, is halogenated under free radical conditions to produce **129**. Stoichiometric addition of tetrachlorocatechol (TCC) cleaves and scavenges the THP protecting group generating the *o*-QM **130**. However, the *o*-QM so generated then undergoes reaction with the TCC limiting this methods application. Boekelheide constructed the *o*-TMS aryl ether benzyl alcohol **132** from the salicylic aldehyde **131** and showed that treatment of **132** with acid cleaves the silyl ether and affords an *o*-QM **135**.[90] Inoue reports a similar sequence with the MOM aryl ether **132** to generate an *o*-QM utilized in various intramolecular cycloadditions.[28] Monneret designed a glycosidase triggering mechanism for **134**; the glycosidase cleaves the carbohydrate and the resulting phenol undergoes elimination of the carbamate to produce the *o*-QM **135**.[1] The problem with processes I, II and III is that the *o*-QM **135** once generated undergoes reaction with weak nucleophiles that are necessary for the generation process. This limits the synthetic applications of I, II and III to intramolecular processes or reactions with the solvent.

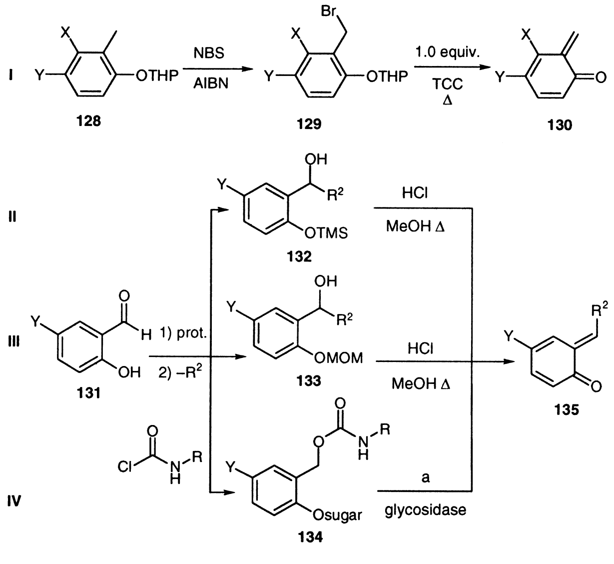


Figure 38.

2.6. Base facilitation and triggers

As with acid, there are two methods by which base can initiate the formation of an *o*-QM; the base either serves to accelerate the thermal or tautomeric processes previously discussed, or it acts as a nucleophile, triggering conversion of the *o*-QM precursor into the *o*-QM. There is, however, one noteworthy benefit associated with base-facilitated procedures; most nucleophiles, by their very nature, tolerate basic conditions to some degree. The same cannot be said for reactions initiated by thermal, photolytic or acidic protocols. Therefore, in principle, a low temperature base initiated process should encompass a greater range of substituents in the reactants than alternative protocols.

Smith was among the first to recognize that quinone tautomerization could be facilitated by base (Fig. 39). He observed that quinone **136** produce a [4+2] dimer in basic solution and suspected that the reaction likely proceeded through the *o*-QM **137**.[91] Jurd[49b–e] capitalized on a similar procedure with benzoquinones. He found that under mildly basic conditions the benzoquinones undergo dimerization via a Michael addition pathway.

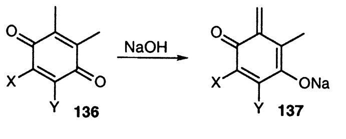


Figure 39.

Gardner was among the first to demonstrate that base assists the formation of *o*-QMs from the *o*-hydroxybenzyl alcohols such as **97** (Fig. 40).[4e] Because very little of the *o*-QM is present at any given time during the reaction, dimerization can be avoided and an intermolecular reaction will proceed in the presence of a high concentration of the intended nucleophile. If an external nucleophile is not present, however, then the protocol leads to diarylmethanes by an ionic dimerization pathway that proves very useful for the synthesis of calix[*n*]arenes.[19]

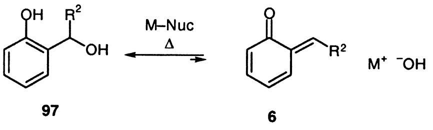


Figure 40.

The delay in developing base facilitation with other protected forms of *o*-hydroxy benzyl alcohols likely stems from the difficulty associated with handling these systems. Consider protecting group strategies that might address the construction of some various acylated benzyloxy-substituents. *The base, which is necessary to attach the protecting group, facilitates the formation of the corresponding o-QM.* To illuminate this problem consider the observation of Ogata concerning the addition of *N*,*N*′-carbonyldiimidazole to the diol **138**.[92] This conditions result in the imidazole **139**, a process which we suspect involves an *o*-QM intermediate (Fig. 41).

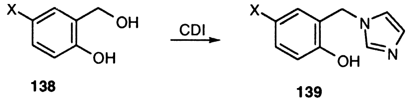


Figure 41.

Consider the reverse strategy of starting with *o*-O-acylated benzaldehydes or phenones such as **140** (Fig. 42). In theory this entity could be reduced to afford some sort of protected *o*-hydroxy benzyl alcohol such as the phenol of **141**. McLoughlin,[93] Mitchell,[94] and Angle[95d] all found, however, that reduction leads to the corresponding *o*-hydroxyalkylated material **143** via the *o*-QM intermediate **142**, which undergoes 1,4-addition of hydride.

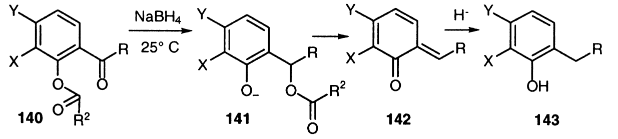


Figure 42.

Loubinoux devised a solution to the issue of constructing an *o*-hydroxy benzyloxy acetate that could serve as an *o*-QM precursor (Fig. 43).[96] The usefulness of the precursor, **150**, resides in the fact that the corresponding *o*-QM (**37**) can be generated by exposure to basic conditions (such as potassium *t*-butoxide) and then serve as an electrophile for nucleophiles other than the initiating base. Loubinoux exploited the precursor in a variety of intermolecular applications. However, the construction of **150** is somewhat tedious. Starting from the salylicyclic aldehyde **144**, the phenol was transformed into the thioether **146**, and then converted into the chloroalkoxyether **147**, which is then transformed into the azide **148**. Reduction furnished the benzyl alcohol **149**. After acylation, the phenol was liberated under mild acidic conditions to produce the acetate **150**.

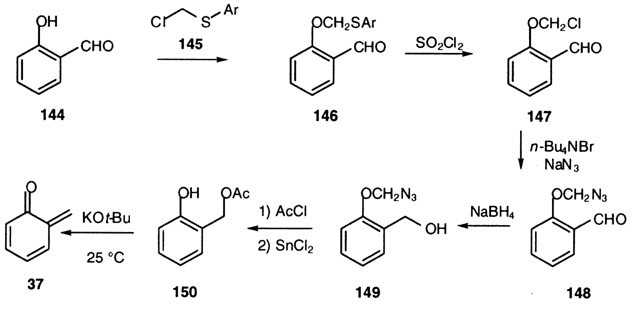


Figure 43.

Koshland found that under acidic or neutral conditions the *o*-hydroxybenzyl bromide **152** (X=Br) displays selectivity for N-alkylation of tryptophan (Fig. 44).[97] Under basic conditions, however, **152** displays no selectivity in its reaction with amino acids suggesting that base accelerates formation of the corresponding *o*-QM. Dean found base in conjunction with **152** (X=Cl) was inappropriate for subsequent [4+2] cycloaddition. However, these conditions were useful for the preparation of dimers and trimers of the corresponding *o*-QM.[52b] Dean also found that the action of base on unsubstituted **152** (X=Cl) was even less controllable, producing polymeric material via trapping of *o*-QM intermediates by C-alkylation of the phenol starting material (a direct S_N2 displacement of the chloride is also possible). Böhmer has studied the kinetics of the formation of **153** from **152** (X=Cl) with various anilines as well as the subsequent addition reaction of the anilines with the *o*-QM.[98] Habicher has examined a similar process utilizing 5α-bromo-α-tocopherol, a brominated derivative of vitamin E (**69**, Fig. 18).[57a,b,d,e] The halogenated precursors are constructed from the corresponding *o*-methylated phenols by oxidation to the *o*-QM with elemental halogen followed immediately by 1,4-addition of the HX concomitantly produced. Additionally, they can be produced by halomethylation of a phenol such as **151** with dimethoxymethane and HX, but, this reaction is only controllable if the para position is blocked with an electron-withdrawing group.[99]

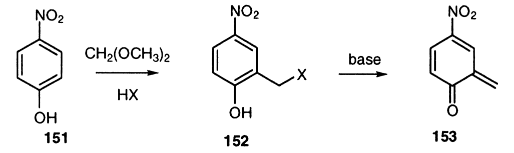


Figure 44.

Kato recently disclosed that 2-(1-chloro-2,2,2-trifluoroethyl)phenols **154** lead to the corresponding *o*-QMs **155** upon the addition of base (Fig. 45).[100] The chlorides are available from the corresponding benzyl alcohol by treatment with thionyl chloride. The benzyl alcohol precursors **154**, in turn, emerge from ZnI_2 mediated reaction of the corresponding phenol with trifluoroacetaldehyde.

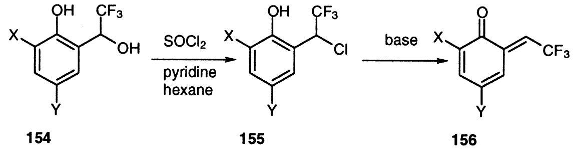


Figure 45.

Freccero has noted that 2-hydroxybenzyltrimethyl ammonium iodide (R^2=H) **103** forms **37** at 80°C under neutral conditions (Fig. 46). However, upon the addition of base, higher yields of the *o*-QM derived product are achieved in shorter reaction times.[10b]

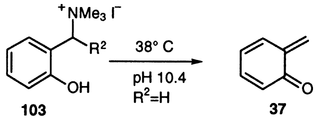


Figure 46.

Unfortunately, the preceding base triggered *o*-QM precursors (Figs. 40–45) are rather unstable. A more stable precursor would be beneficial, permitting addition of the intended nucleophiles to trigger the formation of the desired *o*-QM with which it is intended to react. Nature has developed means to accomplish this strategy. The mechanism is believed to be responsible for the bioactivity of several antitumor agents such as daunomycin **18**,[101] which undergo reduction within an oxygen deficient atmosphere of a tumor cell to form the phenoxide **157** (Fig. 47). This intermediate in turn undergoes subsequent elimination to form the *o*-QM **159** along with its tautomer **158**. These reactive species are believed to then alkylate the DNA within the tumor cell, thereby leading to self-induced apoptosis during replication. Several useful synthetic methods have been developed that mirror or mimic this biological mechanism.

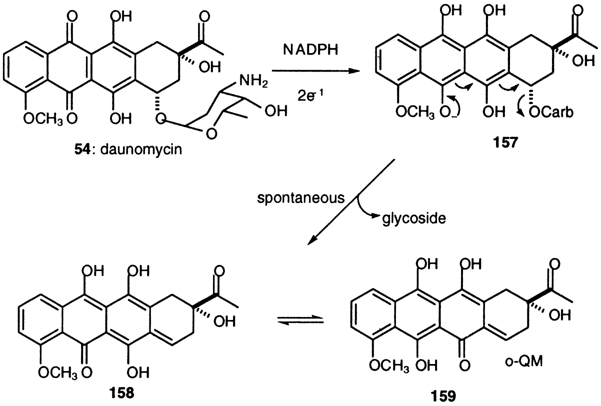


Figure 47.

Reynolds discovered the first examples of base-triggered *o*-QM precursors **163** and **164** (Fig. 48).[102] Compound **163** is available on large scale by a three-step sequence starting from the corresponding phenol **160**. Addition of the imminium salt generated from morpholine and formaldehyde results in the phenol **161**. Treatment of this phenol with acetic anhydride leads to the diacetate **162**. Upon the addition of the sodium salt of thio-urea to **163**, compound **164** forms. Addition of morpholine to **164** triggers a cascade; the aryl acetate is cleaved liberating the corresponding phenoxide, which in turn eliminates the thiourea to form the *o*-QM **165**, which is subsequently trapped by the morpholine nucleophile that cleaved the acetate. The addition of sodium sulfide to the acetate **163** resulted in a similar sequence of events. These results illuminate a conundrum for base-nucleophile triggered processes-preventing the addition of the nucleophile used to initiate the formation of the *o*-QM.

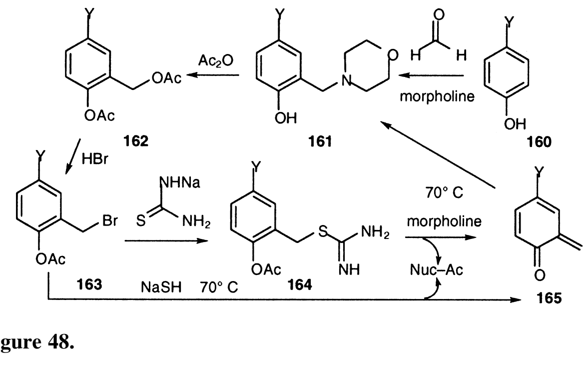


Figure 48.

Rokita has developed a silyl version of this strategy that overcomes this shortcoming by generating the *o*-QM **168** from the corresponding silyl ether **167** with fluoride ion (Fig. 49).[103] The bromide **167** is available from **166** by free radical halogenation and is more robust than the corresponding phenol. Rokita used the dibromide of **111** ($Y{=}CH_2Br$) to crosslink strands of DNA. He further investigated the mono-bromide (**111**; Y=H) in its ability to alkylate deoxynucleosides upon the introduction of F^-, determining their site of alkylation through NMR studies of the isolated adducts. Despite the potential utility of this *o*-QM precursor, it has not found use, to our knowledge, in organic synthesis.

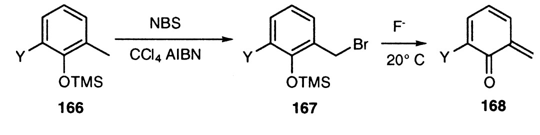


Figure 49.

Moore has developed a conceptually similar procedure for the production of 1,4-benzoquinone derived *o*-QMs (Fig. 50).[6d] In the Moore protocol, however, the silyl 'trigger' is now on the benzylic carbon, which upon attack of a nucleophile yields the vinylogous enolate which *o*-protonates to give the quinone methide **170**. The precursor 2-((trimethylsilyl)methyl)quinones (**169**) are obtained via a thermal ring expansion of 4-alkenyl(or alkynyl)-4-hydroxycyclobutenones.[6b,c] In Moore's study it was shown that nucleophilic addition to the *o*-QM was faster then tautomerization, therefore, the position of the silyl group determined which *o*-QM isomer was formed.

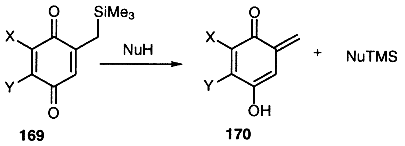


Figure 50.

Recognizing the different hydrolytic behavior of protecting groups attached at the benzyloxy and phenoxy sites, Lhomme designed a new *o*-QM precursor from the dioxin **172** (Fig. 51).[66] The dioxin is available by formylation of the phenol **171**. Thermolysis of **172** in toluene with Ac_2O affords **173**, via an *o*-QM intermediate. Treatment of the fairly robust bis-acetate **173** with any one of an assortment of nucleophiles results in cleavage of the weaker ester bond

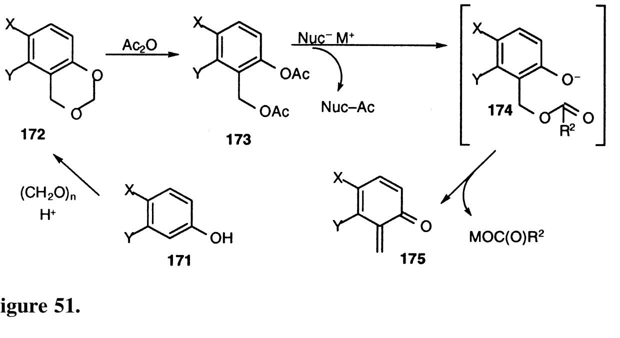


Figure 51.

furnishing the alkoxy anion intermediate **174** that eliminates to form the *o*-QM **175**. The *o*-QM is then trapped by the nucleophile used to trigger its formation. While **175** could also be trapped as its chroman derivative with an electron-rich alkene under aq. base/acetonitrile conditions, this reaction only served to demonstrate the intermediacy of an *o*-QM as the low yield obtained made it unviable synthetically. The problems associated with this sequence are the severity of conditions associated with the conversion of **171–173** and the lack of regiocontrol in conversion of **171→172**.

A concise solution to the problem of devising an accessible *o*-QM precursor that reacts in a controlled manner was recently discovered in our laboratory (Fig. 52).[104] Various *o*-OBOC (*o*-O-*t*-butyl carbonate) salicaldehydes, such as **176**, can be used in combination with assorted organometallics. Depending on the metal used, the formation of the *o*-QM **179** can be prevented until the desired time. This allows for the initiating nucleophile to be differentiated from the nucleophile that subsequently reacts with the *o*-QM formed. For example, aluminum reagents, such as $LiAl(Ot\text{-}Bu)_3$ fail to undergo migration and upon protonation produce the corresponding alcohol such as **178**. Lithium reagents undergo the migration to form **177**, but fail to undergo the elimination necessary to form the *o*-QM **179**. Magnesium, potassium, and sodium reagents and salts proceed to the *o*-QM **179** or can reinitiate its formation from **177** at very low temperatures (−78°C to −20°C). Thus, this procedure allows a one-pot construction of a great many β-substituted *o*-QMs, which can undergo low temperature intermolecular reactions with thiols, alcohols, organomagnesium and organozinc reagents, as well as enamines, imines, furans, and assorted enol ethers.

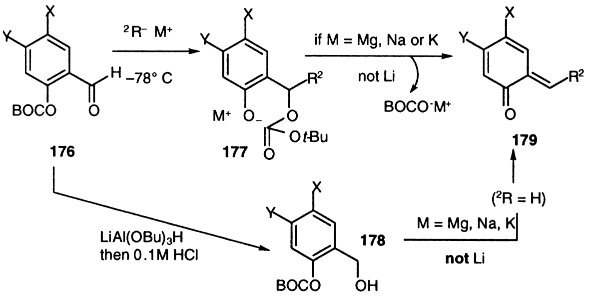


Figure 52.

Katritzky discovered that the *o*-(benzotriazolylmethyl)-phenol **180** is a robust *o*-QM precursor (Fig. 53).[105] Compound **180** is prepared by reaction of phenol **113** with 1-hydroxy-methylbenzotriazole (HOBT) under acidic conditions. Phenol **180**, when treated sequentially with equimolar amounts of *n*-BuLi, TMSCl, and *n*-BuLi, yields the benzylic anion that undergoes reaction with various electrophiles such as alkyl halides to produce derivatives **181** upon acidic workup. Attempts to directly alkylate the dianion without in situ protection of the phenol only led to recovered starting material or O-alkylated material. In a metal based change in reactivity, treatment of the *o*-(benzotriazolylmethyl)phenol **181** or its precursor **180** with potassium, sodium, or magnesium bases, generally at elevated temperatures, results in expulsion of the benzotriazole thereby forming the corresponding *o*-QM **6**. This difference in reactivity is most likely a consequence of the strength of the O–Li bond. The *o*-QMs produced from compounds **180–181** undergo 1,4-addition reactions with amines, thiols, alcohols, hydride, as well as carbon nucleophiles such as active methylene compounds and Grignard reagents. However, **180** and **181**, are less useful as precursors for inverse demand Diels–Alder reactions. High initiation temperatures result in diminished diastereoselectivity and less electron-rich dienophiles (such as styrene derivatives) result in polymerization products with none of the corresponding chroman being produced. The Katritzky protocol is overall very useful for the construction of *o*-alkyl phenols; its only shortcomings are the low yields associated with the preparation of the *o*-functionalized phenol **180** and the generally high temperature requirements for the generation of *o*-QMs from **180** and **181**.

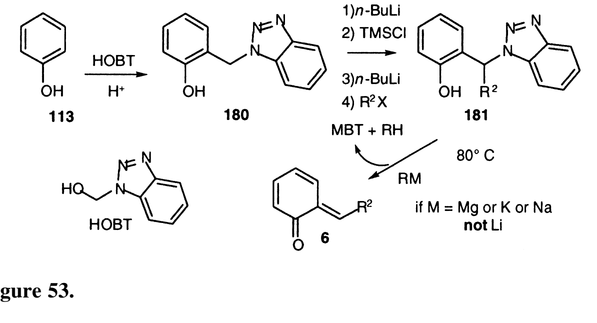


Figure 53.

One fairly unusual example of *o*-QM generation, representing a combination of an acid and nucleophile trigger, has been observed with cyclohexadienone epoxides (Fig. 54). Reiss found that treatment of the dienone **182** with TMSCl affords the [4+2] spirodimer **185**.[106] Presumably this occurs via nucleophilic opening of the epoxide **182** to afford the silyl ether **183**. A migration, where the silyl moiety plays the role of an acid, produces the corresponding *o*-QM **184**, which undergoes subsequent dimerization.

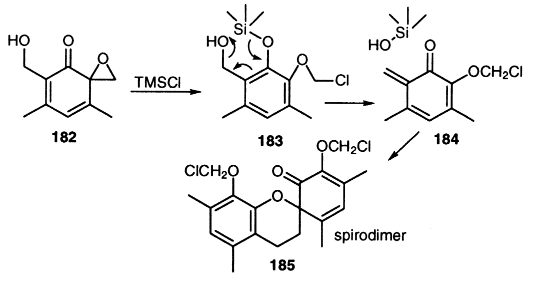


Figure 54.

2.7. Olefination of *o*-quinones

A final method for *o*-QM generation is the mono-olefination of *o*-quinone compounds. This procedure has not found widespread usage and is limited to a few examples in the literature. Therefore, its suitability for a wide variety of *ortho*-quinone substrates is an open question. Widespread application is also hindered by the lack of available *o*-quinones due to their inherent reactivity. Furthermore, with the exception of generating highly stable, conjugated *o*-QMs, those produced in this way are generally consumed by a second equivalent of the olefinating reagent. This is due to the fact that the *o*-QM generated is generally much more reactive towards the olefinating reagent then the corresponding *o*-quinone.

Parrick[107] and subsequently Shechter[108] examined the addition of phosphorous ylides to phenanthraquinones **186** (Fig. 55). They found the addition of both stabilized and non-stabilized ylides produce the corresponding *o*-QMs (**187**). However, the *o*-QMs thus produced can generally only be reacted with another equivalent of the same ylide.

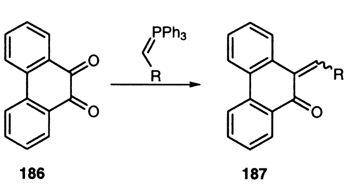


Figure 55.

Bos[109] demonstrated that the condensation of an *o*-quinone (**188**) with an ynamine (**189**) at room temperature yielded the stable *o*-QM **190** (Fig. 56). The reaction proceeds through a net [2+2] reaction of the ynamine with one of the carbonyls of the quinone. An electrocyclic reaction then provides the *o*-QM amide. It should be noted that the *o*-QM **190** is both conjugatively stabilized as well as sterically congested thereby preventing dimerization and allowing it to be isolated.

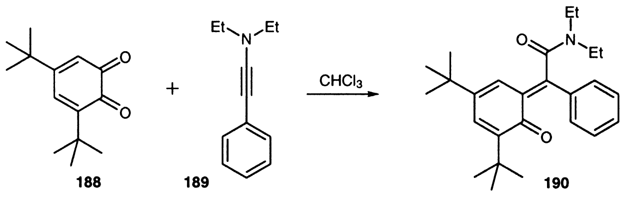


Figure 56.

3. Reactions of *o*-QMs

3.1. [4+2] Cycloadditions resulting in benzopyrans

The most prevalent course of reaction for an *o*-QM is a [4+2] dimerization. Indeed, great care must be taken to prevent this outcome. The preceding sections have detailed several techniques that lead to *o*-QMs in low concentrations to avoid dimerization. The simplest solution is to consume the *o*-QM in some intramolecular event as it is formed. Indeed, *o*-QMs used in this capacity have proven to be very useful. However this tactic can only be applied to a handful of customary targets, most notably the cannabinoids. Reports of intermolecular [4+2] applications of *o*-QMs in total synthesis are even scarcer.

For intermolecular cycloadditions the selectivity among products depends upon: (a) the orientation of the transition state (*endo* vs *exo*), (b) the geometry of the starting *o*-quinone methide ((*E*)-**2** vs (*Z*)-**5**), and (c) the relative stability of the respective diastereomeric products **191** and **192**. The various scenarios are depicted in Fig. 57. Readers should recall that the olefin geometry in *o*-QMs is fairly fluxional and depends upon the steric interactions associated with the methide substituent in its respective *E* and *Z* geometries (cf. R^2, Fig. 57). In cases involving a mono substituted alkene ($R^3\neq H$) as the dienophile and an *o*-QM disposed in an E geometry ($R^1=H$, $R^2\neq H$), the resulting cis diastereomer **192** is favored from a kinetic standpoint, while the trans diastereomer is preferred from a thermodynamic perspective. Thus, in some heat-induced processes a distribution among *endo* and *exo* cycloadducts results. Fortunately, Pochini has utilized an empirical method that allows 2,4-**cis** and *trans* isomers such as **192** and **191** to be rapidly distinguished on the basis of ^{1}H NMR coupling constants alone.[78d]

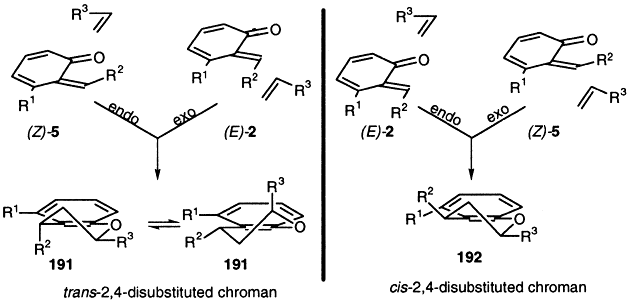


Figure 57.

Of the tautomerization protocols that can be used to initiate *o*-QM formation, most lead to dimerization. Jurd noted that many of these dimerizations could be accelerated by heat or addition of base.[49d] A particularly interesting example discovered by Giraud is shown in Fig. 58.[110] Deprotonation of **193** with lithium methoxide leads to the *o*-QM **194**, which in turn undergoes a surprisingly regioselective Diels–Alder reaction (32:1) with the starting quinone **193** thereby producing the xanthene-1,4-dione **195** in 70% yield. The selectivity is believed to be a consequence of hydrogen bonding between the hydroxy substituent of the quinone with the quinone methide carbonyl.

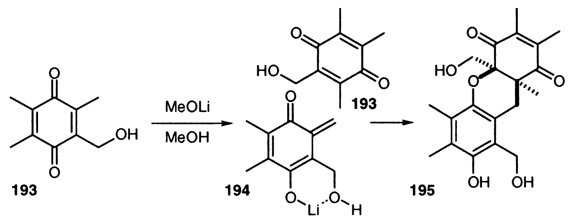


Figure 58.

For cycloadditions initiated by oxidation, there have been several studies. Bolon was among the first to harness an oxidative process for the purpose of preparing various chromans (Fig. 59).[54b] He discovered that an admixture of Ag_2O and phenol **196** resulted in the *o*-QM **197** (R^2=H and R^1=Me), which could be trapped with various alkenes such as ethyl vinyl ether (EVE), styrene,

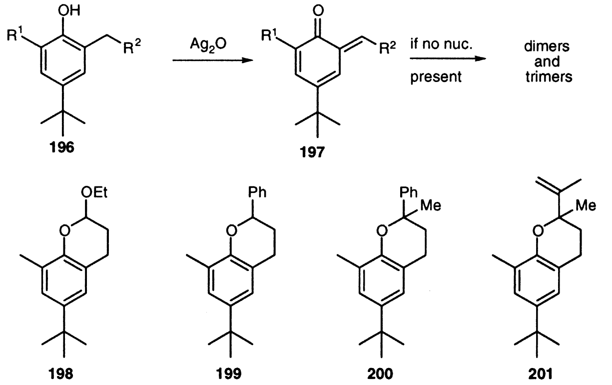


Figure 59.

α-methyl styrene, and 2,3-dimethyl butadiene to afford the respective chromans **198–201**. While EVE and styrene were effective dienophiles, providing the respective chromans in 80% and 40% yields respectively, α-methyl styrene and 2,3-dimethyl butadiene both provided their respective chromans in yields under 30%. Bolon concluded from these studies that a high concentration of the dienophile was crucial in preventing trimerization of the *o*-QM.

Jurd examined oxidations of the phenol **202** with Ag_2O and DDQ. He established that the resulting *o*-QM was stable and could be isolated.[49a] Ponchini subsequently confirmed the *E* geometry of **203** by X-ray crystallography.[78e] Ponchini noted that the room temperature reaction of **203** with the appropriate vinyl ether afforded adducts **204–206** as single diastereomers, providing further evidence that *o*-QMs react via an *endo* transition state with vinyl ethers (Fig. 60). Adducts **204** and **206** were obtained in greater then 90% yield, however, the Z-configured enol ether provided the respective adduct **205** in only 40% yield. This difference in reactivity is a consequence of the increased steric effect in the *endo* transition state with the *Z*-enol ether.

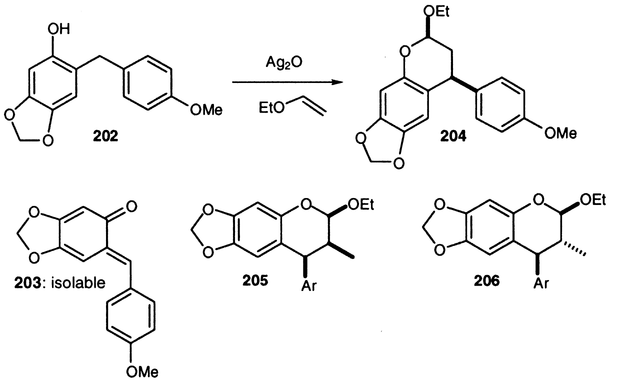


Figure 60.

Habicher, building upon observations of Dean regarding the regioselective oxidations of benzodihydrofurans, found that treatment of **82** with Ag_2O in the presence of EVE produced the chroman **207** (Fig. 61).[57d] However, the *o*-QM derived from **82** is very prone toward dimerization and trimerization and the yield of the cycloadduct **207** is only 22%. The procedure works quite well, however, with the vitamin E **69**. The analogous cycloadduct **208** forms in quantitative yield with ethyl vinyl ether as the trapping agent and in 70% yield when styrene is employed as the dienophile.[57a]

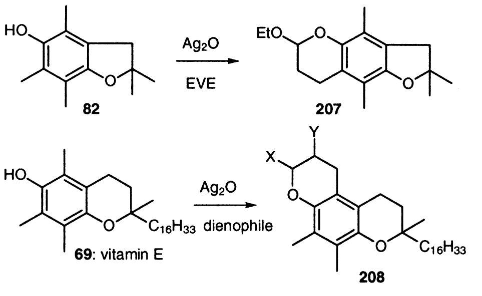


Figure 61.

Kasturi reported that the oxidation of bis-napthols such as **209** with either DDQ or *o*-chloranil results in spirodimers of *o*-QMs.[56b] The proposed mechanism (Fig. 62) suggests that the initial oxidation adduct **210** undergoes disproportionation to yield the phenol **211** and *o*-QM **212**. The latter dimerizes in the usual fashion providing **213** in 40% yield. Kasturi has also reported oxidation processes involving other substrates that are believed to involve *o*-QM intermediates.

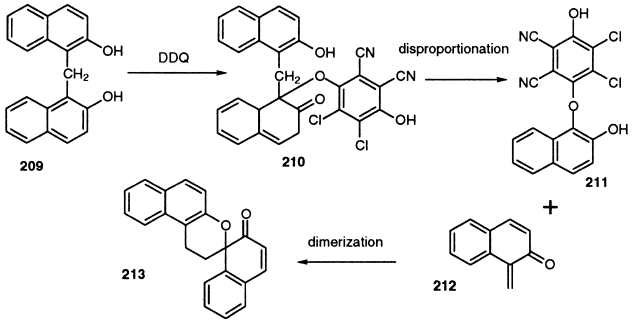


Figure 62.

Adam generated the *o*-QM **93** by the addition of DMDO to the benzofuran **91** at −78°C. The *o*-QM **93** is thought to exist in an equilibrium with its zwitterion contributor **214**.[58] Interestingly the addition of EVE at −40°C affords the expected chroman **215** as a single diastereomer presumably involving an *endo* transition state, while the addition of tetracyanoethylene (TCNE) produces the furan **216** via a [2+3] reaction (Fig. 63). Styrene also proved to be an effective trap for the *o*-QM **93**. Yields for these processes were

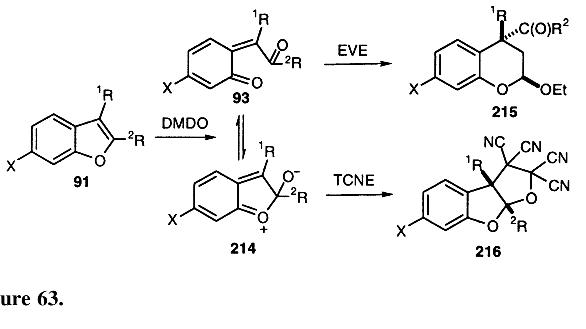


Figure 63.

generally over 80% depending on varying substituents about the aromatic ring. The conversion of **93** into **215** is the only example of a Diels–Alder reaction of which we are aware involving a β-disubstituted *o*-QM ('R≠H).[58d,e,g] The competitive 1,5-hydride shift to produce a styrene is avoided because of the lack of a hydrogen atom.

Pochini thoroughly investigated thermally initiated intermolecular [4+2] reactions of *o*-QMs generated from the corresponding hydroxy benzyl alcohols (cf. **97**, Fig. 64).[78d,e] When the phenol **97** is heated to 170°C in the presence of 2 equiv. of various vinyl ethers, a cycloaddition ensues resulting in a ratio of diastereomers. For the enol ethers investigated, the yield of the predominate adduct in each case (cf. **217–225**) ranged from 35 to 95%. In most cases, the major diastereomer formed appears to result from an *endo* oriented transition state (*cis* relationship between the substituents at the 2,4-positions). Only the reaction proceeding to adduct **224** appears predisposed to an *exo* orientated transition state.

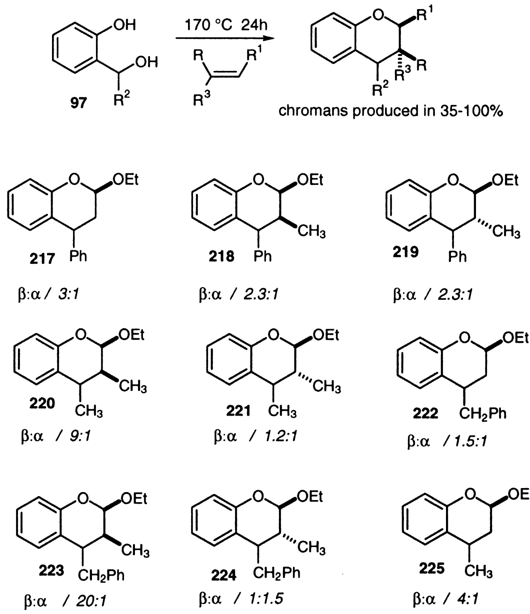


Figure 64.

Yoneda harnessed thermally generated *o*-QMs for the synthesis of 5-deaza-10-oxaflavins (Fig. 65).[111] The chlorouracil **227** undergoes a [4+2] reaction with the *o*-QM generated from the benzyl alcohol **226** (200°C) producing the chromene **228** in 80% yield upon HCl elimination from the initial cycloadduct.

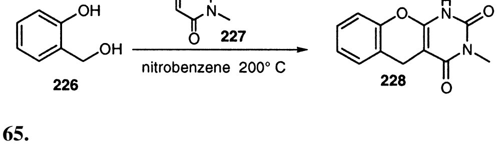


Figure 65.

René has investigated the cycloaddition of β-substituted enamines with *o*-QMs generated from benzyl alcohols such as **229** (Fig. 66).[112] Conducted in Ac_2O, the initial chroman cycloadduct undergoes a subsequent elimination of the morpholine fragment, which is converted into its corresponding acetamide along with the respective chromenes **230–235.** The latter are formed in 35–100% yield. Because the morpholine is sequestered, a potential side reaction, namely conjugate addition of morpholine to the *o*-QM intermediate, is prevented. René reports that an enamine, β-substituted with either a ketone carbonyl residue or a nitro residue, undergo the cycloaddition in respectable yields. Enamines β-substituted with an ester moiety, however, afforded very little if any of the desired product. α-Functionalized enamines give chromenes in lower yields (~40% for **232**). Surprisingly, generation of the identical *o*-QM intermediates from *o*-phenolic Mannich bases (such as **102**, Fig. 25) led to none of the anticipated products.

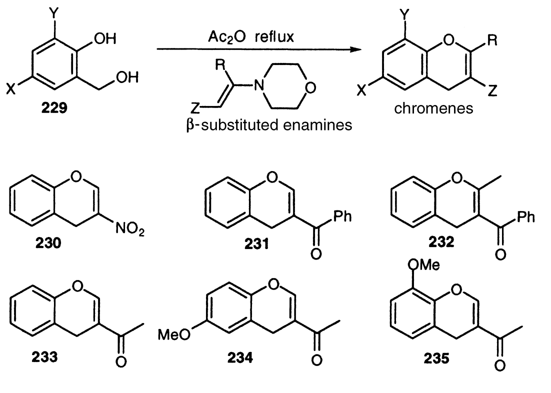


Figure 66.

Eguchi reported that the thermolysis of **226** with C_{60} produces the [4+2] adduct **236** in 31% yield upon heating for two days.[113b] Acid facilitation proved entirely ineffective. Langa subsequently reported that **226** undergoes cycloaddition with C_{60} in 4 min with microwave irradiation at 800 W producing **236** in 27% yield (Fig. 67).[114]

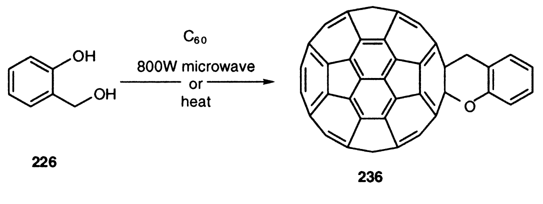


Figure 67.

Yamashita found that the Dözt reaction between the chromium carbene **237** and the alkyne **238** proceeds directly to the 2,4-*trans* substituted chroman [4+2] dimer **242** (Fig. 68).[115] Presumably, the phenol **239** is first formed which subsequently undergoes thermal degradation to produce the Z configured *o*-QM **241** as well as styrene **240**; the latter is the result of a 1,5-hydride shift. An *endo* approach between the styrene and *o*-QM affords the cycloadduct **242** in 68% yield.

Eguchi reported that the *o*-QM generated by thermolysis of either the benzyl alcohol **226** or the Mannich base **243** undergoes cycloadditions with thiocarbonyl compounds

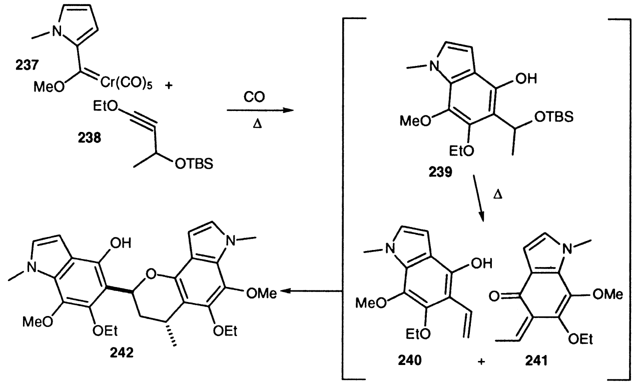


Figure 68.

such as adamantanethione **244** to generate thioacetals of type **245** (Fig. 69). Compound **245** is obtained in 90% yield, with yields of additional examples ranging from 40 to 90%.[113a]

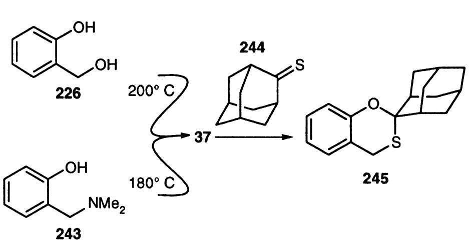


Figure 69.

Katritzky found that 1-[α-(benzotriazol-1-yl)alkyl]-2-napthols such as **246** undergo various thermally triggered [4+2] cycloadditions at 150°C (Fig. 70). Because of the non-bonded interactions in **248**, the *o*-QM exists in the Z configuration **247**, rather than the typical E configuration. Hence, the resulting chroman adducts, **249–252** emerge in a *trans* relationship expected for an *endo* oriented transition state with a Z-configured *o*-QM.[105b] Notably, less electron-rich olefins, such as styrenes, provided none of the desired cycloaddition adducts when employed in the reaction.

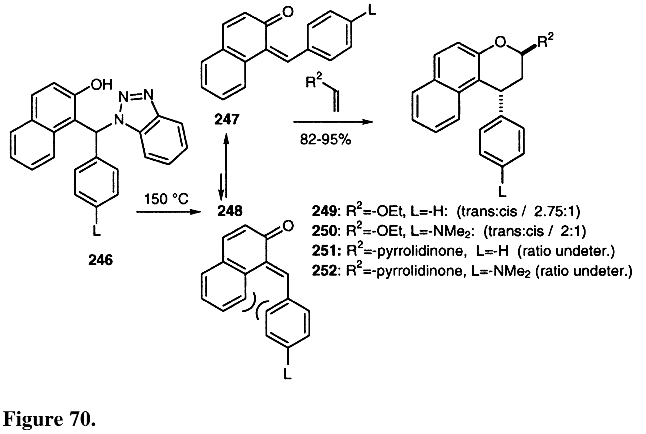


Figure 70.

Habicher utilized an *o*-QM intermediate to prepare less fat-soluble derivatives of vitamin E (**69**, Fig. 18) such as **256.** (i.e. less lipophilic, Fig. 71).[57e] The synthesis entails regio-selective oxidation of vitamin E (des-bromo **253**) with bromine resulting in formation of an *o*-QM that undergoes 1,4-addition with HBr to produce **253**. Thermally promoted loss of HBr and subsequent cycloaddition with the ketene acetal **254** affords the ortho-ester **255** in greater then 80% yield. This material is converted to the desired carboxylic acid **256** when subjected to acid and fluoride.

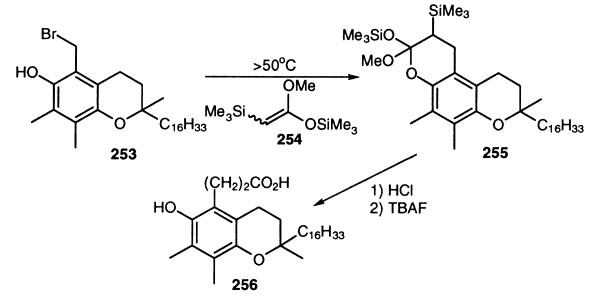


Figure 71.

Witkop reported that the bromoalcohol **152** (Koshland's reagent) undergoes a Diels–Alder reaction at room temperature with 3-methylindole **257** to produce the chroman **258** in 70% yield (Fig. 72).[116]

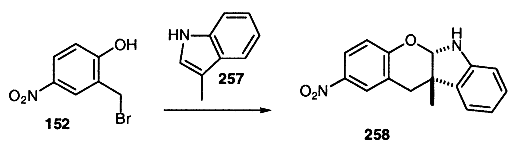


Figure 72.

Lukyanov devised a synthesis of benzooxazinium salts such as **261** via an *o*-QM intermediate (Fig. 73).[117] Refluxing the acetal **259** or the benzyl alcohol **260** in the presence of trityl perchlorate and one of various nitriles furnishes the 1,3-4*H*-benzoaxazinium salt **261**, which is readily converted to the corresponding benzoxazines **262** by addition of triethylamine. Yields for this sequence ranged from 35 to 98%.

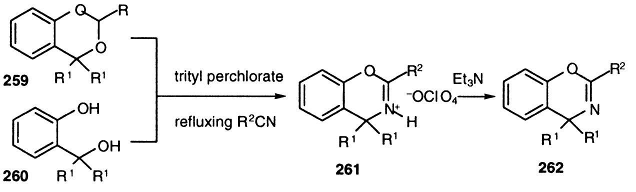


Figure 73.

Lau and Dufresne examined the thermolysis of benzodioxaborins, such as **113**, as a means to generate *o*-QMs (**6**) for intermolecular Diels–Alder reactions. Cycloadditions of the *o*-QMs generated in this fashion with ethyl vinyl ether and dihydropyran led to chromans **264–269** in yields ranging from 53 to 90% (Fig. 74).[17b] Less reactive olefins were also employed as dienophiles but yields of the benzopyran adducts were 50% or less in these examples. Because conversion of the various benzodioxaborins into the corresponding *o*-QMs required 225–300°C the diastereoselectivity of some cycloadditions was severely corrupted

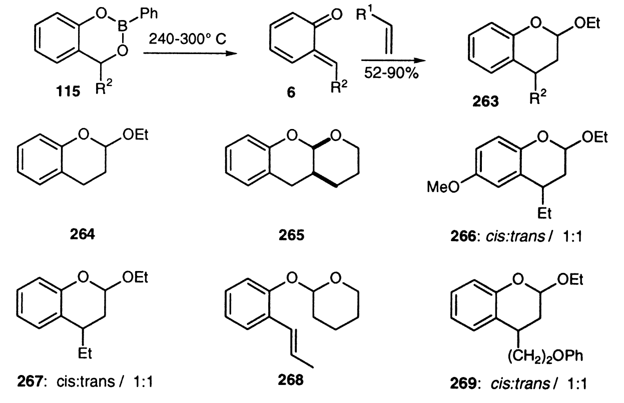


Figure 74.

(cf. **266–267**, **269**). In some instances unexpected products such as **268** were formed.

Strandtmann disclosed that a Mannich base, such as **270**, produces an *o*-QM upon heating in dioxane. Furthermore, this species subsequently undergoes [4+2] cycloadditions with an assortment of enamines to produce *O*,*N*-acetals such as **271** (Fig. 75).[68a] If water is added to the reaction mixture hydrolysis ensues upon completion of the reaction and provides the corresponding α-hydroxypyrans such as **272**–**273**. However, the only yield reported was for **273** (35%).

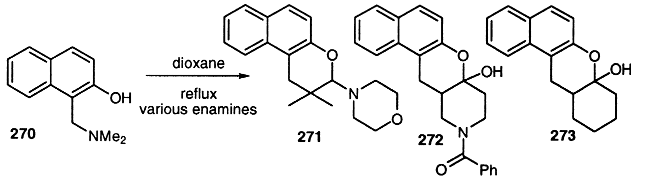


Figure 75.

Fillion observed that the phenol **274** undergoes reaction with an admixture of benzyl amine and benzaldehyde to produce the *N*,*O*-ketal **277** (Fig. 76).[118] Under less forcing conditions the conjugated *o*-QM **275** can actually be isolated. It undergoes reaction with the imine **276** to produce **277**. The *o*-QM could be reformed from **277** via a *retro* Diels–Alder (RDA) reaction in refluxing toluene.

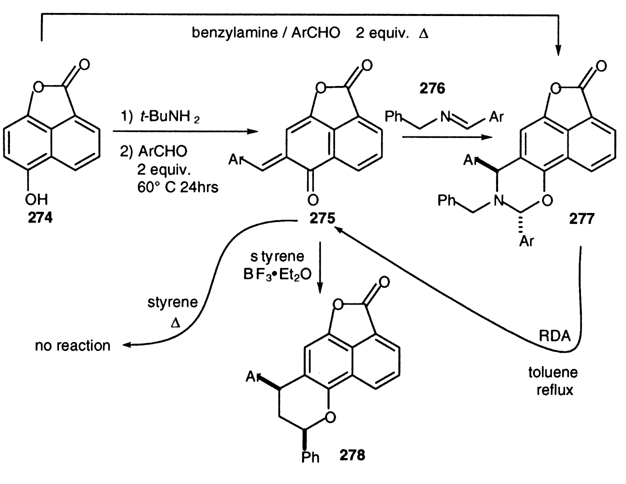


Figure 76.

Although **277** proved unreactive with styrene under these conditions, addition of an equivalent of $BF_3\cdot Et_2O$ enables the cycloaddition to proceed at room temperature in 90% yield. We believe the authors incorrectly assigned the regiochemistry and stereochemistry of this chroman product and suspect that the correct structure is actually **278** as shown in Fig. 76.

Kumanotani reported that heating the neat vinylphenol **279** to 90°C for 12 h affords chroman **281** in 99% yield predominately as the *cis*-isomer (Fig. 77).[119] Presumably the reaction involves a 1,5-sigmatropic shift that results in formation of the *Z o*-QM (**280**(*Z*)) that then equilibrates to the more stable E-configuration (**280**(*E*)) before undergoing reaction with the remaining vinyl phenol providing the chroman.

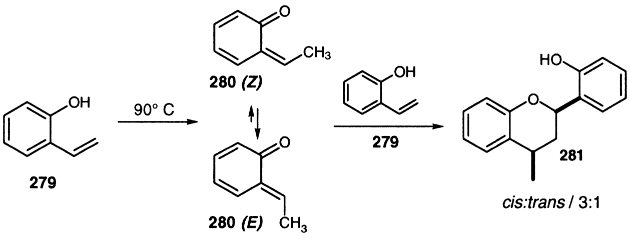


Figure 77.

Chauhan discovered that the spirodimer **282**, which is prepared in a 51% yield by heating the Mannich base (cf. **270**, Fig. 78) to induce self-dimerization, can be cracked in refluxing mesitylene. The resulting *o*-QM undergoes reactions with various uracils (**283**–**285**) to produce the respective tetracyclic compounds **286**–**288** in yields ranging from 56 to 79% (Fig. 78).[120]

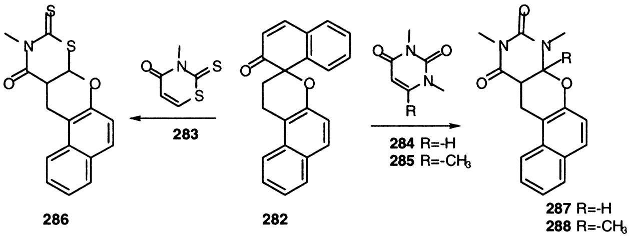


Figure 78.

Shudo found that 4*H*-1,2-benzoxazines such as **107** lead to the corresponding *o*-QMs at 90°C (Fig. 79).[75] The resulting *o*-QMs undergo [4+2] cycloadditions with styrene, phenyl vinyl ether and *N*-vinyl-2-pyrollidinone to produce the respective chromans **290**–**292** in yields ranging from 42

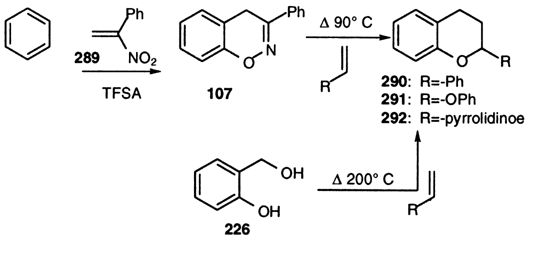


Figure 79.

to 83%. The identical reactions commencing with the *o*-hydroxybenzyl alcohol **226** required elevated temperatures (200°C). The 4*H*-1,2-benzoxazine **107** is obtained in good yield by acid mediated addition of benzene to unsaturated nitro derivatives such as **289**.

Zanirato suggested that the furan **111** undergoes nitrogen expulsion at 60°C to generate the nitrene, **293**, which fragments to the corresponding *o*-QM **112**. A cycloaddition between the *o*-QM and starting benzofuran **111** results in the nitrile **294** in 50% yield (Fig. 80).[77]

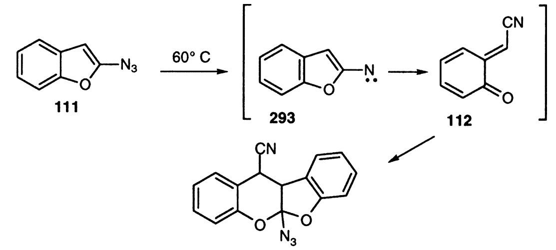


Figure 80.

Wan disclosed that laser flash photolysis of various *o*-hydroxybenzyl alcohols (cf. **97**) in the presence of vinyl ethers results in a [4+2] cycloaddition at room temperature affording adducts **217**, **264**, **265**, and **295–297** in greater then 90% yields.[83c] Less electron-rich olefins, such as terminal olefins, do not undergo the reaction. Instead the *o*-QM intermediate undergoes the addition of water to regenerate the starting material. The product distribution for **217** was initially misconstrued as favoring the trans diastereomer. This mistake was corrected and reported to be that shown in Fig. 81 in a subsequent review.[16]

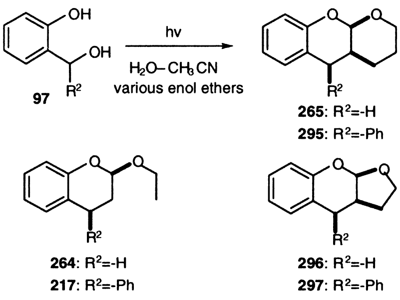


Figure 81.

Saito examined the laser flash photolysis of Mannich bases such as **298** in the presence of various enol ethers.[84] The yield of **264** was 38%. However, extended conjugation in the *o*-QM precursor results in better absorption of light, giving higher yields of the cycloadducts. Compounds **299–301** for example emerge in better than 50% yield (Fig. 82). The generation of a bis-quinone methide, from a bis-Mannich base joined by a biaryl bond, was examined as an agent for potentially cross-linking DNA.

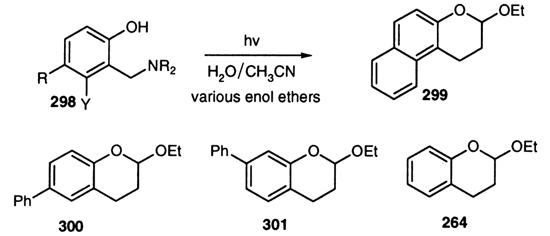


Figure 82.

Schmidt was among the first to examine the possibility of using Lewis-acids to facilitate *o*-QM formation.[61] Application of $SnCl_4$ to *o*-hydroxybenzyl chloride (**152**, X=Cl) as well as the bromide (**152**, X=Br), results in the formation of an *o*-QM at significantly lower temperatures than thermolysis of **152** alone. The *o*-QM generated in this fashion was found to undergo reaction with unactivated alkenes to produce adducts **302–305** in yields ranging from 68 to 88%. These impressive yields with unactivated alkenes can be attributed to lewis acid activation of the *o*-QM, which is further activated by an electron-withdrawing group on the aromatic ring (Fig. 83).

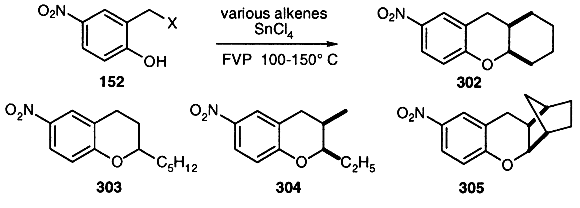


Figure 83.

Chiba disclosed that $LiClO_4$ and wet montmorillonite in CH_3NO_2 induces *o*-quinone methide formation from the *o*-hydroxybenzyl alcohol **306** (method A, Fig. 84). *o*-QMs generated in this fashion undergo reaction with unactivated alkenes to produce chromans **309** and **311**.[34d] However, *method A* appears to be ionic in nature and leads to rearranged products such as the spirane **310**, which is produced in a 1:2 ratio with chroman **309**. Yields for this procedure, including rearranged products, are typically greater then 90%. A milder procedure developed by Chiba

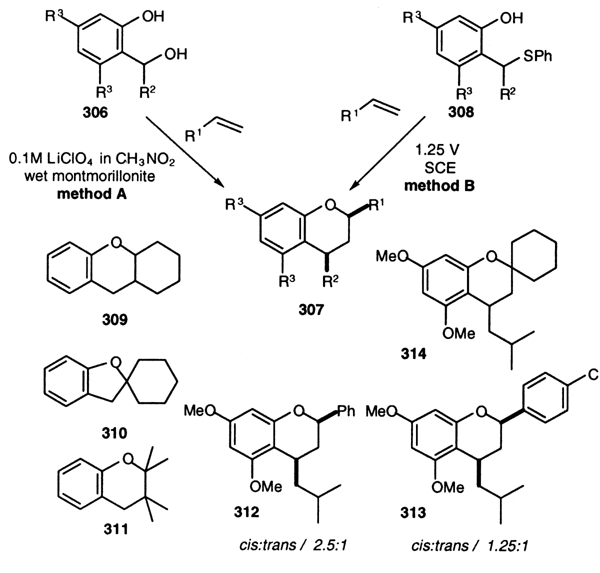


Figure 84.

entails both photochemical excitation and simultaneous electrochemical oxidation of *o*-hydroxybenzyl thioethers such as **308**.[34a–c] The thioethers can be obtained in one step from the corresponding *o*-hydroxybenzyl alcohols by treatment with thiophenol and ZnI_2. These conditions afford *o*-QMs that undergo addition with unactivated alkenes in respectable yields (57–91%) and moderate diastereoselectivity (cf. **312–314**). A shortcoming with the *o*-hydroxybenzyl thioethers, however, is the requirement that only *o*-QMs with electron-donating groups can be generated in this fashion.

Sato reports two methods that can be used in conjunction with *o*-hydroxybenzyl thioethers such as **315** (Fig. 85). Application of a catalytic quantity of $BF_3{\cdot}Et_2O$ to **315** in the presence of alkenes and enol ethers at room temperature affords adducts **317–319** with respectable diastereoselectivity in yields ranging from 48 to 76%.[27b,d] Alternatively, treatment of **55** with silver oxide at room temperature in the presence of an activated alkene as a solvent affords chromans **217**, **267**, and **320** with impressive diastereoselectivity and high yields (64–79%).[27a,c] Because Ag^+ is not converted to Ag° in this latter process, it is believed to serve only as a mild Lewis acid rather than a chemical oxidant. The thioether precursors are prepared by the [2,3]-sigmatropic rearrangement of phenoxysulfonium salts generated from dialkylsulfides, phenols, and thionyl chloride.

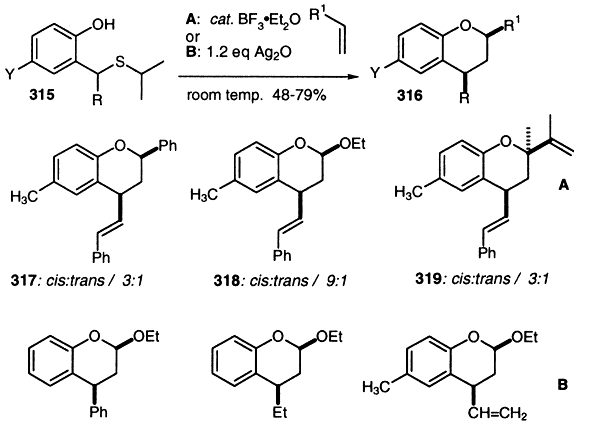


Figure 85.

Lhomme was among the first to develop a base triggering mechanism to initiate a [4+2] cycloaddition. He demonstrated that exposure of **321** to NaOH in the presence of EVE results in the chroman **332** in 17% yield (Fig. 86).[66]

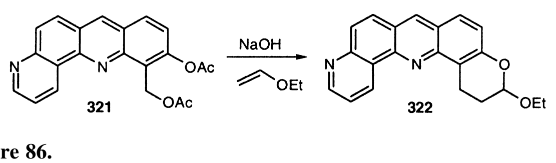


Figure 86.

Pettus disclosed that the addition of Grignard reagents to *o*-OBOC salicylic aldehydes such as **176** in the presence of assorted enols, enamines and imines results in the formation of various chroman derivatives (**324–329**) with excellent diastereoselectivities (Fig. 87). The impressive selectivity is due in part to the low temperatures (−20°C) at which the corresponding *o*-QM can be generated. Alternatively, organolithium reagents can be used if $MgBr_2{\cdot}Et_2O$ is subsequently added to induce the formation of the corresponding *o*-QM. The straightforward procedure leads to a structurally diverse array of cycloadducts in a single pot in good yields (66–94%).[104a,c]

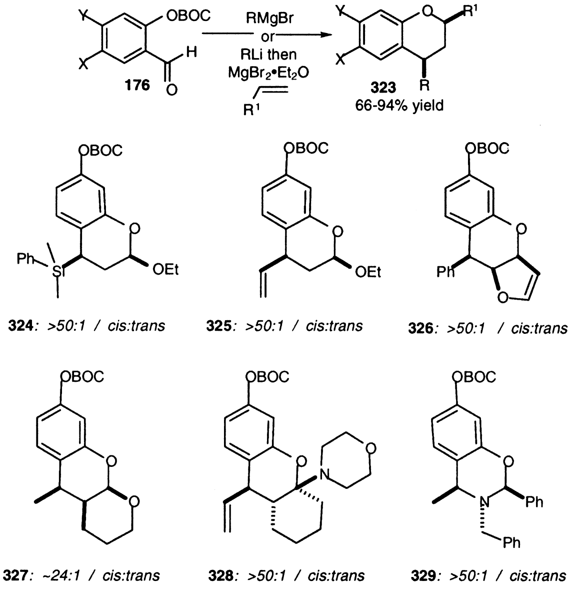


Figure 87.

To the best of our knowledge, the only other example of a nucleophilic attack resulting in an *o*-QM was developed by Moore (Fig. 88).[6d] In this case *o*-QM formation is induced by the nucleophilic attack of water on the benzylic silicon in the quinone **330** thereby yielding an *o*-QM intermediate **331**. The *o*-QM undergoes cycloaddition with n-butyl vinyl ether delivering the chroman **332** in 72% yield.

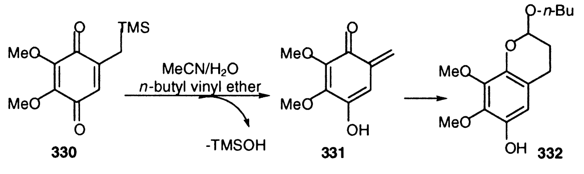


Figure 88.

3.2. Reduction of *o*-QMs

A variety of methods for the reduction of *o*-QMs have been engineered and include addition of various metal hydrides, Meerwein-Pondorf-Verley type reductions, addition of silanes with acid mediation, radical reductions, as well as several types of single electron transfer reductions. The majority of the protocols are fairly high yielding.

Gardner observed the reduction of the quaternary amine **333** with LAH at 65°C to afford *o*-methyl phenols such as **334** (yields for the two examples reported were 85 and 29%)

(Fig. 89).[4a] Gardner postulated that the net displacement reaction likely proceeded through an *o*-QM intermediate.

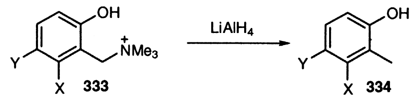


Figure 89.

McLoughlin was among the first to invoke an *o*-QM intermediate to explain the reduction of *ortho*-O-acylated keto aromatics such as **335** (Fig. 90).[93] He speculated that addition of hydride results in a benzyloxyanion that attacks the neighboring acetate. A migration ensues and the resulting phenoxide undergoes a β-elimination thereby producing an *o*-QM that is reduced by a hydride ion to afford the observed product **336**. Yields obtained for this procedure are around 90%.

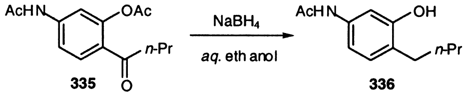


Figure 90.

Minami developed a method for reduction of the salicylic acid **337** to the *o*-methylated phenol **339** in 72% yield overall (Fig. 91).[121] The process requires initial conversion of the acid to the corresponding anhydride *o*-ethyl-carbonate **338**. Subjecting this intermediate to sodium borohydride is believed to initiate a cascade similar to that proposed by McLoughlin.

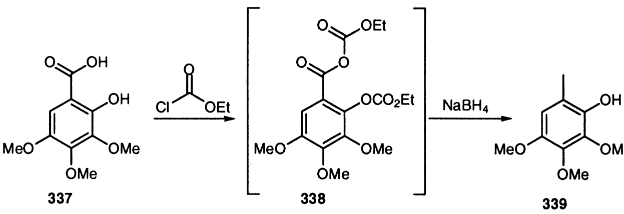
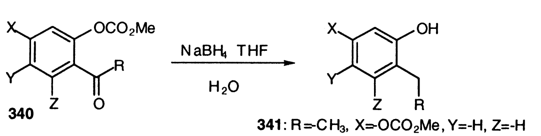


Figure 91.

Mitchell has utilized a similar ploy with *ortho*-O-methyl carbonates of phenones such as **340** (Fig. 92).[94] When these systems are subjected to reduction with sodium borohydride in aqueous THF the corresponding *o*-alkyl phenols **341**–**345** are formed in yields of 76–94%. Substantial water content was found to be advantageous to the reaction and reduced the amount of dimer observed.

Angle has used similar conditions with the tetracyclic ketone **346** (Fig. 93). Exposure of this system to aqueous sodium borohydride in THF affords the phenol **347** in 59% yield.[95d]



341: R=-CH$_3$, X=-OCO$_2$Me, Y=-H, Z=-H
342: R=-CH$_3$, X=-H, Y=-OCO$_2$Me, Z=-H
343: R=-CH$_3$, X=-H, Y=-H, Z=-OCO$_2$Me
344: R=-CH$_3$, X=-OCO$_2$Me, Y=-H, Z=-OCO$_2$Me
345: R=-Ph, X=-OCO$_2$Me, Y=-H, Z=-H

Figure 92.

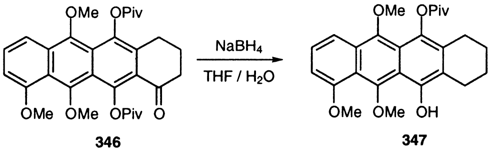


Figure 93.

We have reported that exposure of the *o*-OBOC aryl ketone or aldehyde **348** to sodium borohydride in aqueous THF at room temperature affords the *o*-alkylated phenol **349** in ~80–85% yield by double addition of hydride (Fig. 94). However, the effect of various metal cations on the progression of the cascade was demonstrated and a means to prevent double addition of hydride was developed. Addition of LiAl(O*t*Bu)$_3$H affords the alkoxide **350**, which does not undergo further reaction. The metal alkoxide undergoes dealumination with acid. Upon addition of nucleophiles containing (Mg, K, Na) to the alcohol **351**, the cascade is reinitiated and generates the corresponding *o*-QM, which can be intercepted with a number of nucleophiles including hydride by way of 1,4-conjugate addition.[104a,b]

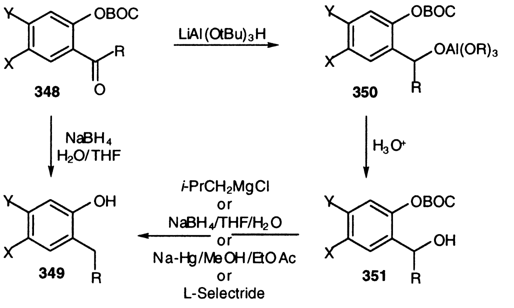
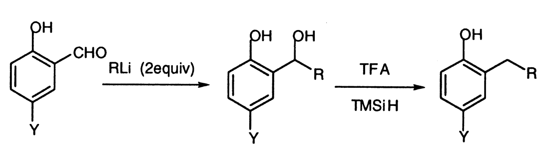


Figure 94.

Swenton has developed a reduction procedure that does not require a protecting group yet most likely still involves an *o*-QM intermediate (Fig. 95).[122] The addition of 2 equiv. of an alkyl lithium to an aldehyde such as **131** results in the alcohol **352**. Exposure of this system to trifluoroacetic acid (TFA) facilitates the formation of an *o*-QM, which under these acidic conditions undergoes 1,4-reduction with trimethylsilane (Me$_3$SiH). The procedure has been used to construct the phenols **353**–**355** in greater then 90% yields.

Borchardt disclosed a four-step procedure for regioselective



131 **352** **353** R=-CH$_3$
354 R=-Et
355 R=-*t*-Bu

Figure 95.

ring C-methylation of phenols. Several of these transformations involve an *o*-QM intermediate (Fig. 96).[123b] The sequence commences with a Mannich reaction of **356** to produce the Mannich base **357**. Acetylolysis of this material affords the bis-acetate **358**, which upon exposure to HCl affords the benzylic chloride **359**. Reduction of this compound at high temperature with $SnCl_2$ affords the *ortho*-methylated material **360** in 85% from the Mannich base without the use of a strong base or hydride reagent and thus without the protection of the aldehyde functionality.

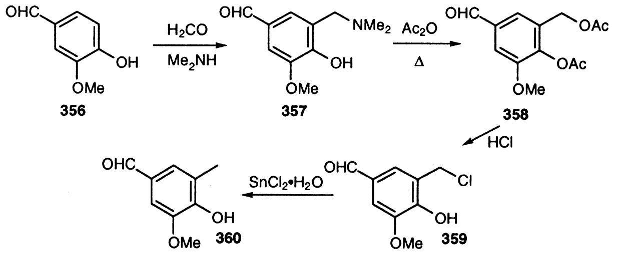


Figure 96.

In a subsequent procedure Borchardt developed a regioselective *p*-methylation of the acid **361** (Fig. 97).[123a] The sequence begins by a regioselective bromination, which is likely assisted by the carboxylic acid to produce **362** in a regioselective manner. The dibromo compound **362** is then subjected to a Mannich reaction to produce **363**. Subjecting this compound to Raney-Nickel under basic conditions results in reduction of the aryl bromides and the amine functionality to afford **364** in 70% yield.

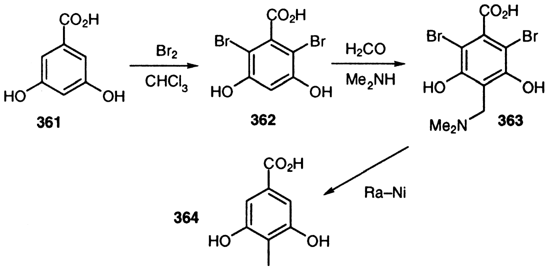


Figure 97.

Chao reported the reduction of Mannich bases such as **365** by heating theses systems to 200°C in neat Bu_3SnH (Fig. 98).[124] Compounds **366**–**367** were prepared in this fashion in good yields (>80%).

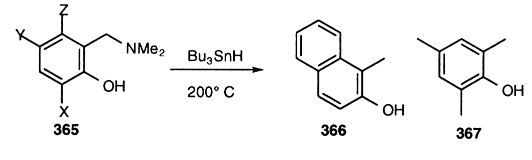


Figure 98.

Lau and Dufresne demonstrated the ability to reduce *o*-QMs generated from benzodioxaborins **368** under Lewis acid conditions (Fig. 99).[17a] In this manner, the *ortho*-alkylated phenols **369**–**372** were produced in yields of 50–98%. Presumably the aluminum trichloride facilitates formation of the *o*-QM, which allows the reductions to be carried out at room temperature. The yields are good, but, the use of *t*-butyl amine borane complex precludes unsaturation in the side chain, while $AlCl_3$ limits the range functional groups that can be expressed by starting materials. However, switching to a Swenton format (R_3SiH, $BF_3{\cdot}Et_2O$) overcomes some of the limitations.

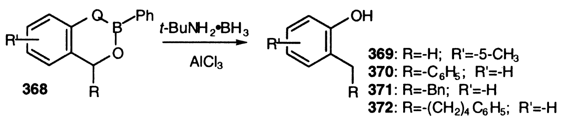


Figure 99.

Katritzky found that benzotriazoles, such as **373**, undergo reduction with lithium aluminum hydride to produce the *o*-alkylated phenols **374**–**376** (Fig. 100).[105c] The reduction is carried out in refluxing THF and the yields range from 50 to 94%.

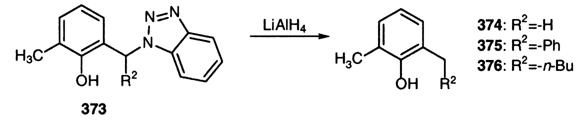


Figure 100.

Kato reported that *o*-hydroxy benzyl chlorides of type **377** undergo reduction with sodium borohydride producing phenols (**378**) in yields ranging from 80 to 97% (Fig. 101).[100] Because the corresponding homologous chloride, lacking an *o*-hydroxy moiety, did not undergo the reduction, the reaction is presumed to involve an *o*-QM intermediate.

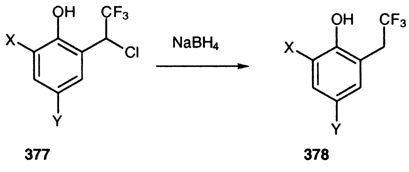


Figure 101.

3.3. Addition of other nucleophiles

Acidic, oxidative and thermal generative conditions inherently pose a number of problems for utilizing the *o*-QM as a conjugate acceptor. First, the range of nucleophiles is limited since these conditions may result in unwanted side reaction with the intended nucleophile. Second, several of these conditions also increase the reactivity of the *o*-QM and thus leads to increased amounts of dimerization. Thus, if these methods are used to trigger the formation of an *o*-QM, it must prove stable towards isolation so that subsequent nucleophiles can be introduced. We speculate this is the reason why *o*-QMs have remained underdeveloped and underutilized intermediates in synthesis.

For example, Brown demonstrated that treatment of the 5-hydroxyflavinoids **379** with acid results in the *o*-QM **380**, which was confirmed by its UV spectra (Fig. 102). Subsequent treatment with sodium benzenesulphinate results in a 1,4-conjugate addition and affords the sulfone **381**.[125]

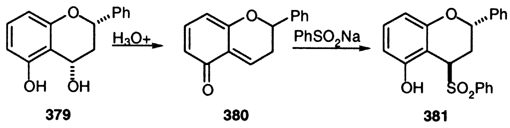


Figure 102.

Angle, studying the chemistry of anthracycline antibiotics, constructed the *o*-QM **383** by oxidation of **382** with Ag_2O (Fig. 103). This *o*-QM, which could be isolated and purified, undergoes conjugate additions with amines, thiols, alcohols, and DNA bases, as expected, resulting in adducts **384**–**387** in 24–63% yields.[95a,c] The low yields in these cases were a result of the adducts being sensitive to chromatography as crude NMR analysis showed yields of greater then 90%.

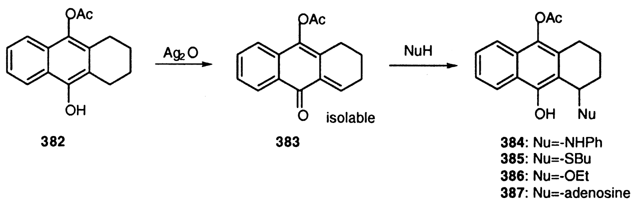


Figure 103.

Using a similar protocol Angle constructed the *o*-QM **388** by oxidation of **347** with Ag_2O (Fig. 104). The nucleophiles used in Fig. 103 undergo reaction with this system as well. Of greater synthetic interest however is its reaction with carbon nucleophiles. The sodium enolate of methyl malonate undergoes reaction with **388** to produce adduct **389** in 57%. Lithium cyanide similarly undergoes reaction with **388** affording the nitrile **390** in 35%.[95d] Both of these sequences would most likely be unsuccessful if the nucleophile were introduced concomitantly with oxidative generation of the *o*-QM.

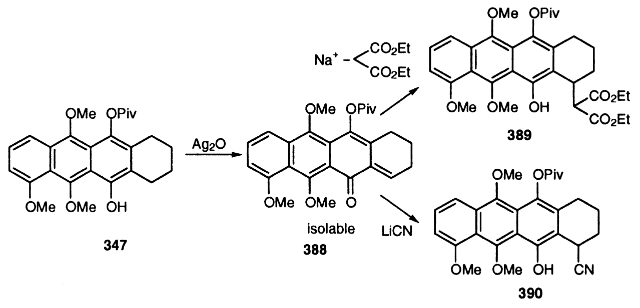


Figure 104.

Exceptions, where the generation method is compatible with the subsequent nucleophile, generally involve specific conditions in which a reagent used to generate the *o*-QM also undergoes reaction with it. Habicher reported one such method. It involves the oxidation of Vitamin E and similar derivatives by Br_2 and subsequent addition of Br^- to the resulting *o*-QM. As a consequence of the Mills-Nixon effect the trimethylated aromatic (**69**) undergoes regioselective oxidation to produce the *o*-QM **70**, which in turn undergoes subsequent addition of HBr to produce the bromide **253** in quantitative yield (Fig. 105).[57a] A free radical mechanism was excluded because of the selectivity observed and the fact that the reaction rate is unaffected when conducted in the dark. Bubbling HCl through the reaction mixture after adding bromine yields the chloride analog of **253** in 82% yield as well as small amounts of the bromide, supporting the view that **70** is an intermediate in this process.

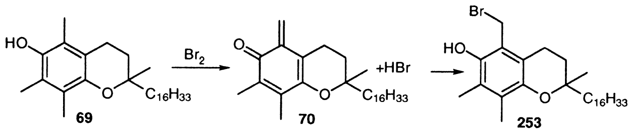


Figure 105.

Lhomme found that treatment of the acetal **392** with acidic methanol produced the methyl ether **393** in 80% yield (Fig. 106).[66] This transformation most likely involves an *o*-QM intermediate generated with acid facilitation and intercepted by the solvent. The identical compound forms upon treatment of the diacetate **321** with methanol and heat. This latter process most likely involves the thermal generation of the *o*-QM, which is then intercepted by the solvent in quantitative yield. The diacetate **321** arises in 95% yield from treatment of **392** with Ac_2O and triflic acid. The acetal **392** is produced in 70% yield by regioselective addition of **391** to formaldehyde. All of these transformations reveal the difficulty of introducing nucleophiles other than those accompanying the generation conditions.

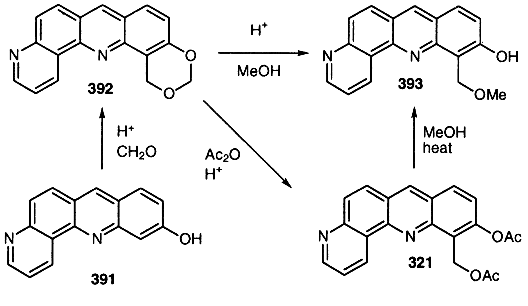


Figure 106.

Lau and Dufresne were among the first to develop a process that allows for the introduction of carbon nucleophiles during the acidic generation of *o*-QMs. The *o*-QM is revealed by treatment of benzodioxoborin **368** with 4–5 equiv. of a Lewis acid such as $BF_3{\cdot}Et_2O$ at 70°C (Fig. 107).[17a,b] Both alcohols and thiols proved to be compatible with protic acid generation of the corresponding *o*-QM from **368** and afforded the respective ethers **396** in 48% yield and thioethers **397** in 29–94% yield. Of greater synthetic potential, however, were the observations concerning carbon nucleophiles. Allylic silanes underwent

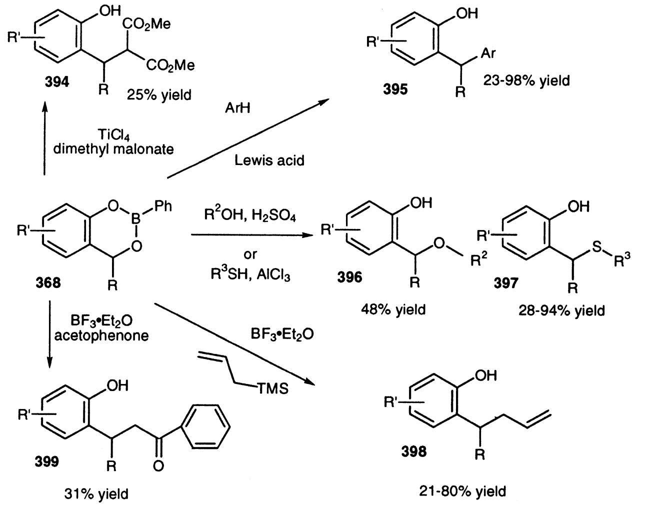


Figure 107.

reaction with the *o*-QMs generated under these conditions to produce ortho-homo allylated phenols such as **398** in good yields (21–80%). *o*-QMs generated from **368** and a Lewis acid underwent reaction with both acetophenone and diethyl malonate to yield adducts **399** and **394** in yields of 31% and 25% respectively. In the presence of very strong Lewis acids, aromatic compounds were found to undergo Friedel–Craft type alkylations to produce the corresponding phenols such as **395** in 23–98%.

Lau and Dufresne extended the methodology to tricyclic benzodioxaborins, such as **400** (Fig. 108).[17e] These materials were generated by an intramolecular ring closure of the corresponding meta-alkylated phenol mediated by $PhB(OH)_2$. The cyclization was relatively efficient for smaller ring sizes (n=2–4). However, larger rings (**400**, $n \geq 5$) could not be generated. These tricyclic benzodioxaborins, however, proved to be useful *o*-QM precursors and upon the addition of boron trifluoride undergo reactions with various allyl silanes (**401**) to form adducts **402–403** (n=4) and **404–405** (n=3) all in greater then 50% yield.

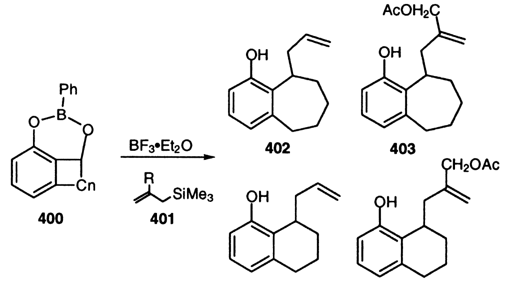


Figure 108.

In regards to base-mediated processes, Cameron reported that primary and secondary amines could induce the tautomerization of *p*-quinones such as **136** into the corresponding *o*-QMs followed by subsequent reaction with these systems to produce phenols such as **406** in ~50% yield.[126] Thomson, profiting from Cameron's and later Jurd's observations regarding base mediated tautomerization of alkyl-substituted *p*-quinones, devised a method for the thiolation of *p*-quinones (Fig. 109).[127] In a solution of a sodium alkyl thiolate, the napthaquinone **136** presumably exists in equilibrium with tautomer **407**. This *o*-QM in turn undergoes a 1,4-conjugate addition under these conditions to produce the hydronapthaquinone **408**. The sequence stops at monothiolation if oxygen is absent from the reaction. However, in the presence of oxygen the phenol **408** oxidizes to the quinone **409**, and the process repeats itself via **410** to produce the bis thiolated *p*-quinone **411**.

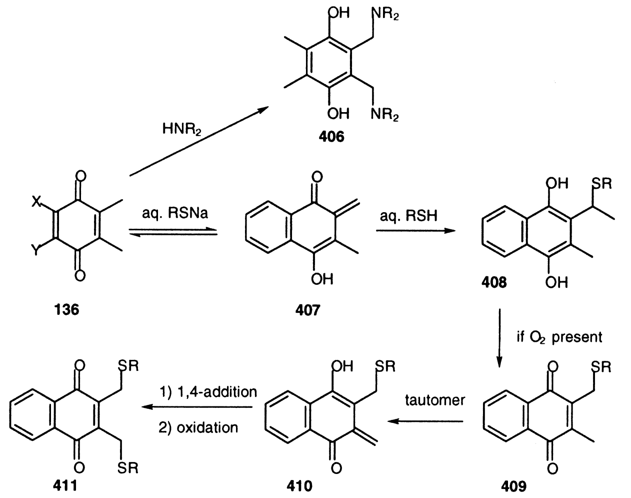


Figure 109.

Habicher demonstrated that the addition of excess TMSCl to *para*-tocopherol quinone **412** leads to the ketal **413** and ultimately, via 1,4-elimination, to the *o*-QM **414**. The *o*-QM undergoes further addition of TMSCl to produce the benzyl chloride **415** in greater then 95% yield (Fig. 110).[57c]

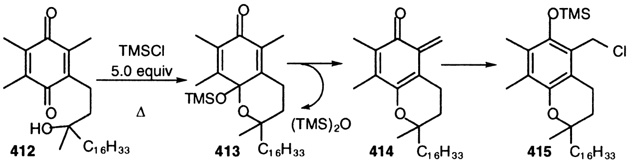


Figure 110.

Gardner was among the first to combine carbon nucleophiles with *o*-QMs under basic conditions (Fig. 111).[4a,e] In a NaOMe solution, **416** (R=H) exists in equilibrium with its corresponding *o*-QM **4** and the *o*-hydroxybenzyl methoxyether **416** (R=Me). If a significant quantity of another nucleophile is present, it can intercept the intermediate *o*-QM and afford a new product. For example, addition of NaCN/NaOMe to **416** affords **417** in 78% yield, while addition of $CH_2(CO_2Et)_2$ in NaOEt yields the diacid **418** after saponification of the corresponding diester intermediate with KOH in 46% yield. If no nucleophile is available, however, the intermediate *o*-QM tends to undergo reaction with the starting *o*-hydroxybenzyl methoxyether resulting in

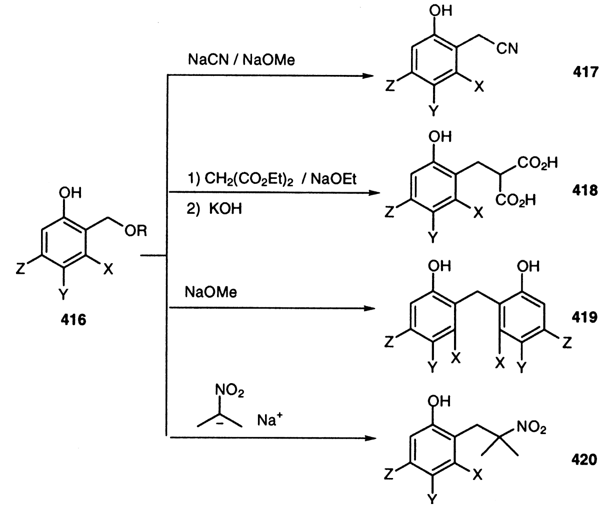


Figure 111.

the dimer **419**, which was isolated in 31% yield. In a related study, Renger finds that addition of the sodium salt of 1-nitropropane to **416** (R=–H) furnishes phenols of type **420** in approximately 50% yield.[128a] Surprisingly, the corresponding Mannich bases (**102**, Fig. 25) fail to undergo this reaction, as do the corresponding ammonium salts (**103**, Fig. 25). The only shortcomings for these equilibrium dependent procedures are: (1) the tolerance of functional groups elsewhere in the system towards these caustic conditions, (2) the inability to address the incorporation of other substituents on the benzylic carbon atom (i.e. reactions involving β-substituted *o*-QM) and (3) the propensity towards dimerization.

Murphy has noted intramolecular cyclizations of aryl-substituted phenols that probably involve *o*-QM intermediates (Fig. 112).[26a,b] Treatment of the triol **421** (*n*=1) with EtMgBr in results in the formation of **422** in 71% yield. Less then 1% of the regioisomer **423** is observed. A potential explanation for the high regioselectivity is chelation between the magnesium phenoxide and the oxygen of the *o*-QM intermediate. Regioselective closure has also been observed during the formation of larger rings (*n*=2), however, to a lesser extent. Compound **424** predominates **425** in an 88:12 ratio with an overall yield of 90%. Surprisingly, lithium and sodium bases proved ineffective for initiating this type of intramolecular cyclization. Proof for the intermediacy of an *o*-QM was demonstrated by a trapping experiment with EVE to produce **420**, however, the relative stereochemistry in this cycloadduct was not assigned.

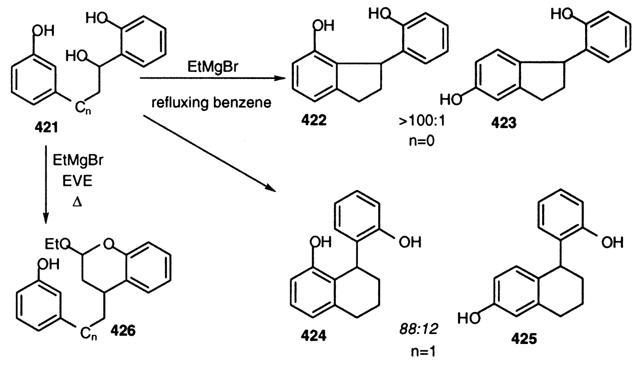


Figure 112.

Decodts reported that the *o*-hydroxymethyl phenol **427**, the Mannich base **428**, and the halide **429** all undergo thermal promoted reactions with the indole **430** to produce the corresponding *o*-indolemethyl phenol **431** (Fig. 113).[64b] Yields for this procedure ranged from 60 to 85% with a few examples under 50%. In general, the *o*-hydroxymethyl phenols and benzyl halides proved to be more effective as the *o*-QM precursor for this transformation. Mono substituted indoles at the 3-position undergo the addition at the 2-position while 2,3-disubstituted indoles undergo reaction at the nitrogen atom.

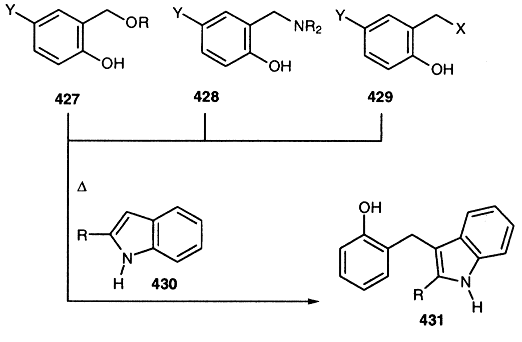


Figure 113.

Ogata constructed the benzylic imidazoles **433** and **435** by subjecting the phenol **226** to N,N-carbonyldiimidazole (**432**, X=O), or *N*,*N*-thionyldiimidazole (**432**, X=S) in the case of **433** and the thionyl reagent **434** in the case of **435** (Fig. 114).[92] The yields were approximately 50% for this procedure.

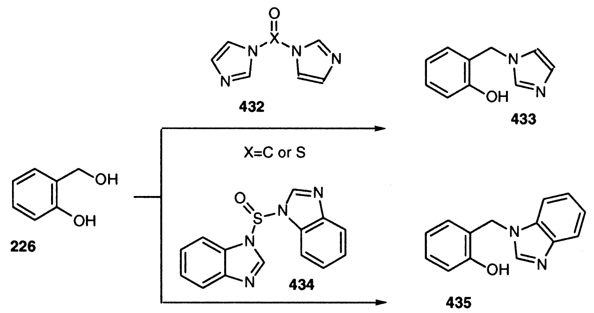


Figure 114.

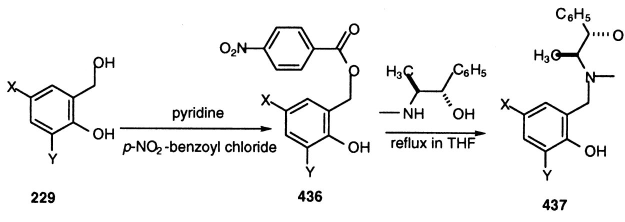


Figure 115.

Corey found that acylation of **229** with *p*-nitrobenzoyl chloride and pyridine affords the acylated benzyloxy compound **436** (Fig. 115). Exposure of this material to 2 equiv. of *N*-methyl ephedrine produced the amine **437** in 77% yield, which can serve as a chiral ligand for the addition of dialkyl zinc reagents to some aromatic aldehydes.[129]

Loubinoux reported that the acetate **149**, obtained in a rather circuitous manner, undergoes addition with amines, thiols alcohols, and enolates to produce adducts **438–444** in yields of 55–98% (Fig. 116).[96]

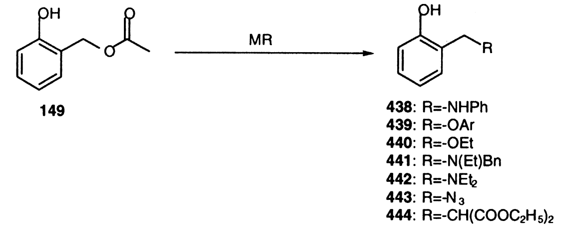


Figure 116.

Fisher observed similar transformations with anthracycline glycosides, such as 11-deoxydaunomycin **445**, while researching the mode of action of these cancer agents. The corresponding hydroquinone **446** of this system, produced in situ via enzyme-catalyzed reduction, eliminates the glycoside to form the *o*-QM **447**, which undergoes reaction with potassium ethyl xanthate to generate **448** in 87% yield upon in situ oxidation (Fig. 117).[101]

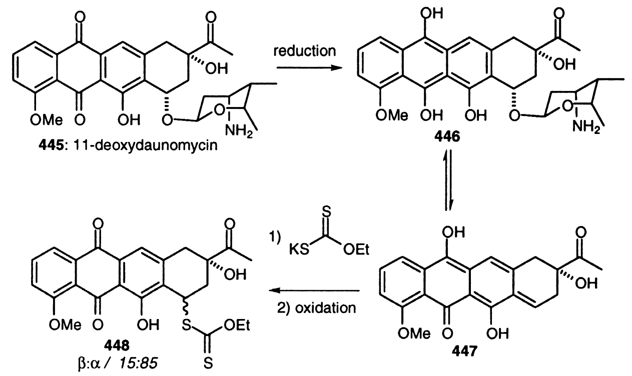


Figure 117.

We found that the addition of Grignard reagents to t-butyl carbonate protected salicylic aldehyde derivatives (**176**) results in the formation of an *o*-QM, which undergoes subsequent 1,4-addition with an excess of the Grignard reagent to afford compounds such as **450–452** in yields of 86–97% (Fig. 118). Furthermore, the addition of a second separate nucleophile was demonstrated. If the first nucleophile is added as the corresponding lithium species then the *o*-QM does not form. However, upon subsequent addition of an organomagnesium reagent, the *o*-QM forms and undergoes subsequent 1,4-conjugate addition. In this manner adducts **453–459** are prepared in 50–86% yield.[104a,b]

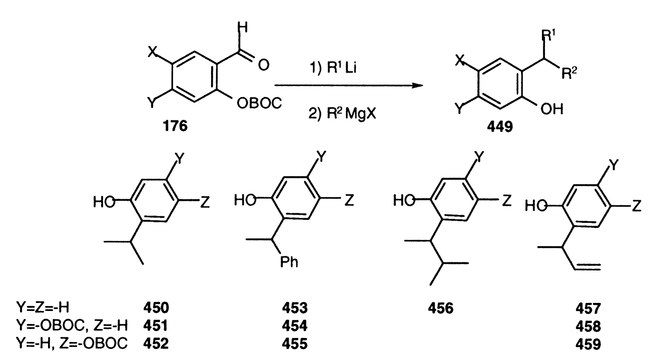


Figure 118.

Pettus further showed that non-branched systems could be constructed from the corresponding alcohol **178** by addition of >2.0 equiv of a magnesium, sodium, or potassium species (Fig. 119).[104a,b] In this manner adducts **460–468** were constructed in respectable yields (52–88%) (Fig. 119).

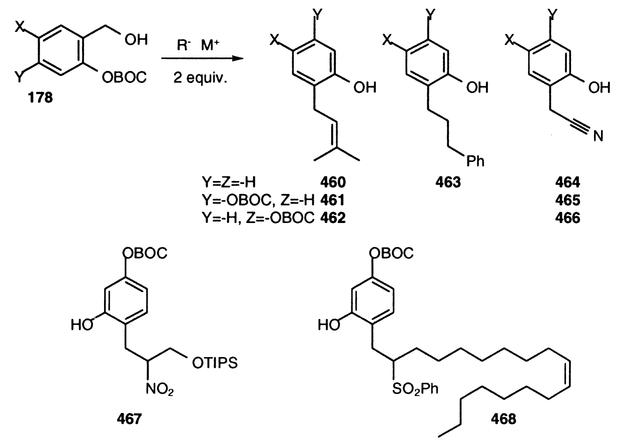


Figure 119.

Kato recently reported a procedure for generating 1-trifluoromethylalkylphenols such as **469** in 70–90% yield from the corresponding chloride derivative **377** (Fig. 120).[100] The Grignard reagent most likely serves as a base to generate the *o*-QM by elimination of the chloride and it then intercepts the *o*-QM by 1,4-addition.

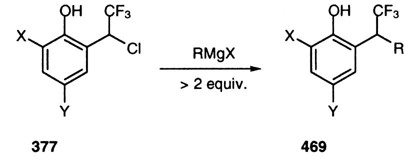


Figure 120.

Habicher has reported a similar process involving the brominated vitamin E derivative **253**. Under basic conditions this compound undergoes 1,4-addition with ascorbic acid (vitamin C) to produce the ether **472**, which he named 'vitamin CE' (Fig. 121).[57b] The coupling reaction was very sensitive to its conditions. If the reaction were too basic then

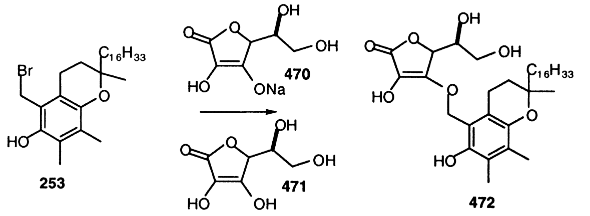


Figure 121.

the resulting high concentrations *o*-QM result in its dimerization. A mixture of sodium ascorbate with a tenfold excess of ascorbic acid in DMSO was found to be optimal, leading to 'vitamin CE' in greater than 90% yield.

Nakanishi confirmed that Koshland's 2-hydroxy-5-nitrobenzyl bromide **152** (X=Br), often referred to as (HNNB), undergoes reaction with tryptophan to produce the tricycle compound **474** in 70% yield (Fig. 122).[130] The indole, which is fairly basic, likely facilitates the formation of the *o*-QM by β-elimination of the bromide and then intercepts it by undergoing reaction as an enamine. Cyclization of the primary amine on the resulting iminium ion affords the third ring.

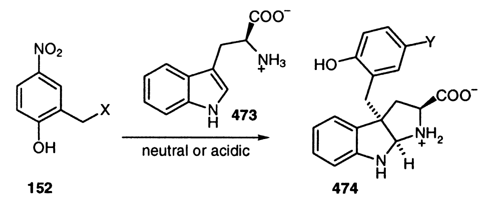


Figure 122.

Gardner reported the alkylation of quaternized *o*-phenolic Mannich bases such as **475** with various active methylene compounds under base mediation (Fig. 123).[4a] The nitrile **417**, β-ketoester **476** and the β-keto nitrile **477** emerge as expected. Balasubramanian, however, reported that addition of $PhSO_2CH_2C(O)Ph$ to **475** under base mediation affords the unsubstituted sulfone **480** directly.[131] In this case it appears that after 1,4-addition the resulting phenoxide adds to the aryl ketone and that this anionic intermediate **478** collapses to give the benzoylated phenol **479**. Saponification of the benzoylated phenol with the remaining NaOMe results in the ultimate isolation of the phenol **480** in yields ranging from 40 to 50%.

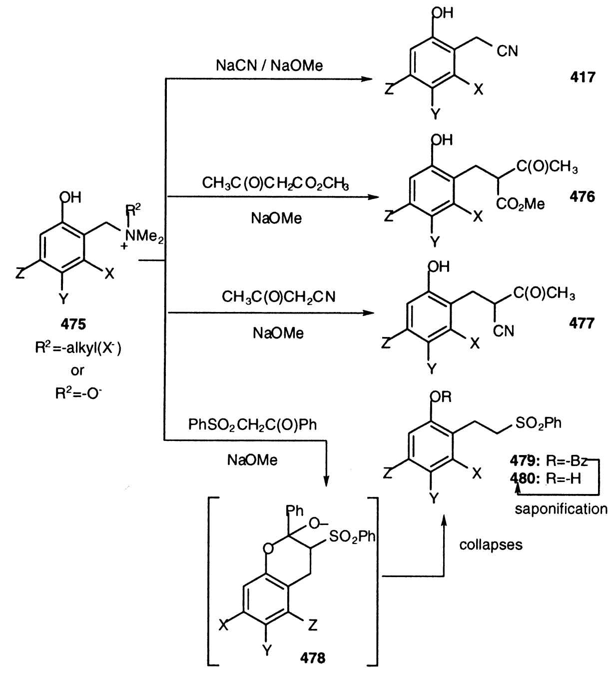


Figure 123.

Sharma, using a Mannich reaction of phenol **160**, produced a 6:1 ratio of **481** and **482.** Acetolysis of this mixture with Ac_2O in refluxing toluene affords the bis acetate **162** and tris acetate **483** in greater then 80% yield, presumably via addition of acetic acid across the *o*-QM generated from **481** and **482** respectively (Fig. 124).[132] Crisp investigated the acetolysis of similar Mannich bases.[133]

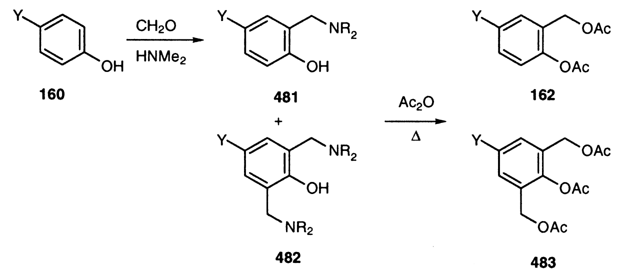


Figure 124.

Young developed an interesting method for preparing polycyclic heteroaromatic compounds such as **486–488** from the Mannich bases of the β-napthol **270** (Fig. 125).[134] The procedure entails *ortho*-C-addition of aniline derivatives such as **484** to the *o*-QM generated from **270** under thermal conditions Prolonged heating of the initial 1,4-addition adduct **485** results in an intramolecular cyclization of the amine to the adjoining phenol expelling water and generating the corresponding polycyclic heteroaromatic compounds. The process affords **394–396** in yields of better than 50% Attempts to extend this method to monocyclic quinone methides led to only 7% of the desired acridine.

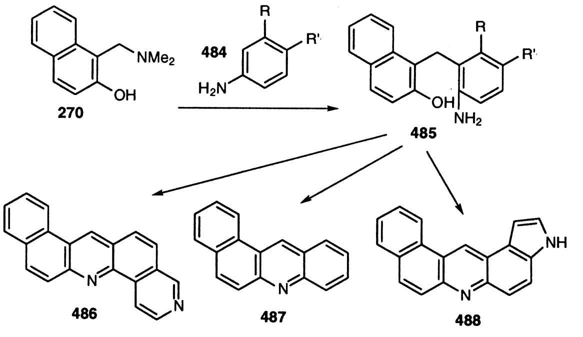


Figure 125.

Pernak has observed an Arbusov like reaction with the *o*-QM that is generated from the quaternary amine **489** (Fig. 126).[135] Addition of triethyl phosphite affords the phosphate ester **490** in 65–80% yields.

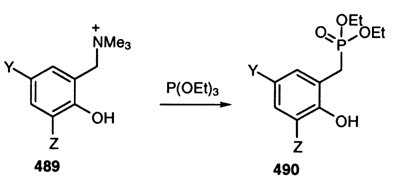


Figure 126.

Katritzky found that benzotriazole derivatives of **373** undergo addition with an excess of various Grignard reagents to afford the corresponding phenols **491–494** (Fig. 127).[105c] The first equivalent of the Grignard deprotonates the phenol, causing a 1,4-elimination of the benzotriazole thereby providing the *o*-QM intermediate. Conjugate addition of a second equivalent of the Grignard reagent with the *o*-QM results in the corresponding phenol. However, when R^2=H in **373** the reaction requires vigorous conditions and proceeds in lower overall yields. For example, refluxing **373** (R^2=H) with the respective Grignard reagent in toluene, leads to **491** and **492** in yields of less than 50%, while a more substituted derivative (**373**; R^2=Me), affords **493** and **494** at refluxing THF temperatures in yields of 80% and 66%, respectively.

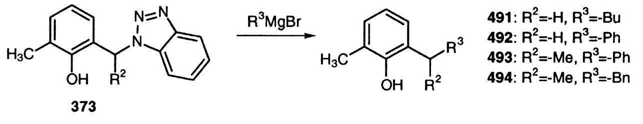


Figure 127.

3.4. δ-Lactone formation

Three methods have been developed for the construction of δ-lactones via *o*-QMs.

Bestmann and Lang reported a double addition of ester stabilized phosphonium ylides to symmetric *o*-quinones such as **186** (Fig. 128).[136] The first equivalent generates an *o*-QM intermediate, which subsequently undergoes 1,4-addition with the second equivalent. Cyclization of the resulting phenoxide leads to intermediate **495**. Elimination of triphenyl phosphine oxide and hydrolysis of the resulting ketene acetal delivers the phenanthropyran-2-one, **496** in yields ranging from 46 to 85%. Nicolaides and El-Kateb have observed similar behavior with other types of symmetric *o*-quinones.[137,138]

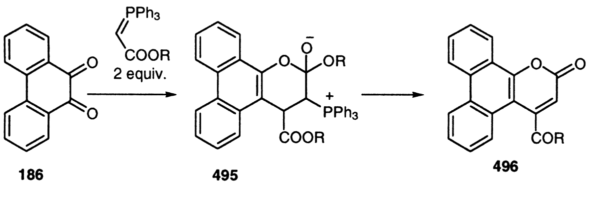


Figure 128.

Pettus constructed the δ-lactone **497** by the sequential addition of a Grignard reagent (PhMgBr) to the aldehyde **176** followed by the addition of the sodium enolate of dimethyl malonate (Fig. 129). This protocol leads to the substituted lactone **497** in yields of 62–73%.[104b]

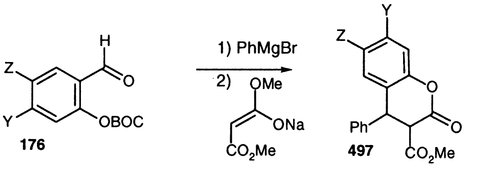


Figure 129.

3.5. γ-Lactone and furan formation

Tolmach devised a concise synthesis of the *o*-benzofuran substituted phenol **500** (Fig. 130).[139] Treatment of **498** with DCC is believed to result in an *o*-QM that undergoes intramolecular 1,4-conjugate addition with the adjacent phenol to produce intermediate **499**. Subsequent in situ elimination of the benzylic hydroxyl produces **500** in 47% yield.

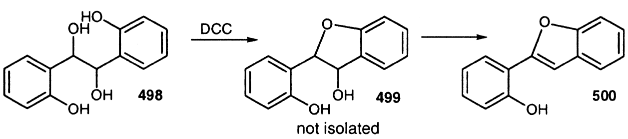


Figure 130.

Shechter[108] and Nicolaides[137] reported that addition of 2 equiv. of various non-stabilized phosphonium ylides to the *o*-quinone **186** produces derivatives of the tetrahydrofuran **502** (Fig. 131). The first equivalent generates an *o*-QM intermediate that undergoes subsequent reaction with the second equivalent, generating intermediate **501**. This compound in turn undergoes a S_N2 displacement to yield the corresponding furan **502**. Yields for this procedure range from 46 to 86%.

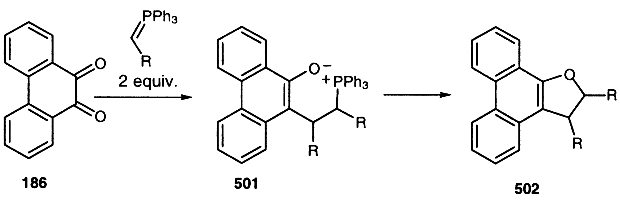


Figure 131.

Miura observed palladium-mediated carbonylation of *o*-QMs at elevated temperatures resulting in the formation of γ-lactones (Fig. 132). The sequence entails formation of an *o*-hydroxybenzyl alcohol **504** via condensation of the phenol **503** and aldehyde upon the addition of acid. That intermediate likely forms the *o*-QM **505** under acidic conditions and then undergoes Pd° mediated carbonylation resulting in **506** that subsequently undergoes a reductive elimination producing lactones **507–509** in approximate yields of 50%.

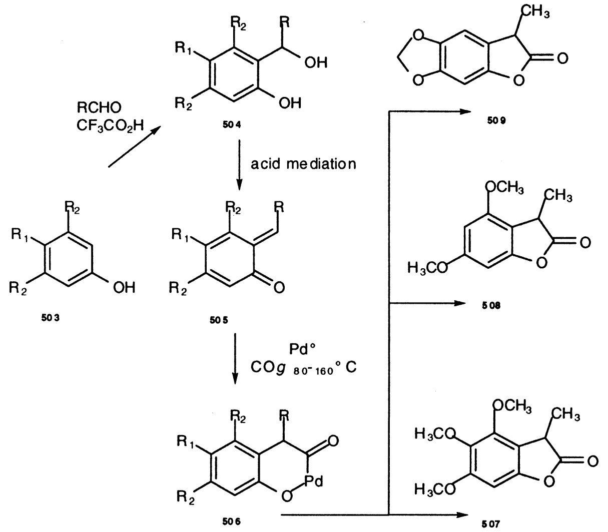


Figure 132.

Breuer reported formation of benzohydrofurans **511–513** in approximately 50% yields upon the addition of dimethylsulfoxonium methylide to the quaternary amine salt **510** in DMSO (Fig. 133).[70] The process most likely follows a pathway resembling the addition of non-stabilized phosphonium ylides to *o*-QMs discussed previously.

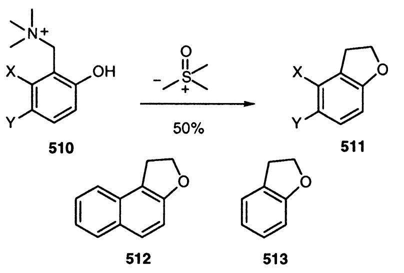


Figure 133.

Fanghänel reported the synthesis of benzohydrofurans **517–519** in yields of 65–86% by the addition of the enolate of 2-chloro-1,3-dicarbonyl derivatives to quaternary amine salts such as **515**, which can be constructed from the benzyl chloride **514** by the addition of triethyl amine (Fig. 134).[140]

Bladé-Font investigated the addition of diazomethane and dimethylsulphoxonium ylide to the *N*-oxide **520** to produce benzohydrofurans of type **521** in yields of 53–97% (Fig. 135).[141] N-oxides typically required more vigorous conditions (refluxing THF) than the corresponding quaternary amine salts (30–50°C) The dimethylsulphoxonium methylide consistently gave higher yields than diazomethane.

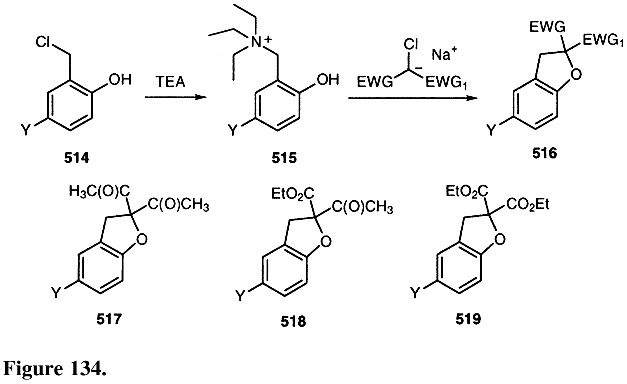


Figure 134.

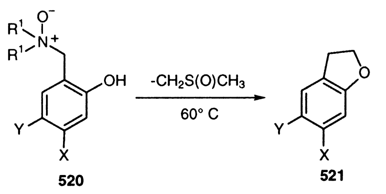


Figure 135.

3.6. Net [4+4] reactions

A net [4+4] dimerization has been observed by Soucek with *o*-hydroxyaryl(diaryl)methyl chlorides such as **522** in yields of 78–92% (Fig. 136).[7b] The dimerization, which leads to adducts such as the dioxins **523** and **524**, is facilitated by addition of triethyl amine or the polymeric base DEAE. The pathway is believed to entail a step-wise ionic cyclization.

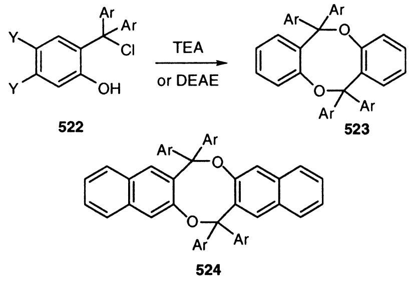


Figure 136.

3.7. Rearrangements

o-QMs predominately undergo two types of electrocyclic rearrangements. The most common are a $2\pi+2\pi+2\pi$ electrocyclization and a $2\pi+2\pi+2\sigma$ 1,5-hydride shift.

Wan observed that irradiation ($\lambda=254$ nm) of biaryl phenols, such as **525**, produced the pyran **527** (Fig. 137).[83d,g] The presumably intermediate *o*-QM, **526**, was not observable by laser flash photolysis due to the rapid electrocyclization reaction pathway. The reverse reaction results when the pyran is irradiated ($\lambda>350$ nm) in a MeCN/H_2O solution. Schuster investigated the photochemistry of **525** and **527** in order to assess its suitability as a photochromic optical trigger.[142]

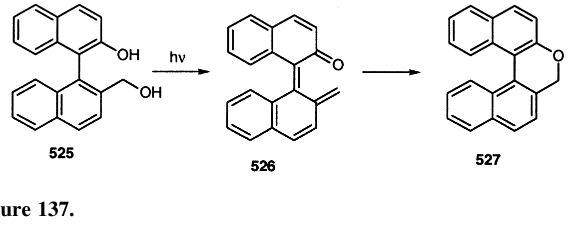


Figure 137.

Padwa has found that irradiation of the lactone **528** in methanol affords the *o*-QM **529**, which undergoes electrocyclization to the xanthane **530** (Fig. 138).[81] The electrocyclization is the minor reaction pathway with most of the *o*-QM generated adding methanol to form the corresponding ether. However, more of the xanthane can be obtained with extended reaction times as the derived ether reforms the *o*-QM with irradiation.

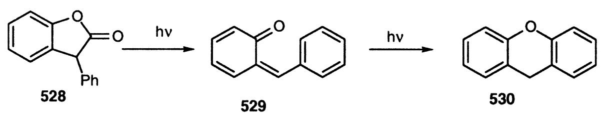


Figure 138.

Jurd demonstrated that **531** yields the *o*-QM **532** upon oxidation with Ag_2O. Because of extended conjugation this *o*-QM is isolable. In refluxing benzene, it exist in equilibrium with its geometrical isomer **533**, which undergoes electrocyclic cyclization to produce the pyran **534**.[49b] Acid catalysis allowed the cyclization reaction to occur at room temperature in 90% yield, presumably by facilitating the geometrical isomerization (Fig. 139).

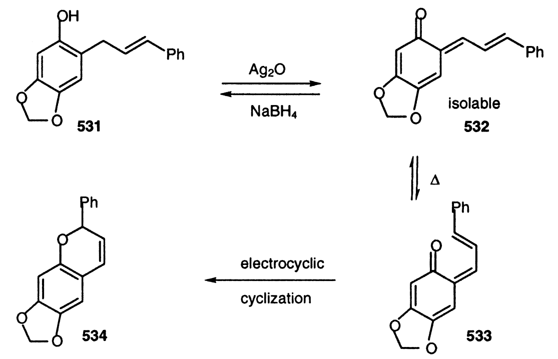


Figure 139.

In a similar example, Trivedi showed that silver oxide was an effective oxidant for the generation of *o*-QMs **536** from sasfrole **535** (Fig. 140).[21] This *o*-QM undergoes isomerization to **537** followed by a subsequent electrocyclization to produce **538** in 80% yield.

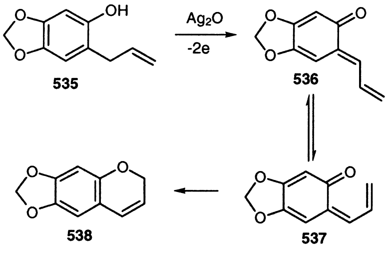


Figure 140.

A careful review of *o*-QMs shows an absence of examples where the methide portion is disubstituted with alkyl residues. The reason for this oversight is the speed with which 1,5-sigmatropic shifts occur on a structure such as **539** resulting in the styrene **540** (Fig. 141).

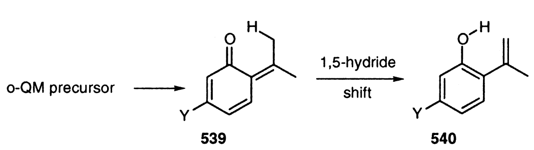


Figure 141.

The only reaction of which we are aware that is competitive with a 1,5-hydride shift was developed by us (Fig. 142). The addition of excess methyl Grignard to either the t-butyl carbonate acetophenone **541** or the mixed anhydride **544** yielded the corresponding *ortho*-*t*-butyl phenols **543** in yields of 75–90%.[104a,b] In this case, the disubstituted *o*-QM **542** formed has a long enough lifetime to be trapped with another equivalent of the Grignard reagent before a sigmatropic shift that results in the styrene **545** can occur. Reactions conducted with less than the require amount of Grignard reagent did indeed result in sizable amounts of the styrene **545**.

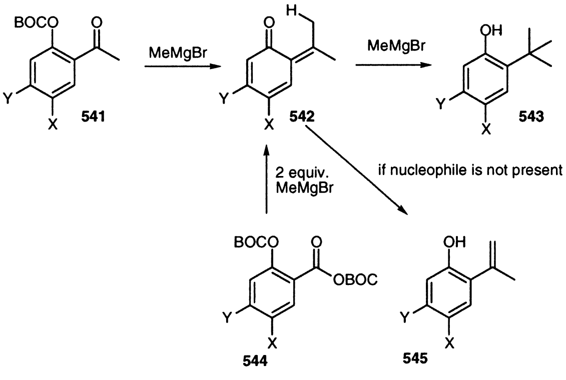


Figure 142.

Longridge has observed a different kind of intramolecular hydride delivery (Fig. 143).[143] Under acidic conditions, compound **546** undergoes standard acetal hydrolysis to yield the expected triol. However, under basic conditions, initial 1,4-elimination occurs to yield the *o*-QM **547**. An internal hydride delivery ensues to produce the ester **548**, which undergoes further hydrolysis to the corresponding diol.

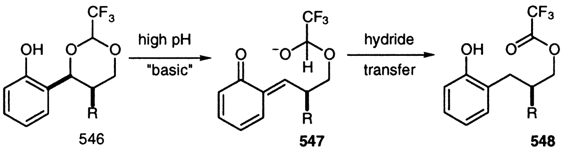


Figure 143.

3.8. Photochemical reactions

Beyond just initiating the formation of *o*-QMs, excitation with light can also change the reaction pathway available to the *o*-QM intermediate. Reactions, which are not possible thermally, have been induced using UV radiation.

Ettlinger observed that the hydroxynaphthaquinone **116** oxidizes to the ketone **549** when a wet ether solution is exposed to light (Fig. 144).[79] The mechanism was postulated to involve photochemical induced tautomerization to the corresponding *o*-QM, which then undergoes allylic oxidation with molecular oxygen to produce **549**. This intermediate is postulated to undergo a 1,5-hydride shift to yield the enol of **550**, which hydrolyzes with water to produce ketone **550**. Creed has isolated allylic peroxides similar to **549**.[80] His results indicate that perhaps the light is only necessary for excitation of the molecular oxygen.

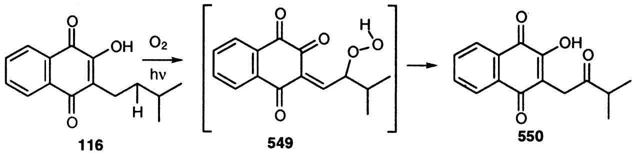


Figure 144.

While investigating the photochemistry of enols, Padwa observed that irradiation of **551** in benzene results in formation of the cyclopropane **553** as the only product formed (Fig. 145).[81c] He suggests that the *o*-QM **552** may be an intermediate in this transformation.

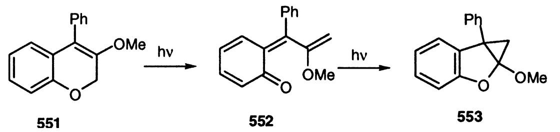


Figure 145.

Bos[109] and Adam[58c] independently investigated the photochemistry of β-disubstituted *o*-QMs such as **554** (Fig. 146). Both find that irradiation of the *o*-QMs **554** results in the cycloheptatrienes **558**, presumably through the intermediate norcaradiene **557** shown, which likely forms via the biradical **556**. Interestingly, when **554** is heated an electrocyclization occurs to provide the xanthane **559**, demonstrating yet again the apparent fluxional nature of the olefin geometry in *o*-QMs. Since the cycloheptatriene was ultimately shown to transform into the xanthane **559** upon heating, the photochemical process is presumed to be thermally reversible.

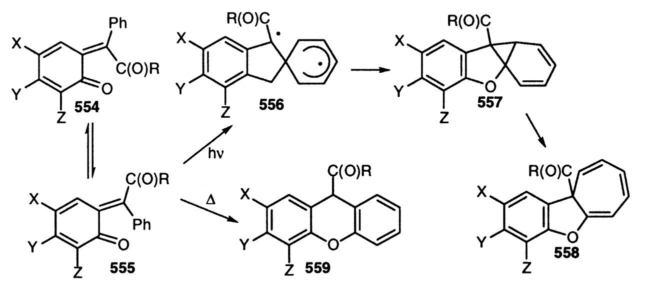


Figure 146.

Sheridan[89] studied the photochemistry of 2-benzylfuryl-chlorodiazirine **125**, which was isolated in a nitrogen matrix at 10 K (Fig. 147). He found that irradiation at 433 nm resulted in the formation of the carbene **126**. Brief irradiation at 313 nm then resulted in the formation of the Z-configured *o*-QM intermediate **127**. Compound **127** can be transformed into the allenic didehydrobenzopyran **560** or the benzocyclobutadinyl acyl chloride **561** depending on the wavelength used for irradiation.

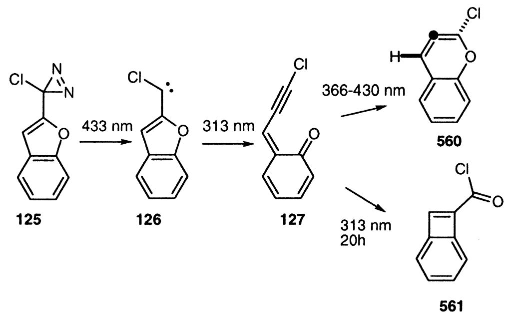


Figure 147.

4. Conclusions

Over the past century, chemists' perspectives of *o*-QMs have evolved from the idea that these species are just a curiously reactive intermediate to the notion that these species may be of some synthetic use. Several *o*-QM precursors in particular have begun to harness the synthetic potential of these highly reactive intermediates. The Katritzky, Lau–Dufresne, and Pettus procedures for the generation of *o*-QMs and their subsequent reaction with nucleophiles have led to a variety of aromatic phenols in an efficient manner. *ortho*-Functionalized phenols, benzopyrans and α-branched *o*-alkylated phenols can be obtained in respectable yields. In addition, the Chiba and Sato procedures for chroman synthesis have proven useful with unactivated alkenes, leading to products not readily obtained with other *o*-QM methods. With these new *o*-QM generation strategies, it appears that these species will find new application in the synthesis of a variety of complex natural products.

4.1. Syntheses of *o*-alkylated aromatics

For example, consider the synthesis of various *o*-alkylated phenols such as **565** from phenol **113** (Fig. 148). The most

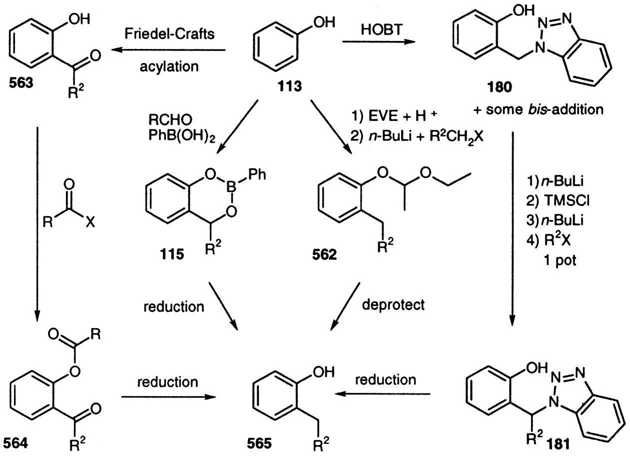


Figure 148.

prevalent route involves a three-step sequence that begins with protection of the phenol with EVE or carbamyl chloride followed by directed *ortho*-lithiation and coupling of the aryl lithium species with an electrophile to produce **562**. This compound, in turn, is then submitted to conditions for deprotection to produce **565**. The Snieckus procedure[144] (or DoM procedure: directed *ortho* metalation), as it has become known, is tremendously useful but has limitations. First, carbamyl protected phenols are prone to Fries rearrangement upon lithiation. Second, rather than acting as a nucleophile, the aryl lithium can act as a base causing the R_2CH_2X fragment to undergo elimination rather than S_N2 coupling. Third, both coupling partners must be tolerant of highly basic conditions. Fourth, deprotonation of electron rich aryl systems (more than one oxygen substituent) can prove problematic. For these reasons, the Katritzky, Lau–Dufresne, and McLoughlin–Mitchell–Pettus procedures can often provide an aromatic system that is inaccessible to the DoM protocol.

The Lau–Dufresne method is the most efficient and atom economical process for producing a phenol such as **565** as it requires only two-steps; however, attendant functional groups must tolerate acidic conditions (Fig. 148). The first transformation involves a $PhB(OH)_2$ mediated aldol of the phenol with an aldehyde to produce the stable and isolable benzodioxoborin **115**. Because the benzodioxoborin **115** is less electron-rich than the starting phenol, the coupling stops after just one substitution of the aromatic ring. Reduction of **115** affords the phenol **565**.

In the case of the Katritzky method, reaction of the phenol **113** with HOBT leads predominately to **180** because of chelation (Fig. 148). However **180** is slightly more reactive and some bis-addition is observed. Deprotonation of **180** with n-BuLi (1 equiv.) and in situ protection of the phenol as the corresponding TMS ether is then followed by a second deprotonation and reaction with an electrophile affording **181**. This compound can then be subsequently reduced to **565**. Although the procedure at first glance may appear to resemble the Snieckus DoM protocol, the Katritzky process would facilitate the functionalization of many electron rich phenols that would prove resistant to the DoM process.

The McLoughlin, Mitchell and Pettus reduction protocols are useful for producing *ortho*-functionalized phenols such as **565** provided that the corresponding aryl ketone **565** is readily accessible (Fig. 148). Many are commercially available or readily obtained by Friedel–Crafts acylation of phenols. Subsequent *o*-Acylation of the phenolic hydroxyl group followed by reduction affords the corresponding *o*-alkylated phenols **565**.

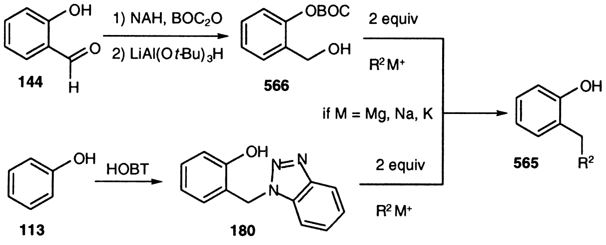


Figure 149.

The Katritzky and Pettus protocols, which begin with the benzyl benzotriazole **180** and the benzyl alcohol **566** respectively, allow for a very mild installation of variety of R^2 substituents (Fig. 149). These *o*-QM precursors can be used for the construction of *o*-allylated phenols, which would have succumbed to 1,6-reduction in the process shown in Fig. 148. Moreover, these processes are very tolerant of sensitive functional groups in the R^2-fragment. Provided the desired salicylic aldehyde such as **144** is available, the Pettus procedure tolerates a variety of functional groups in the aryl portion as well.

4.2. Chroman synthesis

Because they readily lead to chromans substituted at the benzylic position (R_2), the Katritzky, Lau–Dufresne, Pettus, Chiba, and Sato processes represent significant improvements over past *o*-QM generation protocols. In addition, with the exception of the Chiba precursor **97**, the respective precursors **181**, **115**, **144**, and **567** are stable and can be easily purified (Fig. 150). The Lau–Dufresne, Chiba, and Sato procedures, when mediated by $BF_3{\cdot}Et_2O$ or wet montmorillonite, are useful in reactions with unactivated alkenes. However, these reactions can be ionic in character leading to mixtures of diastereomers as well as products from carbocation rearrangements. For more electron-rich alkenes, the Sato protocol utilizing AgO_2 results in benzopyrans with excellent diastereoselectivity. The Pettus protocol, which proceeds at low temperatures, results in impressive *endo*/*exo* selectivity and leads to adducts that are in many cases inaccessible by other methods since these compound undergo rearrangements (cf. adducts in Figs. 66 and 74). Moreover, the Pettus process allows for three fragments to be annealed in one pot, a true multicomponent reaction. Furthermore, the advent of a low temperature protocol certainly argues for the invention of asymmetric procedures implementing non-racemic electron-rich dienophiles as the 2π component in these reactions.

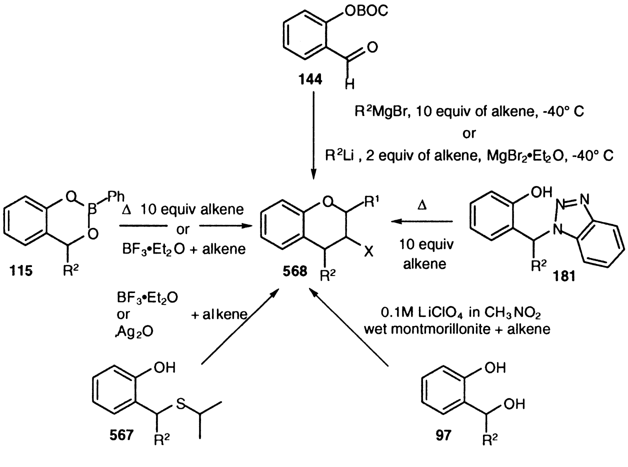


Figure 150.

4.3. Synthesis of α-branched phenols

In regards to the construction of α-branched phenols, the

Lau-Dufresne procedure is limited to allyl silanes and activated methylene compounds (such as malonates) as these nucleophiles are stable to the acidic conditions used to generate the corresponding *o*-QM (Fig. 151). For example, addition of allyltrimethylsilane to **115** in the presence of $BF_3{\cdot}Et_2O$ affords the homo-allylated phenol **569**. Presumably this transformation would proceed in an enantioselective manner with chiral allyl silanes and tin reagents. The Pettus and Katritzky precursors **144** and **181**, on the other hand, could lead to a non-racemic product by application of organometallic reagents in the presence of a chiral ligand such as ephedrine.

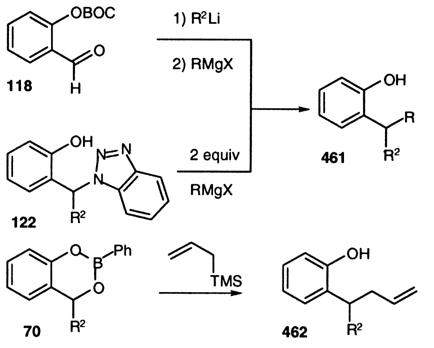


Figure 151.

4.4. Future synthetic applications

The importance of developing asymmetric synthetic protocols for use with *o*-QMs is evident in such simple molecular structures as mimosifoliol **571** (Fig. 152).[145] Careful scrutiny of the literature reveals only two asymmetric procedures for installing a non-heteroatom stereocenter alpha to an aromatic ring. Neither is readily amenable to construction of **571**. Using a synthetic strategy that involved an *o*-QM, one could imagine either an asymmetric 1,4-addition to **573** or the conversion of **573** into the chroman **572**, which could then be relayed into **571**.

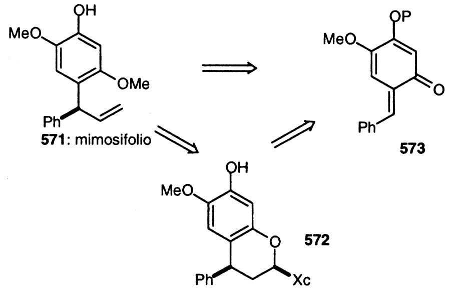


Figure 152.

Even more complex molecules could be envisioned to arise from *o*-QMs. For example, diinsininol **574**[146] might be addressed by addition of the *o*-QM **578** to the enol ether **577**, followed by reformulation of the ketal. Desymmetrization of **576** to **575** and glycosylation completes the synthesis (Fig. 153).

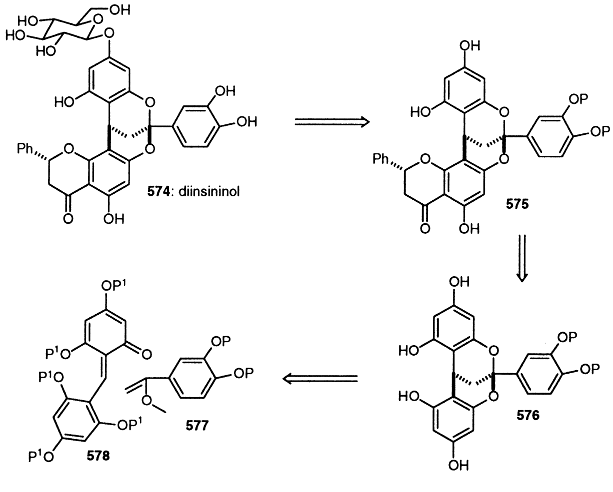


Figure 153.

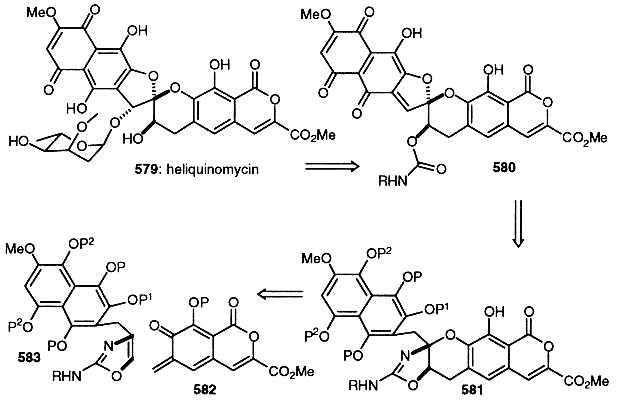


Figure 154.

The cymarose moiety in helioquinomycin (**579**)[147] could, in principle, be attached via the *o*-QM **580**. This species in turn could potentially be formulated from the benzopyran **581**, which in turn might arise from the addition of the *o*-OM **582** to **583** (Fig. 154).

We believe that *o*-QMs possess tremendous potential as intermediate in organic synthesis, and we hope that this discussion has encouraged others to consider application of these highly reactive intermediates in their future synthetic pursuits.

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