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4.28.12.1 Product Subclass 1:

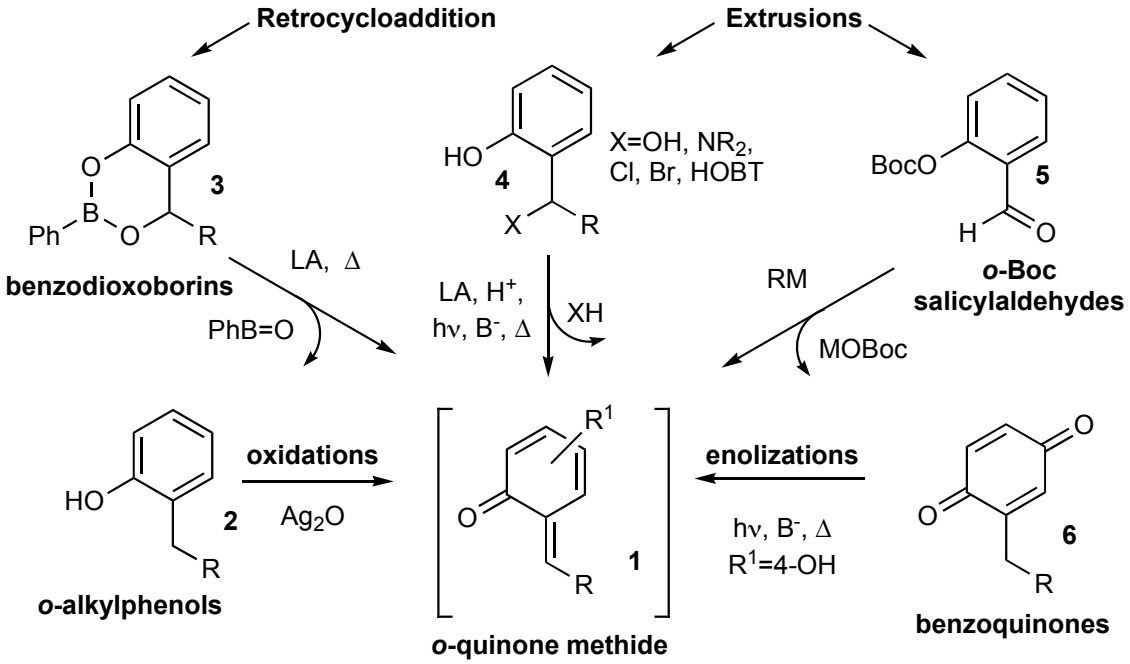
o-Quinone Methide

T. R. R. Pettus and C. Selenski

General Introduction

Unlike *p*-quinone methides (*p*-QMs), *o*-quinone methides (*o*-QMs) are ephemeral intermediates, which typically cannot be isolated. Nevertheless, chemists have harnessed *o*-QMs for sophisticated syntheses, where the *o*-QM is generated and consumed in situ. In these examples the methods used for *o*-QM preparation have profound influences on their subsequent applications. These generation methods include enolization, oxidation, and various extrusion reactions performed under acidic, basic, photochemical and thermal conditions (Scheme 1). Each method for *o*-QM generation poses different problems and displays different synthetic ramifications. New generation techniques commencing in the 1980's exposed a plethora of novel synthetic applications for these venerable intermediates. The syntheses of lucidene (**7**), tanzanene (**8**), hexahydrocannabinol (**9**), and carpanone (**10**) have all utilized a key *o*-QM intermediate (Scheme 2).

Scheme 1 Various Precursors used for *o*-QM Formation



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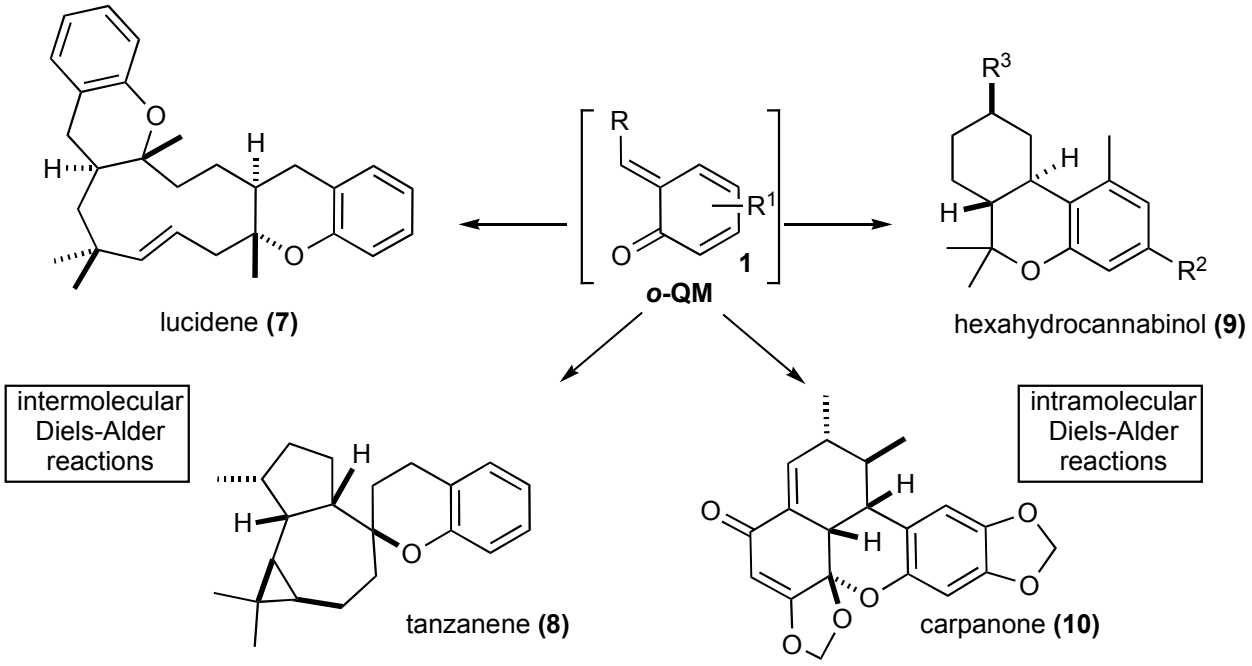
Scheme 2 Natural Product Syntheses utilizing an *o*-QM



When discussing chemistry that involves both the preparation and consumption of a transient species, the existence of that species may be questioned. However, there is an abundance of evidence proving the existence of *o*-QMs from spectroscopic studies and structural identification of their resulting products. In 1907, an *o*-QM intermediate was first proposed to explain the formation of dimers and trimers from a particular reaction.[1] Fifty years later, an *o*-QM generated by pyrolysis of 2-(methoxymethyl)phenol (**11**) (1-5mm, 500-650 °C, quartz tube) at –50°C was collected and spectroscopically analyzed (Scheme 3).[2] Upon warming the liquid pyrolysate **12** to 0 °C the trimer **13** forms in 70% yield. On the other hand, exposure of **12** to cold ethereal lithium aluminum hydride or cold ethereal methylmagnesium iodide affords the *o*-cresol (**14**) or *o*-ethylphenol (**15**), respectively. The starting phenol **11** does not undergo reaction with either cold ethereal lithium aluminum hydride or cold ethereal methylmagnesium iodide.

Scheme 3 An "o-Quinonone Methide"

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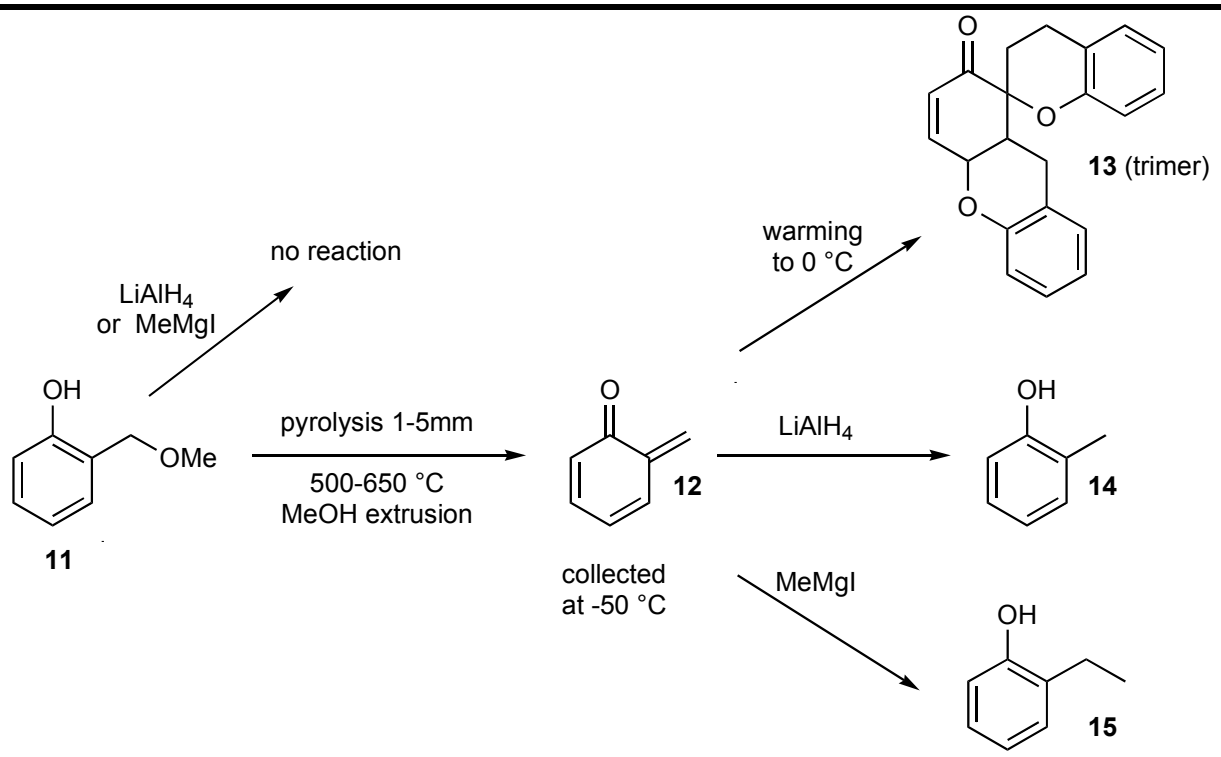

More recently structural elements such as electron-donating groups, heteroatoms, or extended conjugation have been shown to facilitate isolation and characterization of *o*-QMs. In 1996, the first crystal structure of an iridium complexed *o*-QM was reported, not long after, a rhodium complexed *o*-QM was also reported. Interestingly, metal complexation reverses the inherent reactivity of the *o*-QM; the oxygen atom becomes electropositive while the methylene carbon becomes electronegative as demonstrated by the nucleophilic addition of **20** with succinimide **22** to form adduct **23** (Scheme 4). The synthesis of the metal complexed *o*-QM begins by forming the appropriate η^6 metal complex such as **16** or **17** from an *o*-phenol. Upon treatment with base, the corresponding η^5 carbonyl species **18** or **19** are formed respectively. Upon treatment with a stronger base these species afford the corresponding neutral η^4 *o*-QM complexes **20** and **21**.[3]

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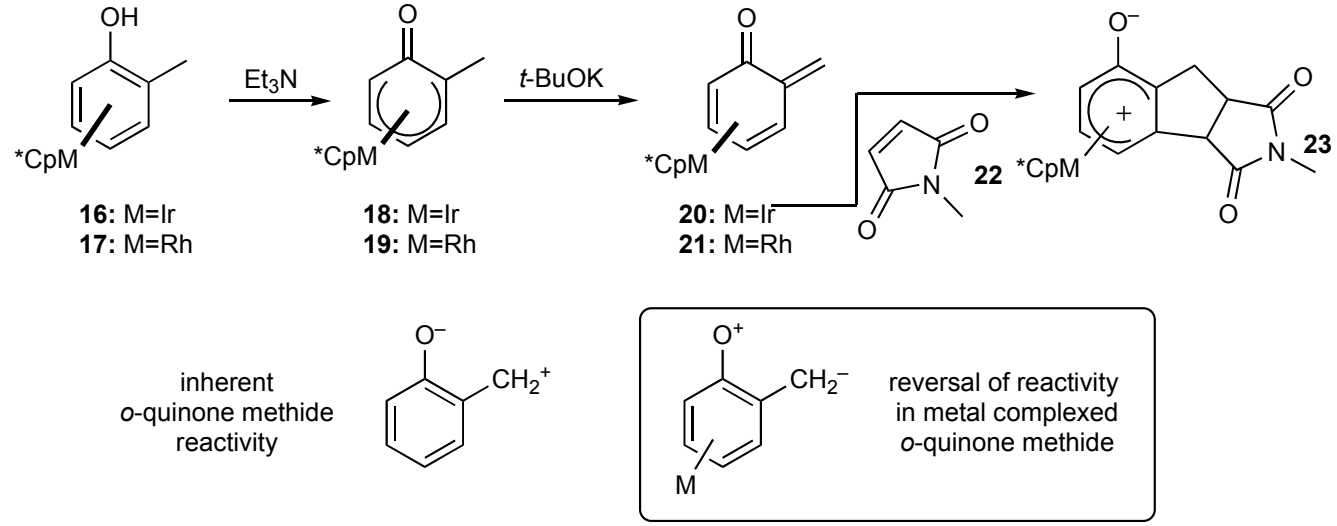
Scheme 4 Ir and Rh Stabilized *o*-QMs



If an alkyl residue is substituted on methylene carbon, then *o*-QMs display *E* or *Z* olefin geometry, which appears to be far more fluxional than traditional enones. The distribution among geometric isomers such as **24** and **25** reflects the energy difference between these conformations. For example, if the R^1 substituent is smaller from a steric standpoint than the carbonyl oxygen of the *o*-QM, then the *E* geometry is preferred. Increasing the size of the R^1 substituent, however, can cause the *Z* geometry to predominate. The equilibrium between isomers were revealed by a deuterium isotope study.[4d] The mobility of the *E* and *Z*-isomers was exploited in the one-pot synthesis of precocene I (**29**). In this synthesis, benzodioxoborin **26** collapses upon heating to give *E* *o*-QM **27**, which is in equilibrium with its minor *Z*-isomer **28**. However, the *Z* *o*-QM undergoes an electrocyclization resulting in precocene I (**29**) (Scheme 5).[5] While the olefin geometry in an *o*-QM can prove somewhat fluxional, in most cases it can be controlled effectively by steric interactions. [4+2] cycloadditions of the equilibrating mixture (**24**-**25**) usually proceed in a diastereoselective fashion provided R^1 and R^2 are of significantly different sizes (–H *vs.* $–CH_3$).

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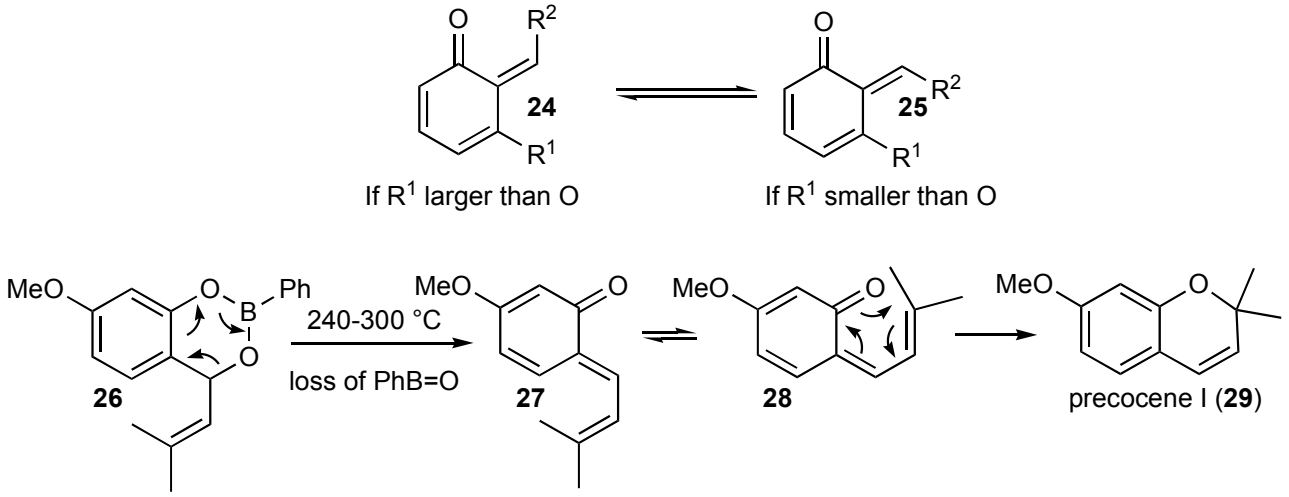
Scheme 5 Fluxional Olefin Conformations of *o-QM*s



SAFETY:

o-QMs are invoked as the bioactive species in many natural products (Scheme 6). Some plants and insects even use *o*-QMs for defense and regulation. Once generated, *o*-QMs can irreversibly alkylate many nucleophiles including essential enzymes and DNA. For example, the bark and leaves of the willow tree contains salicortin, which inactivates β-glucosidase enzymes of the infesting organism via an *o*-QM intermediate.[6] In addition, it has been proposed the anti-tumor qualities of compounds such as daunomycin, adriamycin, and menogaril are due in part to the formation of a reactive *o*-QM intermediate *in vivo* upon bio-reductive activation.[7] The benzoquinones mitomycin C (**30**)[8] and kalafungin (**32**)[9] are believed to be biologically active for similar reasons forming *o*-QMs **31** and **33**, respectively. Therefore, care should be exercised when working with *o*-QMs and their immediate precursors as with any powerful electrophile.

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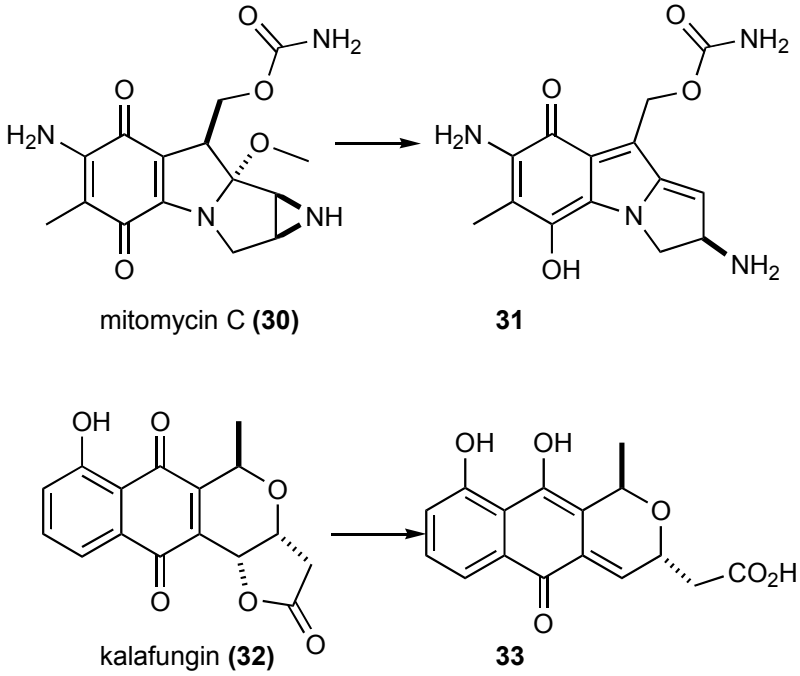
Scheme 6 *o*-QM Formation in Biological Systems



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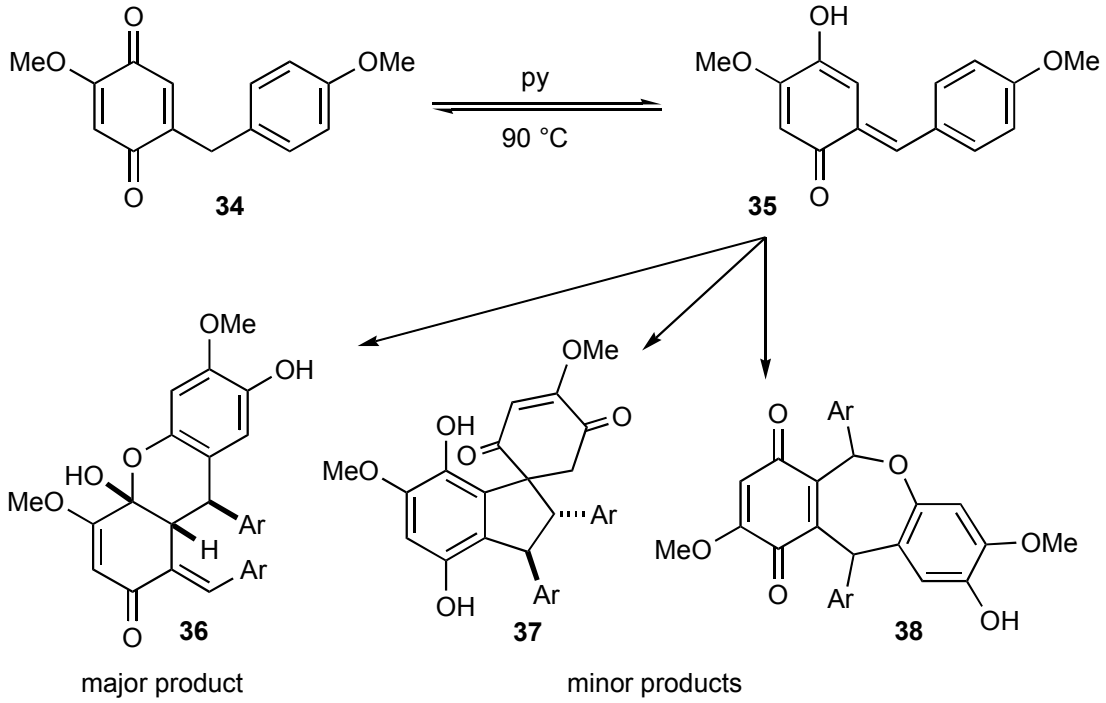
4.28.12.1.1 Method 1: Quinone enolization

4.28.12.1.1.1 Heat assisted quinone enolization

The dimerization of duroquinone in the presence of alkaline reagents was mentioned early in the literature, but the characterization of these products proved to be a difficult task. It was revealed later that the duroquinone dimer was a chroman, a result of a [4+2] cycloaddition of duroquinone with its tautomer, an *o*-QM.[10] The base assisted enolization of quinones was subsequently studied in greater detail.[11] For example, heating benzoquinone **34** in pyridine leads to the hemi-ketal **36** in 55% yield along with minor amounts of the spirocycle dimer **37** and the cyclic ether dimer **38** (Scheme 7).[11a]The *o*-QM **35** is proposed as the intermediate for these products. This enolization process has been used for dimerization, electrocyclization, and the introduction of soft nucleophiles such as thiols, amines, and halides at the benzylic position in *p*-quinones.

Scheme 7 Enolization



1,4a,9,9a-Tetrahydro-4a,7-dihydroxy-4,6-dimethoxy-9-[4-methoxyphenol]-1-[4-methoxyphenyl methylene]-xanthen-2-one (36**)**; **Typical Procedure**:[11a]

A soln of the *p*-quinone **34** (40 g, 0.146 mol, 0.73 M) in pyridine (200 mL) was heated on a steam-bath for 1 h and diluted with water (1.5 L). The solid, which separated on standing, was collected and heated

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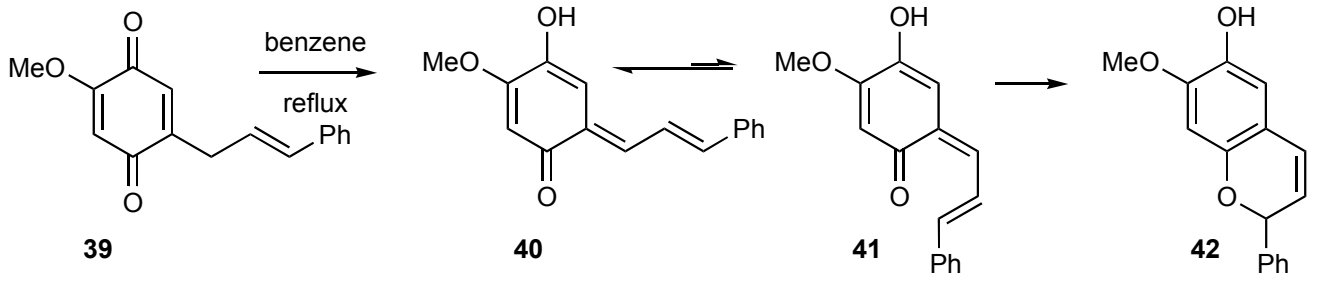
with MeOH (250 mL), leaving the hemihydrate **36** as a cream-colored solid; yield: 26g (47%). Recrystallization (Me_2CO-MeOH) gave glistening, cream-colored needles, mp 220-222°C.

This process was also useful for intramolecular [4+2] cyclizations. For example, warming 2-cinnamyl-5-methoxy-1,4-benzoquinone (**39**) in boiling benzene for 21 hours yields chromene **42** in excellent yield (Scheme 8).[11b] Presumably *o*-QM **40** exists in equilibrium with its less stable geometric isomer **41**, which is trapped by an electrocyclization.

Scheme 8



6-Hydroxy-7-methoxyflav-3-ene (42**); Typical Proedure:**[11b]

A soln of **39** (20 g, 0.0787 mol) in benzene (400 mL) was refluxed under argon for 22 h and evaporated to dryness. A soln of the residue in Et_2O (100 mL) was diluted with warm petroleum ether (500 mL), filtered from a small quantity of flocculent solid, and concentrated. The crystals separated upon cooling and were recrystallized (Et_2O-petroleum ether) to give cream-colored, glistening needles; yield: 15.1g (75.5%), mp 84-85°C.

4.28.12.1.1.2 Base assisted quinone enolization

variation 1: ROLi

A related case reveals deprotonation of benzoquinone **43** with lithium methoxide leads to *o*-QM **44** (Scheme 9).[12] The *o*-QM then undergoes a regioselective [4+2] cycloaddition with quinone **43** thereby producing the xanthene-1,4-dione **45** in 70% yield with a 32:1 ratio. The selectivity is attributed to hydrogen bonding between the hydroxyl substituent of the quinone **43** and the carbonyl of the *o*-QM **44**.

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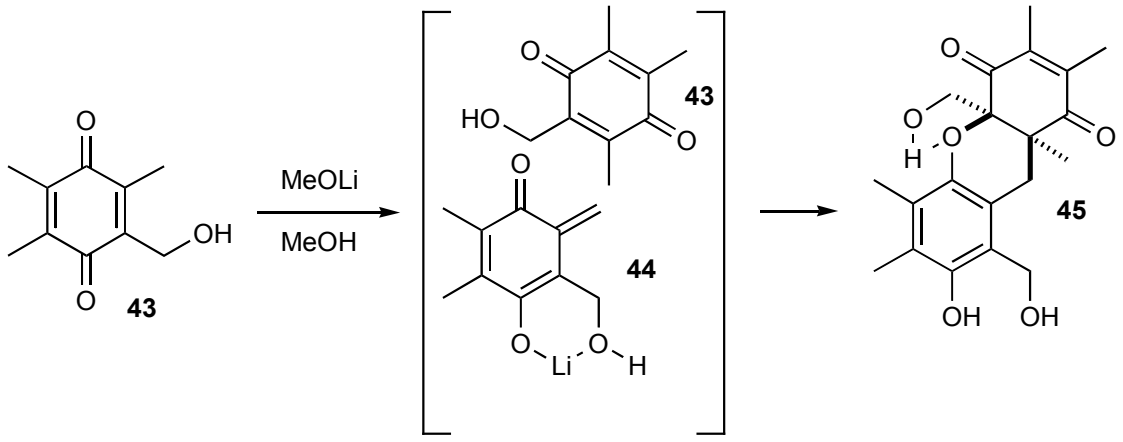
Scheme 9



(4a*S,9a*S**)-7-Hydroxy-4a,8-bis(hydroxymethyl)-2,3,5,6,9a-pentamethyl-4,4a,9,9a-tetrahydro-1H-xanthene-1,4-dione (**42**)**; **Typical Procedure**:[12]

A soln of MeOLi (106 mg, 2.77 mmol, 0.514 M MeOH) was added to a soln of quinone **40** (500 mg, 2.77 mmol, 0.129 M) with a syringe pump over 12 h at rt. The mixture was stirred for 24 h, the solvent evaporated, and the residue dissolved in EtOAc (50 mL). The organic layer was washed with water (3 x 50 mL) and dried ($MgSO_4$). Evaporation of the solvent gave the crude product, which was purified by flash chromatography in hexane/Et_2O (1:1). Recrystallization (Et_2O) gave an orange solid; yield: 350 mg (70%); mp 191°C.

variation 2: RSLi

The thiolation of *p*-quinones can be accomplished by base assisted enolization (Scheme 10).[13] In a solution of a sodium methyl thiolate, naphthoquinone **46** exists in equilibrium with its *o*-QM tautomer **47**, which in turn undergoes a 1,4-conjugate addition with methanethiol to produce hydronaphthoquinone **48**. In the absence of oxygen this sequence stops at the mono-thiolated product; however, in the presence of oxygen, phenol **48** oxidizes to the quinone **49** and the process repeats itself via **50** to produce the *bis*-thiolated *p*-quinone **51**.

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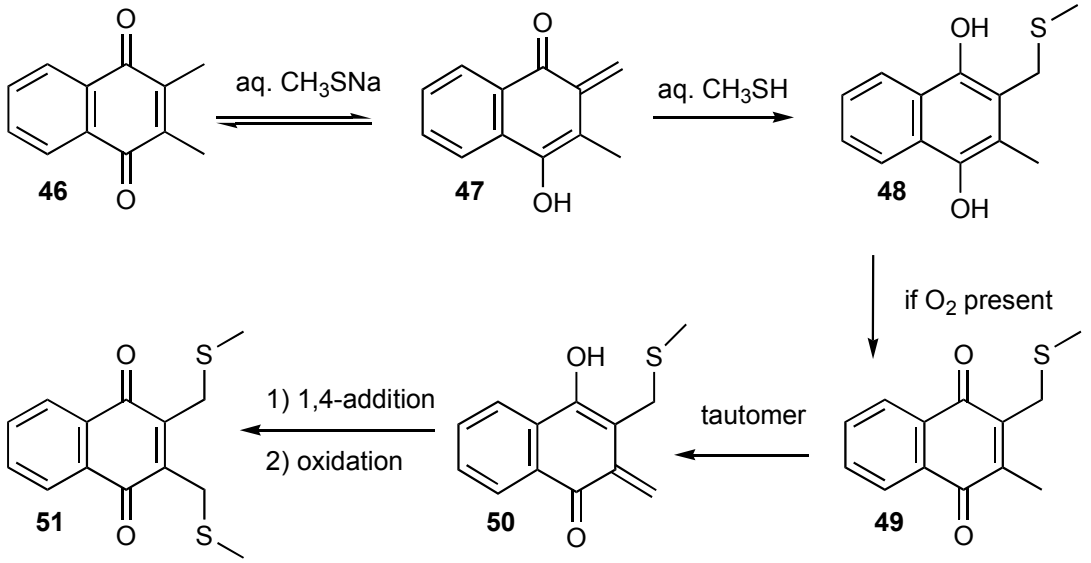
Scheme 10



2,3-bis(Methylthiomethyl)-1,4-naphthooquinone (51**)**:[13]

2,3-Dimethyl-1,4-naphthooquinone (**46**) (0.508 g, 2.730 mmol) in benzene (10 mL) was stirred with sodium methanethiolate (3.82 g, 20 mol) in MeOH for 12 h in a flask equipped with a drying tube. The mixture was added to benzene (50 mL) and aq potassium dihydrogen phosphate, and the organic phase was washed with water, dried over Na_2SO_4, and evaporated to give a crystalline residue; yield: 0.67 g (88%). Recrystallization (EtOH) gave orange-red needles; yield: 0.43g (57%); mp 85-86°C.

variation 3: RR'NH

The amination of *p*-quinones can be accomplished with primary and secondary amines in the presence of oxygen (Scheme 11). Piperidine (**53**) induces tautomerization of duroquinone (**52**) and in the presence of oxygen leads to hydroquinone **54** in ~50% yield.[14]

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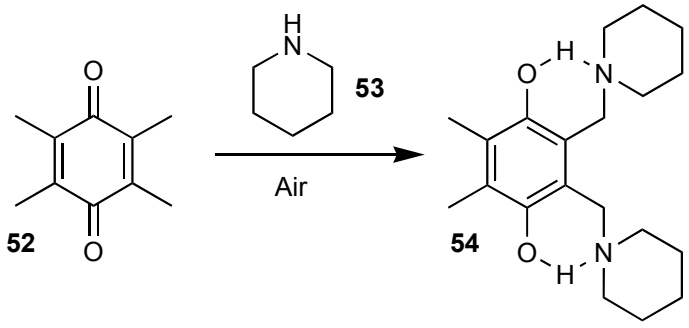
Scheme 11



2,3-Dimethyl-5,6-bispiperidinomethylquinol (54**)**:[14]

A soln of duroquinone (**52**) (1.0 g, 0.61 mmol) in distilled piperidine (**53**) was left at rt for 35 h, then evaporated. The residue was recrystallized (EtOH) to give long colorless, needles; yield: 1.1 g (54%); mp 161- 162°C.

4.28.12.1.1.3 Photochemical assisted quinone enolization

Photochemical excitation for *o*-QM generation uses ambient or low temperature conditions for enolization. The interest in photochemical excitation stems from the recognition that quinones, such as Vitamin K_1 and its benzoquinone analog coenzyme Q_n, play essential roles in the plant and animal kingdoms through electron transport. The photochemistry of tocoquinone-1, menaquinone-1, and related systems has been studied to gain insight into their role in photobiology.[15] For example, irradiation (365 nm) of Vitamin K_1 (**55**) under N_2 in 95% ethanol at ambient temperatures results in a dramatic color change from yellow to orange (Scheme 12).[16] Upon standing for two hours, the orange solution, which presumably accounts for the *o*-QM **56**, changes to a dim red color. After solvent evaporation at 40°C, preparative thin layer chromatography affords the known chromenol **57** in good yield.

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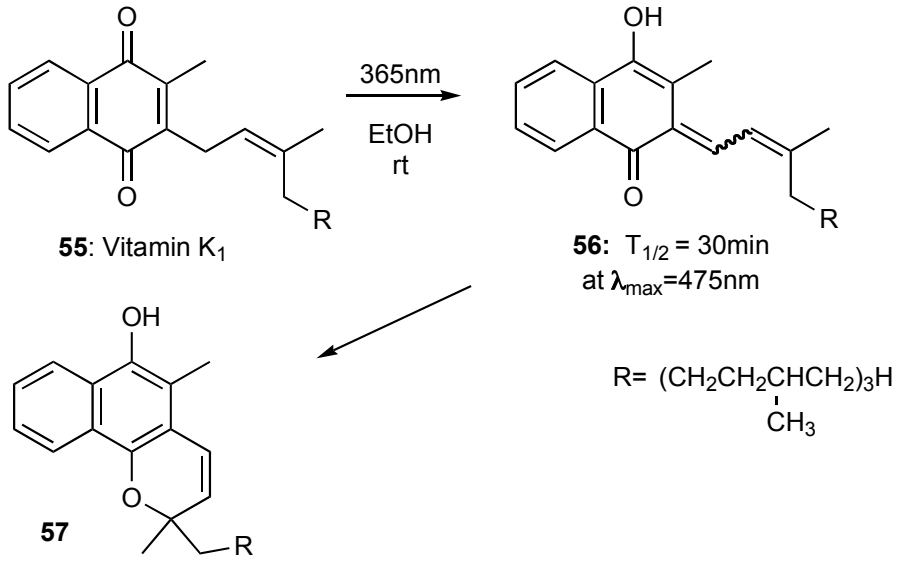
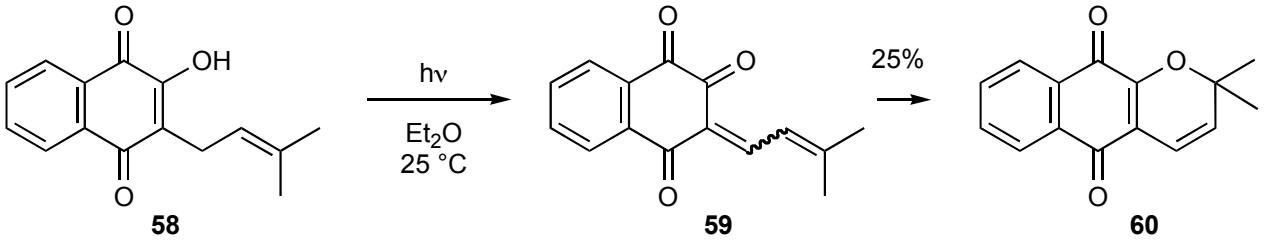
Scheme 12 Light assisted enolization



Similarly, irradiation of the naphthoaquinone **58** in ether affords a related chromene **60** via *o*-QM **59** (Scheme 13).[17]

Scheme 13



Interestingly, if irradiation is suspended and oxygen is bubbled through the system, a ketone is formed after one week (Scheme 14).[17] The autoxidation of the β-methylene may be most simply represented by the following mechanism. The first step is an oxidation to the *o*-QM **62** followed by allylic oxidation of the original β-methylene group **63**, most likely through a hydroperoxide. The double bond shifts away from the carbonyl group and ketolization of the side-chain forms ketone **65**.

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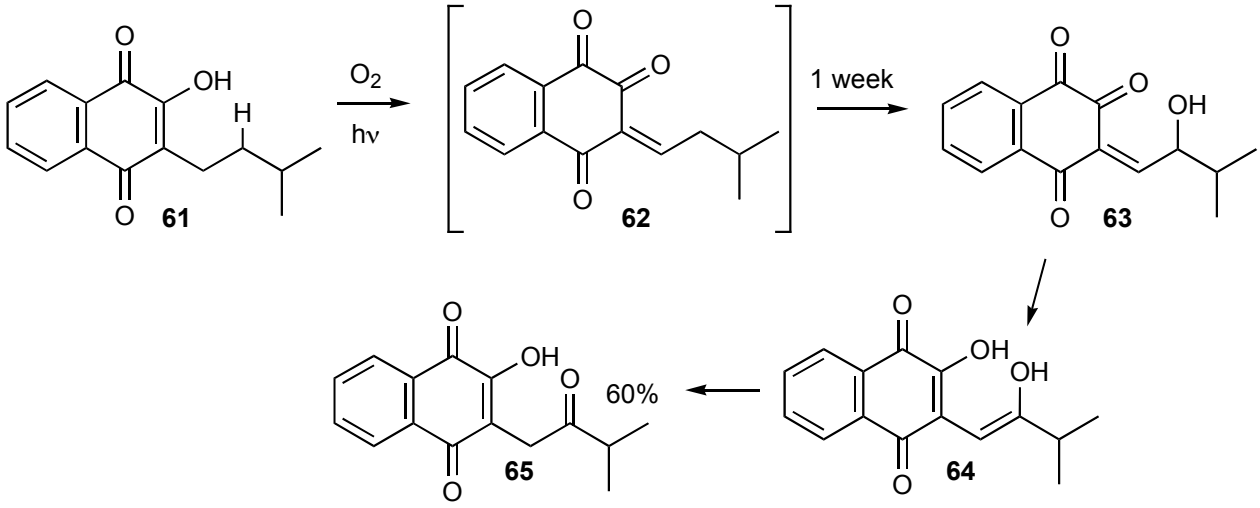
Scheme 14



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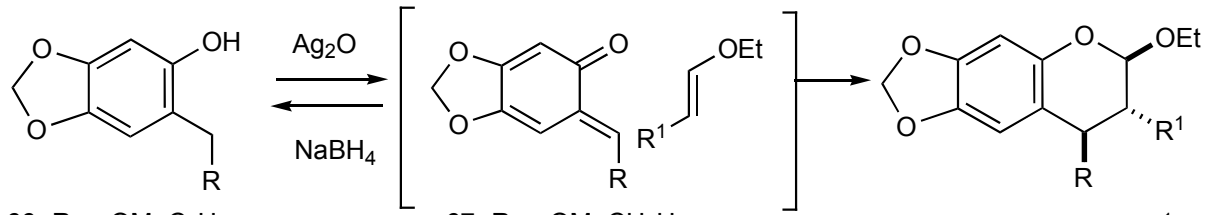
4.28.12.1.2 Method 2: Oxidation

The oxidation of *o*-alkyl phenols to generate *o*-QMs has found abundant use for initiating cycloadditions and for adding soft nucleophiles in a 1,4 fashion. The oxidative method, however, is restricted to systems lacking *p*-substituents with α-protons because *p*-quinone methides (*p*-QMs) are more easily formed due to their decreased polarization and increased stability than their corresponding *o*-QM counterparts. Although this limits the synthetic potential, a variety of chemical oxidations can be employed to generate *o*-QMs. It has been demonstrated that potassium hexacyanoferrate and lead oxide are effective oxidants.[18] Applications using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[19] and bromine[20] for the oxidative generation of *o*-QMs have been established. However, silver oxide is undoubtedly the oxidant of choice and has been used most often.

4.28.12.1.2.1 Silver oxide

The generation of *o*-QMs using chemical oxidation was explored[21] and it was concluded that silver oxide was a superior oxidant for this reaction and subsequent dimerization, intramolecular, and intermolecular reactions.[24] The oxidation of phenol **66** with silver oxide produces the isolable *o*-QM **67**, which can be reduced with $NaBH_4$ to regenerate the starting material (Scheme 15).[22] The *E* olefin geometry of the stable *o*-QM **67** was confirmed by X-Ray crystallography. At room temperature, the reaction of phenol **66**, silver oxide, and the appropriate vinyl ether affords cycloadducts **68** and **69** as single diastereomers, providing further evidence that *o*-QMs react via an *endo*-transition state with vinyl ethers.[23]

Scheme 15



66: R=*p*-$OMeC_6H_4$ **67:** R=*p*-$OMeCH_6H_4$ **68:** R=*p*-$OMeCH_6H_4$, R^1=H **69:** R=*p*-$OMeCH_6H_4$, R^1=Me

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6-(4-Methoxybenzylidene)-3,4-methylenedioxy-cyclohexa-2,4-dienone (67); General Procedure:[22]

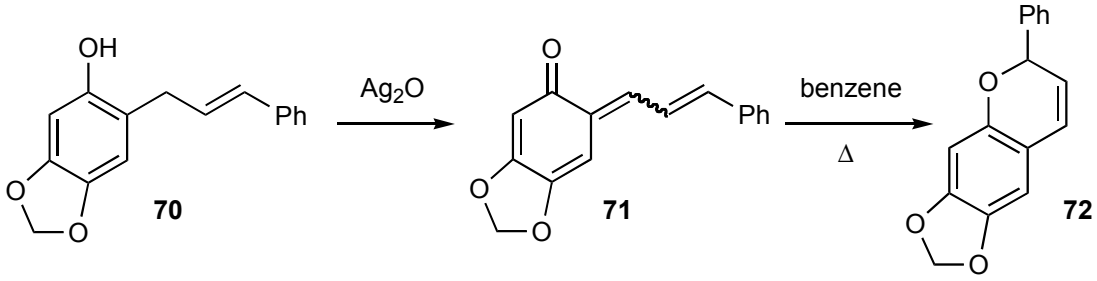
A soln of 2-(4-methoxybenzyl)-4,5-methylenedioxyphenol (**66**) (2.0 g, 7.74 mmol, 0.051 M Et_2O) was heated under reflux with Ag_2O (6.0 g, 26.11 mmol) for 3.5 h and filtered. Orange crystals separated from the filtrate upon standing. The soln was concentrated to 70 mL, cooled, and the colored product was collected (0.76 g; mp 143°). The ether filtrate was diluted (100 mL) and treated once again with Ag_2O (3.0 g, 13.05 mmol) for 2 h to give an additional quantity of the orange product; combined yield: 0.96 g (50%). Recrystallization (benzene-petroleum ether) afforded orange needles, mp 143-144°C.

Chromans (68) and (69); Typical Procedure:[23]

A mixture of **66** (1 mmol), Ag_2O (1.2 mmol), and the appropriate vinyl ether (3 mL) was kept at rt for 48 h. The reaction mixture was filtered, the filtrate evaporated in vacuo. Recrystallization (Et_2O) of **68** gave colorless needles, mp 114-116°C. Recrystallization (Et_2O) of **69** gave colorless needles, mp 122-124°C.

Stirring a solution 2-cinnamyl-4,5-methylenedioxyphenol (**70**) with silver oxide at room temperature yields the crystalline *o*-QM **71**, which undergoes thermal cyclization to 6,7-methylene-dioxyflav-3-ene (**72**) in refluxing benzene (Scheme 16). [22]

Scheme 16



6-Cinnnamylidene-3, 4-methylenedioxy-cyclohexa-2,4-dienone (71); General Procedure:[22]

A soln of **70** (10.0 g) in dry Et_2O (100 mL) was stirred with Ag_2O (20.0 g) at rt for 20 h. Orange crystals separated from the soln. The reaction was filtered and the solid was extracted with boiling acetone (3 x 250 mL). The acetone soln was concentrated to 40 mL and cooled, whereupon the product

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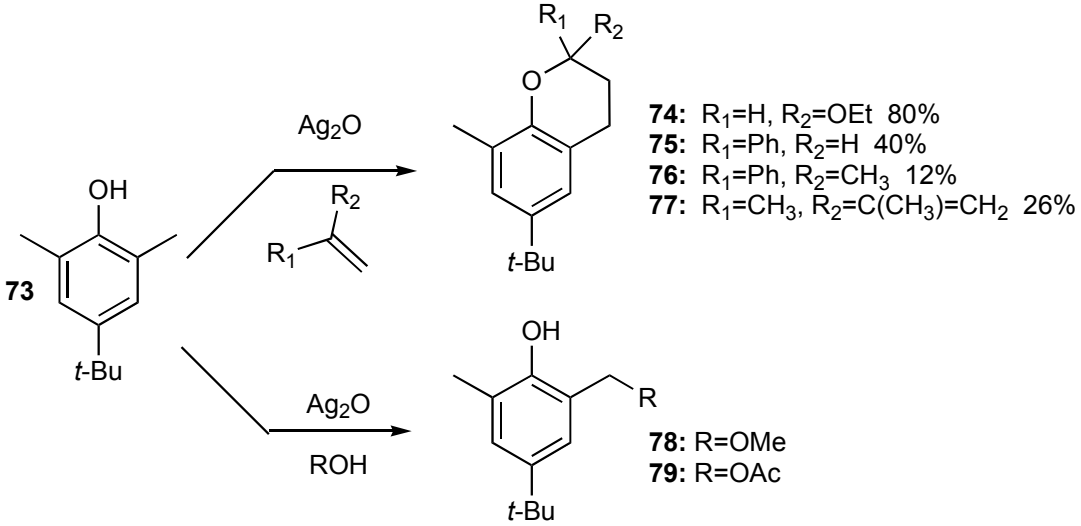
precipitated; yield: 9.4 g (94%); mp 162-163°C. Recrystallization (acetone) gave glistening, orange-red plates, mp 164°C.

6,7-Methylenedioxyflav-3-ene (72**); General Procedure**:[22]

o-QM **71** (3.0 g) was heated under reflux in a benzene soln (150 mL) for 2 h, at which time TLC showed complete conversion to the flavene. The soln was evaporated and the residue was extracted with boiling petroleum ether. On concentration and cooling the crystalline flavene precipitated. Recrystallization (petroleum ether) gave colorless plates; yield: 2.3 g (73%); mp 73°C.

The mixture of silver oxide, 4-*t*-butyl-2,6-dimethyl phenol (**73**), and the appropriate ethyl vinyl ether stirring at ambient temperature results in the formation of chromans **74**-**77** (Scheme 17).[24b] High concentration of the dienophile is crucial for preventing trimerization of the *o*-QM and electron rich dienophiles are better suited for [4+2] cyclizations of *o*-QMs. When 4-*t*-butyl-2,6-dimethyl phenol (**73**) is oxidized in the presence of methanol or acetic acid, the anticipated hydroxymethyl ether **72** and acetate **73** are formed.[24b] If excess silver oxide is used in the case of the methoxy residue, the corresponding dimethyl ketal is observed.

Scheme 17



2-Ethoxy-6-*tert*-butyl-8-methylchroman (74**)**; **General Procedure**:[24b]

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In a magnetically stirred, water-cooled flask, 4-*t*-butyl-2,6-dimethylphenol (**73**) (8.9 g, 0.05 mol), the appropriate dienophile (10 mL), and Ag_2O (15 g, 0.06 mol) were added. The mixture was stirred until the dark color of the Ag_2O turned into the light grey of reduced silver (0.5 h). The slurry was filtered and the filtrate distilled. After the reaction was condensed in vacuo, the chroman **74** was obtained as a pale yellow oil; yield: 80%. Redistillation gave the pure chroman, bp 106-107°C (0.6 mm); **2-Phenyl-6-*tert*-butyl-8-methylchroman (**75**)** bp 158°C (0.5mm); **2,8-Dimethyl-2-phenyl-6-*tert*-butylchroman (**76**)** bp 162-166°C (0.5mm); **2,8-Dimethyl-2-isoprop-phenyl-6-*tert*- butylchroman (**77**)** bp 113°C (0.4mm).

4-*tert*-Butyl-2-methoxymethyl-6-methylphenol (78**)**; **General Procedure**:[24b]

The oxidation of **73** is run in MeOH with an excess of the phenol over the oxidizing agent, Ag_2O.

2-(α-Acetoxymethyl)-6-methyl-4-*tert*-butylphenol (79**)**; **General Procedure**:[24b]

The oxidation of **73** with Ag_2O is run in the presence of acetic acid. This material could not be isolated because the *o*-QM was generated, releasing acetic acid, and trimerized. The phenol was isolated by converting it to the trimethylsilyl ether using bis(trimethylsilyl)acetamide.[25] This ether could be distilled and the free phenol then reisolated by hydrolysis.

4.28.12.1.3 Method 3: Extrusions and retrocycloadditions

Extrusion has been the method of choice among synthetic chemists for generating *o*-QMs. Light, base, acid, and heat can facilitate this type of reaction. It should be noted that all thermal generation techniques preclude the application of thermally unstable nucleophilic traps. Moreover, most thermal extrusions can result in the corruption of stereochemistry in reactions that can lead to diastereomeric mixtures. With any given precursor, there is a substantial temperature range for 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. 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. The addition of acid in extrusion

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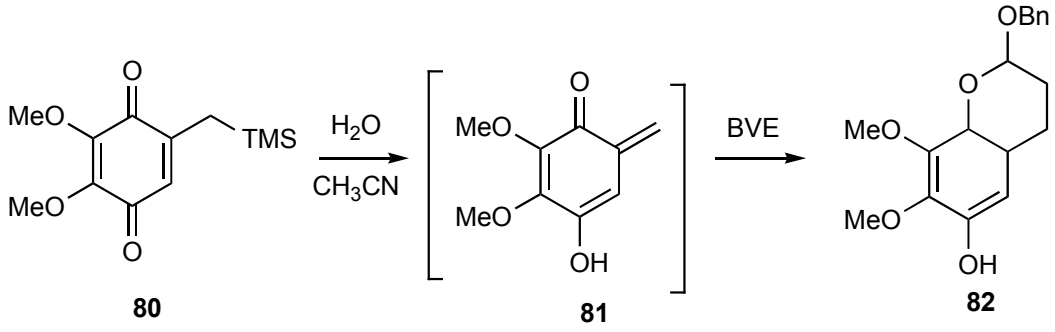
reactions typically enhances the overall reactivity of the system. Unfortunately, this often decreases the diastereoselectivity of subsequent transformations, especially in the case of [4+2] cycloadditions, which become more ionic in nature. In some cases, acid results in unexpected rearrangement products. Moreover, acidic conditions reduce the range of nucleophiles that can be deployed in the reaction mixture.

4.28.12.1.3.1 Nucleophilic Displacement

o-QM formation can be envisaged from the nucleophilic attack of the trimethylsilyl group of **80** to give the corresponding vinylogous enolate anion which leads to *o*-QM **81** upon O-protonation (Scheme 18).[7b] The *o*-QM generation in 10% aqueous acetonitrile and excess *n*-butyl vinyl ether (BVE) yields the chromanol **82** in 72%.

Scheme 18



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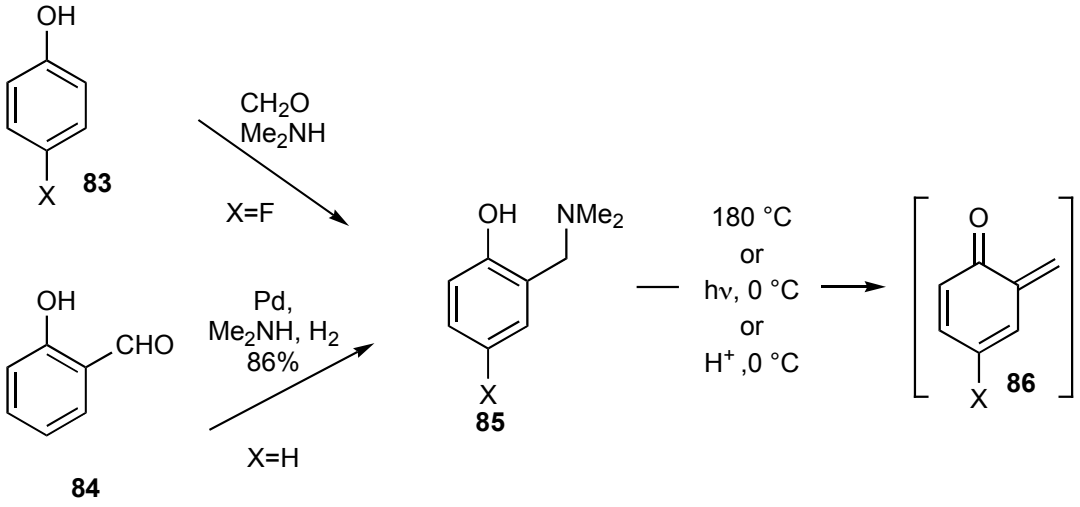
4.28.12.1.3.2 Mannich Base Precursors

Although Mannich bases are among some of the more robust *o*-QM precursors, derivatives can prove difficult to construct. In most instances the process has only been used to construct non-substituted *o*-QMs. Mannich base precursors can be made from shaking the salicylaldehyde (**84**) with palladium, dimethyl amine under 30 psi of H_2 to afford the *o*-dimethylaminomethyl phenol (**85**) in excellent yield (Scheme 19).[2c] The Mannich base can also be prepared by the addition of phenols like **83** to formaldehyde and dimethyl amine, however, the process is difficult to control.[26] The formation and reactivity of Mannich bases as precursors to *o*-QM chemistry have been well investigated. [27]

Scheme 19 Mannich Bases Precursors



Variation 1: Thermal induction

o-QM generation is achieved by the thermolysis of Mannich base **87**, which undergoes cycloaddition with thiocarbonyl compound adamantanethione (**88**) to generate thioacetal **89** in 90% yield (Scheme 20).[28] Mannich base **87** undergoes thermally promoted reaction with indole **90** to produce *o*-indolemethyl phenol **91** in good yield.[29b]

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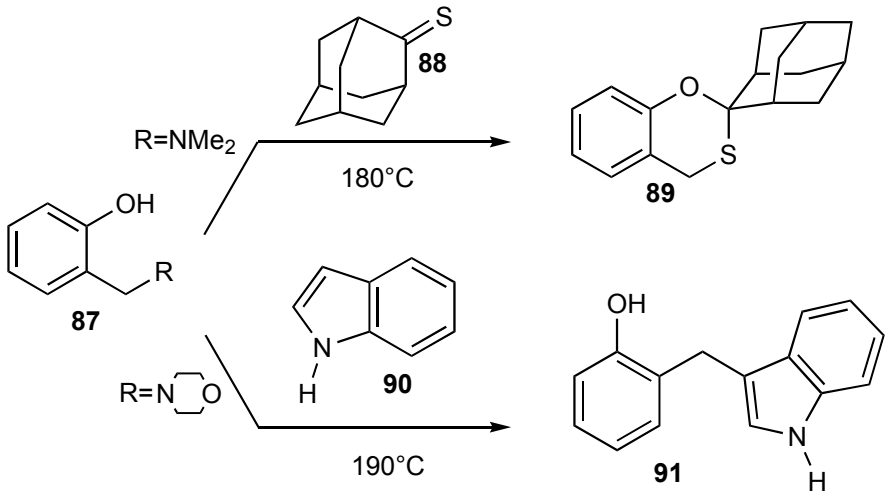
Scheme 20



Adamantane-2-spiro-2'-[1,3] benzoxathiine (89**); Typical Procedure:**[28]

A mixture of compound **88** (166 mg, 1.00 mmol), **87** (173 mg, 1.40 mmol), and hydroquinone (5 mg, 0.05 mmol) in dry xylene (4 mL) was heated at 180°C in a sealed tube for 6 h under argon. The orange color of the soln gradually faded during this time. After removal of the solvent in vacuo, the resulting residue was chromatographed on silica gel with *n*-hexane/benzene (8:1). Recrystallization (*n*-hexane/$CHCl_3$ (5:1)) gave a white solid; yield: 243 mg (90%). ^{1}H NMR ($CHCl_3$): δ 7.30-6.80 (m, 4H), 3.82 (s, 2H), 2.55-1.40 (m, 14H).

2-((1H-Indol-3-yl)methyl)phenol (91**); General Procedure**: [29b]

A homogeneous mixture of the indole (**90**) (2 mmol) and the Mannich base (**87**) (1 mmol) was heated to 190°C for 8 h in a sealed tube. The oil was dissolved in Et_2O, washed with 10% HCl, dried with Na_2SO_4 and chromatographed on florisil.

Mannich base **92** produces an *o*-QM upon heating in dioxane (Scheme 21). The resulting *o*-QM undergoes [4+2] cycloadditions with enamine **93**, to produce O, N-acetal **94**.[30] The likely mechanism is a 1,4- conjugate addition of the enamine to the *o*-QM, followed by cyclization on the iminium to form an α-aminopyran. If water is added, hydrolysis ensues to provide the corresponding α-hydroxypyran **95**. A preparation for polycyclic hetero-aromatic compounds like **98** from Mannich bases of β-naphthols such as **92** also uses thermal conditions.[31] The procedure entails *o*-C-addition of aniline derivatives such as **96** to the *o*-QMs generated from **92** under thermal conditions. Prolonged

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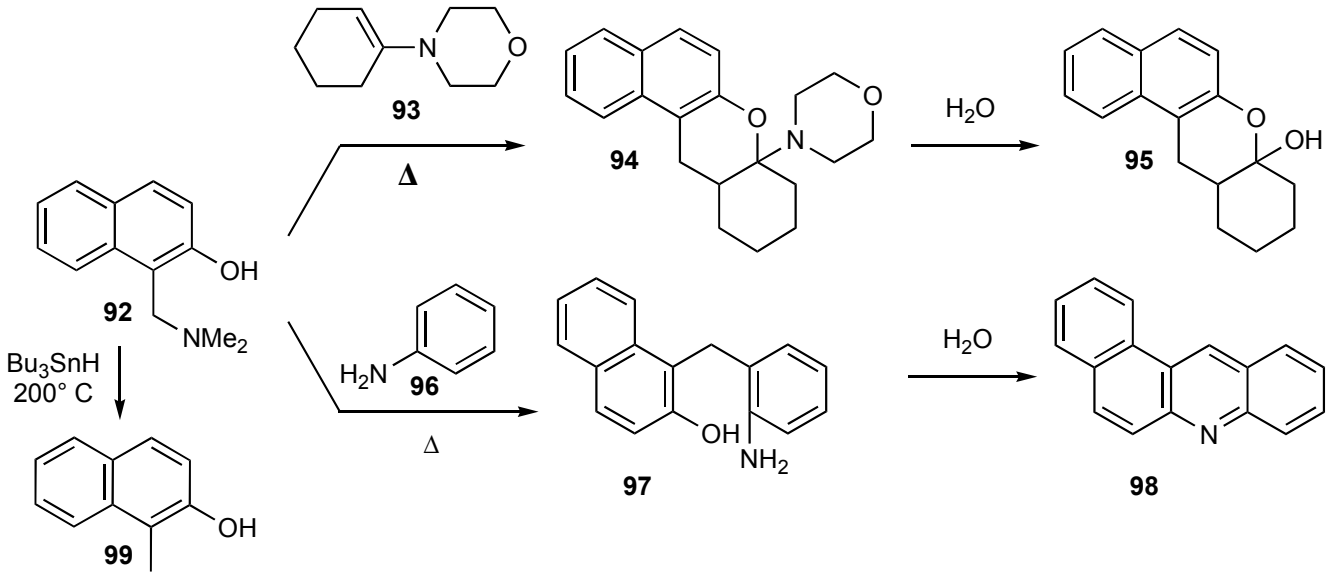
heating of the initial 1,4-addition adduct **97** results in an intramolecular cyclization of the amine to the adjoining phenol, expelling water and generating the corresponding polycyclic hetero-aromatic compound. The reduction of Mannich bases, such as **92,** can be accomplished by heating the Mannich base to 200°C in neat Bu_3SnH to yield **99** in 89%.[32]

Scheme 21



8,9,10,11,11a,12-Hexahydro-7aH-benzo[a]xanthen-7a-ol (95**)**; **General Procedure**:[30]

Mannich base **92** (1 equiv) and enamine **93** (1 equiv) in dioxane were refluxed until evolution of basic fumes ceased, resulted in the pyran nucleus **94**. Water was added to the reaction mixture and hydrolysis occurred to produce **95**, mp 143.5- 145°C.

Benz[a]acridine (98**); Typical Procedure:**[31]

The Mannich base **92** (1 g, 5 mmol) was heated to 198°C with distilled aniline (**96**) (9 mL) in diphenyl ether (10 mL) for 4 h under nitrogen. The solvent was removed in vacuo to yield a yellow gum, which was purified by preparative silica TLC (EtOAc/hexane (4:6)); yield: 286 mg (25%); mp 130-131°C.

1-Methylnaphthalen-2-ol (99**)**; **Typical Procedure**:[32]

To a three-necked flask equipped with a stir-bar, condenser, and nitrogen inlet was added the Mannich base **92** (1 equiv). Tri-*n*-butyltin hydride (1.2-1.3 equiv) was then charged through a syringe under

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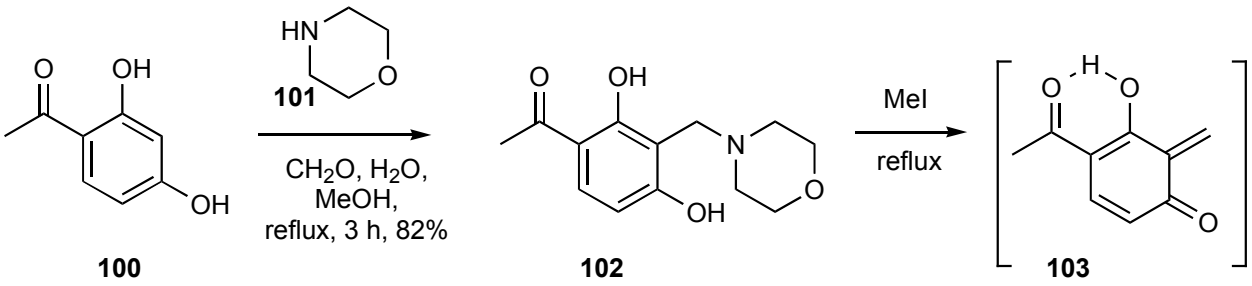
nitrogen. The reaction mixture was gradually heated to 200°C (oil bath) and heated for 30 min. The reaction was cooled to rt and purified by flash column chromatography (Et_2O:pentane); 89% yield.

Variation 2: Quaternization

Mannich base **102** with methyl iodide under reflux forms *o*-QMs **103** (Scheme 22).[33] The Mannich base **102** is prepared in good yield as a single regioisomer from 2,4-dihydroxyacetophenone **100**, formaldehyde, and morpholine.

Scheme 22



This method was applied in the synthesis of (±)-xyloketal A (**106**). Mannich base **104**, 4,5-dihydro-2-methylfuran (**105**) (9 equiv), methyl iodide (3 equiv) in refluxing benzene affords an inseparable mixture (1:4) of the desired symmetric (±)-xyloketal A (**106**) and its diastereomer **107** (Scheme 23). The yield of the reaction (19%) is quite respectable when one considers that the process involves three alkylations, three eliminations, and three cycloadditions.

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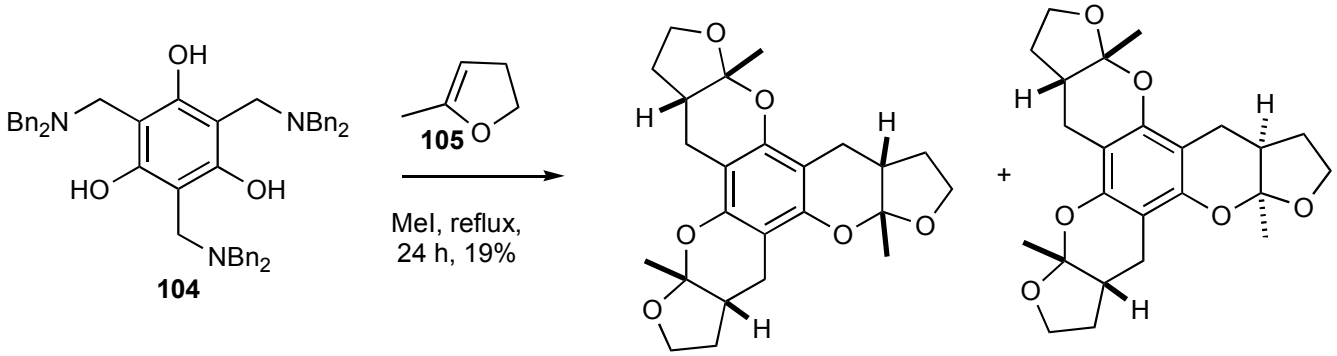
Scheme 23



(±)-**xyloketal A** (106);**Typical Procedure**:[33]

4,5-dihydro-2-methylfuran **105** (8.99 mmol) and methyl iodide (3.05 mmol) were added to a soln of the Mannich base **104** (1.00 mmol) in benzene (10 mL) at rt. The resulting soln was heated at reflux until TLC analysis indicated that the Mannich base had completely reacted (24 h). The reaction mixture was then cooled to rt, filtered, and concentrated in vacuo. Purification by repetitive column chromatography hexane/ Et_2O (1:1) then CH_2Cl_2 / Et_2O (18:1) afforded the desired compound.

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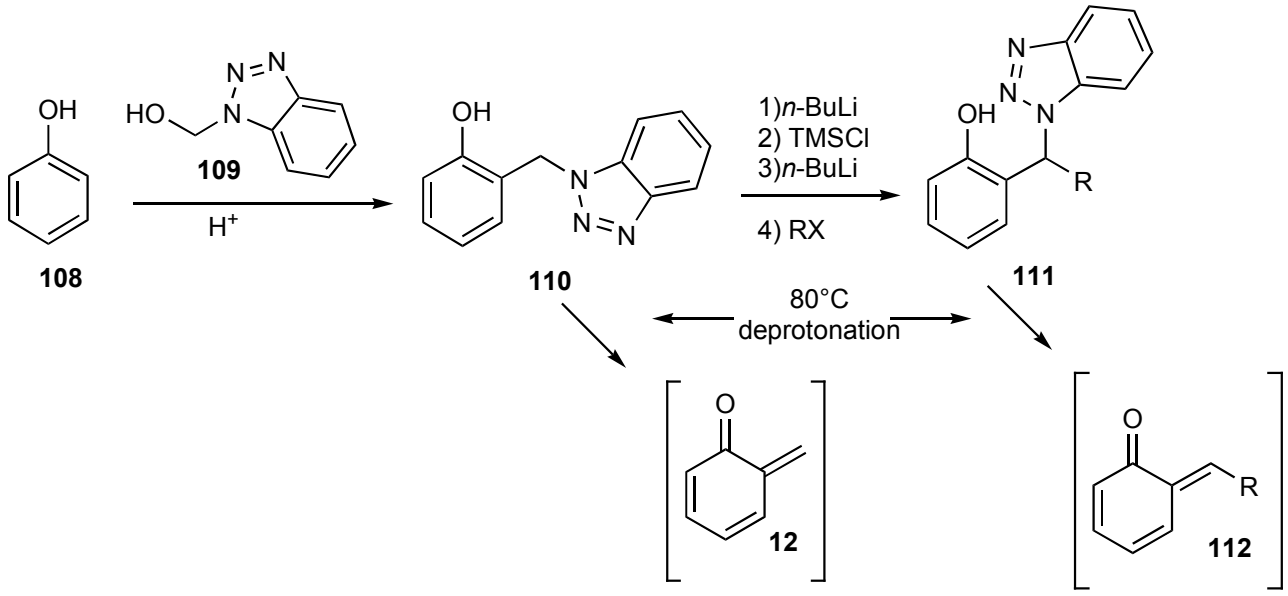
4.28.12.1.3.3 *o*-(benzotriazolylmethyl)phenol precursors

o-(Benzotriazolylmethyl)phenol **110** is a robust *o*-QM precursor (Scheme 24).[34] Compound **110** is prepared by the reaction of phenol (**108**) with 1-hydroxy-methylbenzotriazole (**109**) under acidic conditions. Phenol **110,** when treated sequentially with equimolar amounts of butyllithium, chlorotrimethylsilane, followed by butyllithium, yields the benzylic anion that undergoes reaction with various electrophiles such as alkyl halides to produce derivatives of **111**. Direct alkylation of the dianion without protection of the phenol leads to recovered starting material or O-alkylated material. Treatment of *o*-(benzotriazolylmethyl)phenol **111** or its precursor **110** with potassium, sodium, or magnesium bases at elevated temperature results in expulsion of the benzotriazole thereby forming the corresponding *o*-QMs **112** and **12,** respectively. The *o*-QMs **12** and **112** undergo 1,4-addition reactions with amines, thiols, alcohols, hydride, as well as carbon nucleophiles such as active methylene compounds and Grignard reagents. However, **110** and **111** are less useful as precursors for inverse demand [4+2] cycloadditions. High initiation temperatures result in diminished diastereoselectivity and less electron–rich dienophiles (such as styrene derivatives) result in polymerization. Overall, the protocol is useful for the construction of *o*-alkyl phenols; its only shortcomings are low yield associated with the preparation of *o*-functionalized phenol **110** and the high temperature requirement for *o*-QMs generation.

Scheme 24



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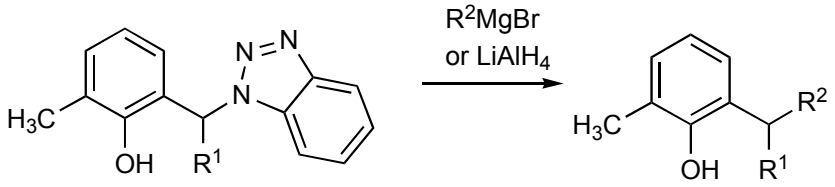
Variation 1: Basic Conditions

o-Benzotriazoles, such as **113**, undergo reduction with lithium aluminum hydride or Grignard reagents to produce *o*-alkylated phenols, such as **114** (Scheme 25).[34c] Although the reductive procedure may resemble the directed *o*-metalation (DoM) protocol, it enables the functionalization of many electron-rich phenols that prove resistant to the DoM process. Two equivalents of organometallic reagent is needed for this process. One equivalent to deprotonate the phenol and provide the *o*-QM, followed by conjugate addition of the second equivalent to the *o*-QM. Unfortunately, when R^1=H longer reaction time is required and a low yield results. For example, refluxing **113** (R^1=H) with phenylmagnesium bromide, leads to the desired products in 45% yield, while a more substituted derivative **113** (R^1=Me), affords the desired product in 80% yield.

Scheme 25



113 **114**

R^1	R^2	Reagent	Time, h	Yield (%)
H	Ph	PhMgBr	72	45
H	Bu	*n*-BuMgBr	24	29
Me	Ph	PhMgBr	17	80
Me	$PhCH_2$	$PhCH_2MgBr$	12	66
Me	H	$LiAlH_4$	48	59
Bu	H	$LiAlH_4$	48	62

Reductive procedure:[34c]

To a soln of the corresponding benzotriazole adduct **113** (1.0 mmol) in toluene (15 mL) was added $LiAlH_4$ (2.5 mmol). The resulting soln was refluxed for the appropriate time cooled, then poured into an ice/water slurry(20 mL). The soln was acidified with 2N HCl and the mixture extracted with Et_2O

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(3 x 30 mL). The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude residue was chromatographed (petroleum ether/EtOAc) on silica gel.

Grignard reagent procedure: [34c]

To a soln of the appropriate benzotriazole adduct **113** (2 mmol) in toluene (20 mL) at rt was added the corresponding Grignard reagent (12 mmol). The reaction mixture was refluxed for the given time, (Et_2O was distilled off until the temp reached the boiling point of toluene) until TLC indicated that the starting material was consumed. The mixture was poured into an ice/water slurry(20 mL), acidified with 2 N HCl, extracted with Et_2O (3 x 30 mL), and dried over $MgSO_4$. The solvent was removed in vacuo and the crude residue was chromatographed (petroleum ether/ EtOAc) on silica gel.

Variation 2: Thermal Conditions

Thermally generated *o*-QMs of 1-[α-(benzotriazol-1-yl)alkyl]-2-naphthols, such as **115**, undergo [4+2] cycloadditions with various dienophiles (Scheme 26).[34b] The *o*-QM may appear to exist in equilibrium with both olefin geometries, but in order to reduce the non-bonded interactions in the *E*-configuration of *o*-QM **117**, the *o*-QM exists primarily in the *Z*-configuration **116**. If an *E*-configuration is adopted, the strong H-H interactions prevent coplanarity of the phenyl and naphthol rings. Thus, the *Z-endo*-cyclization affords the *trans*-chroman adducts **118**. Less electron-rich olefins, such as styrene, provide none of the desired cycloaddition adducts using this protocol.

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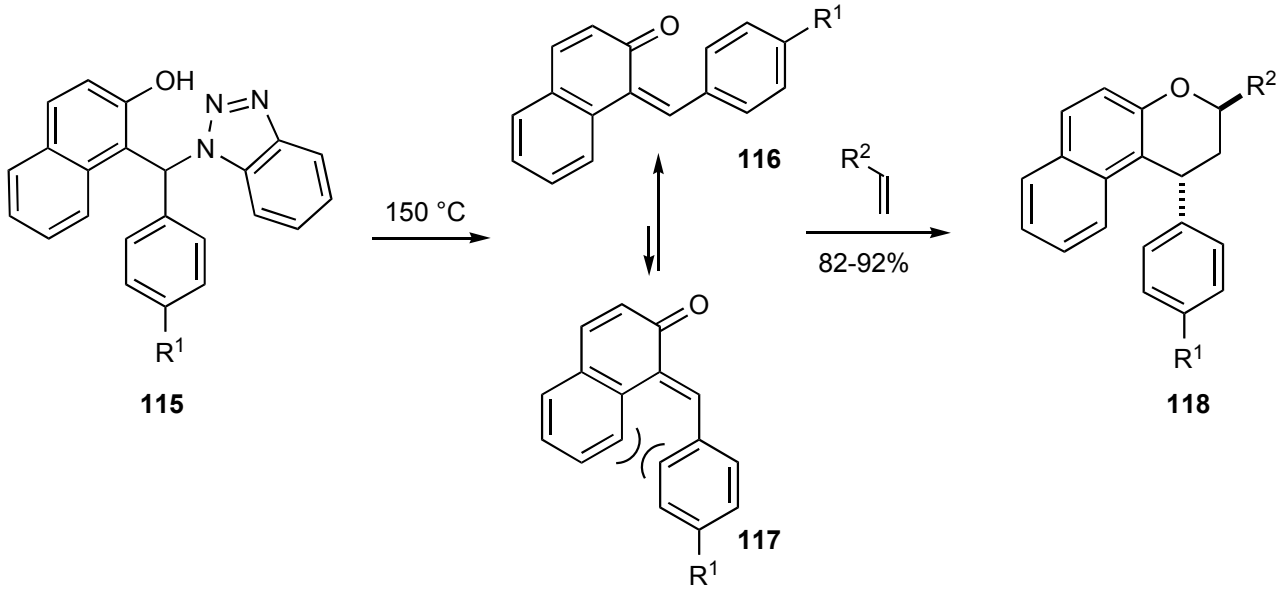
Scheme 26



R^1	R^2	Time (h)	*dr* (*trans*:*cis*)	Yield (%)
H	OEt	5	2.75: 1	92
H	pyrr[c]	3	na[b]	82
-NMe_2	OEt	5	2:1	49 (92)[a]
-NMe_2	pyrr[c]	3	na[b]	27 (87)[a]

[a] Total yields of products including mixtures
[b] Unable to determine *dr* due to peak overlap in NMR
[c] pyrrolidin-2-one

Chroman (118**); Typical Procedure**:[34b]

A mixture of *o*-(α-benzotriazolylalkyl)phenol **115** (1.0 mmol) and the appropriate olefin (2.0 mmol) was heated at 150°C in a sealed tube for the appropriate time. The resulting mixture was chromatographed on a silica gel (hexane/CH_2Cl_2).

4.28.12.1.3.4 4H-1,2-benzoxazine precursors (thermal extrusion)

The thermolysis of 4H-1,2-benzoxazines **122** or **125** leads to retro-[4+2] cycloaddition producing an *o*-QM which then can be consumed in a [4+2] cycloaddition (Scheme 27).[35] A convenient approach for the synthesis of 4H-1,3-benzoxazine systems uses tandem retro-[4+2] cycloadditions followed by [4+2] cycloaddition rearrangements of benzoxazines.[36] 4H-1,2-Benzoxazine **125** is obtained in good yield by acid mediated addition of benzene (**123**) to unsaturated nitro derivatives such as **124**.[35a] 4H-1,2-

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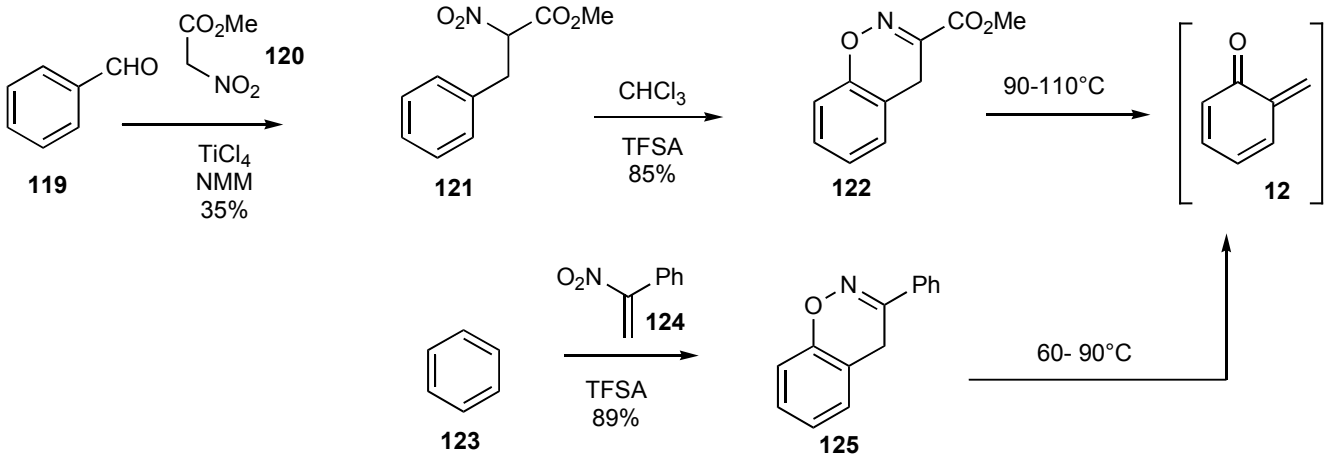
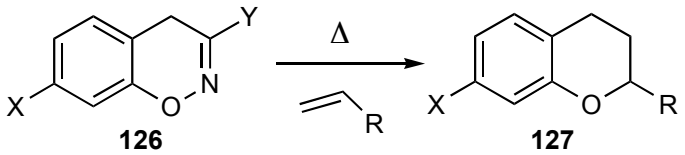
Benzoxazine **122** can be obtained from the treatment of benzaldehyde (**119**) with titanium chloride, N-methylmorpholine, and methylnitroacetate **120** followed by acidic conditions.[35b]

Scheme 27



4H-1,2-Benzoxazines, such as **126** (Y=CH_3, Ph), lead to the corresponding *o*-QMs around 90°C (Scheme 28).[35a] The resulting *o*-QMs undergo [4+2] cycloadditions with styrene, phenyl vinyl ether and 1-vinyl-2-pyrrolidinone to produce the respective chromans **127** in yields ranging from 42-83%. Various electron-withdrawing substitutents on 4H-1,2-benzoxazines like **126** (R=CO_2Me) were used in cycloadditions with styrene at temperatures between 90-110°C, producing chromans in respectable yields.[35b]

Scheme 28



X	Y	R	Temp, °C	Time, h	Yield, %
H	Ph	Ph	90	6.5	64
H	Ph	Oph	90	5.5	55
H	Ph	Pyrr	90	7	83
H	CH_3	Ph	60	10.5	42
H	CH_3	Oph	60	18	59

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H	CH_3	pyrr	60	5	62
H	CO_2Me	Ph			56
Cl	CO_2Me	Ph			84
CO_2Me	CO_2Me	Ph			77
CON(*i*-Pr)$_2$	CO_2Me	Ph			93

Chromans (127**)**; **Typical Procedure**:[35a]

A soln of **126** (0.65 mmol) in toluene (15 mL) and the appropriate dienophile (13.1 mmol, 20 equiv) was heated to 90°C with stirring for 12 h. The solvent was removed in vacuo and the residue chromatographed on silica gel (*n*-hexane/ EtOAc (30:1)). Recrystallization (*n*-hexane) gave a white solid, mp 39.0- 39.5°C.

4.28.12.1.3.5 *o*-OBoc benzaldehyde and *o*-OBoc benzylalcohol (basic conditions)

o-OBoc benzaldehyde and *o*-OBoc benzylalcohol precursors are accessible *o*-QM precursors that react in a controlled manner and the generation conditions are amenable to subsequent diastereoselective reactions.[37] Various *o*-Boc (*o*-*t*-butyl carbonate) salicylaldehydes, such as **5**, and *o*-OBoc benzylalcohols, such as **128**, can be used in combination with an assorted of organometallic nucleophiles to form *o*-QMs **12** and **112**, respectively (Scheme 29). The reaction tolerates a variety of aromatic backbones, organometallic initiators, and dienophiles. A modification of this method uses an *o*-OAc benzaldehyde as an *o*-QM precursor in the synthesis of (±)-Alboatrin.[38]

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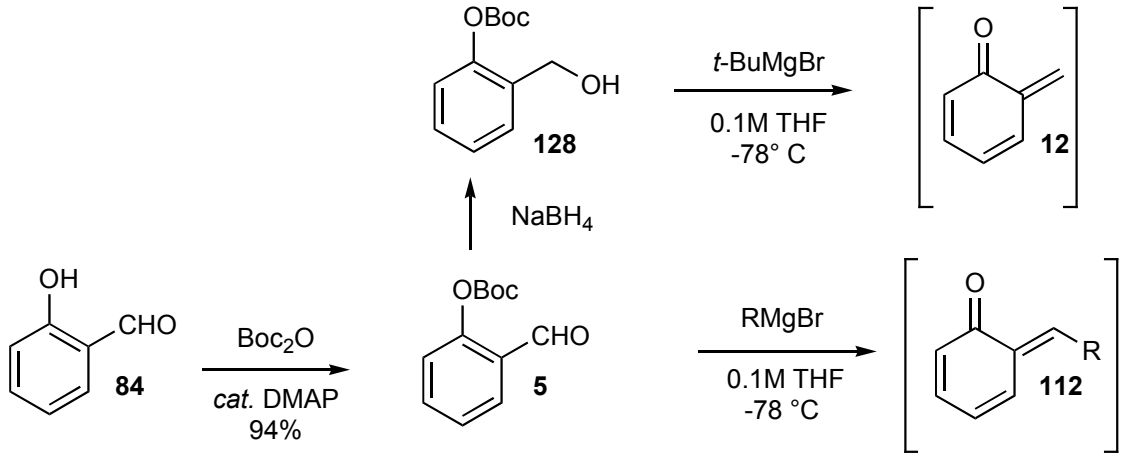
Scheme 29



Four stages deemed the "cascade" explain *o*-QM formation by this method. Four stages of the "cascade" include: nucleophilic attack, cyclization, -Boc migration, and MOBoc elimination (Scheme 30). Two driving forces of the cascade are -Boc migration to form the more stable phenoxide (Stage III) and MOBoc elimination, which further decomposes to release CO_2 (g) (Stage IV). Depending on the metal used, the cascade can be manipulated at different stages. This allows for the initiating nucleophile to be distinct from the nucleophile that reacts with the resulting *o*-QM. Aluminum reagents, such as $LiAl(O\textit{t}\text{-}Bu)_3$, fail to undergo migration and produce the corresponding alcohol such as **129**. Lithium reagents undergo the migration to form **131**, but fail to undergo the elimination necessary to form the *o*-QM. Magnesium, potassium, sodium reagents, and salts proceed to the *o*-QM **112** or can reinitiate its formation by adding them after the initial nucleophile. Thus, this procedure allows a one-pot construction of a many β-substituted *o*-QMs, which can undergo low temperature intermolecular reactions with thiols, alcohols, organomagnesium and organozinc reagents, enamines, imines, furans, and enol ethers.

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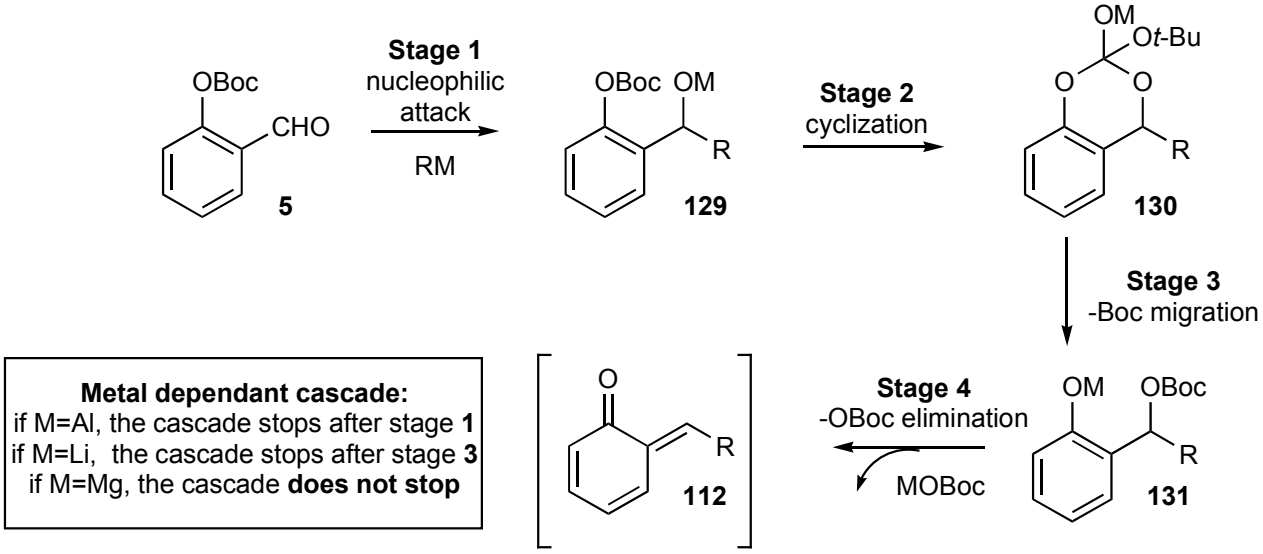
Scheme 30 "*o*-QM cascade"



The addition of excess Grignard reagent to *o*-Boc salicylaldehydes such as **5**, **132**, and **133** affords compounds such as **134**-**136** (Scheme 31). Two different Grignard reagents can be used when added sequentially to form aromatics such as **137**-**139**. It should be noted that the Grignard reagent, which results in the most stable *o*-QM should be used to initiate the cascade. For example, the addition of the phenyl Grignard reagent results in an *o*-QM with extended conjugation, which increases its stability and allows sufficient time for the second nucleophile to add before dimerization occurs. The preferred method for the addition of two different nucleophiles is the addition of an alkyllithium reagent followed by a Grignard reagent. The lithium reagent, due to the strength of the O-Li bond, does not cause *o*-QM formation, but subsequent addition of an organomagnesium reagent, due to the Lewis acidity of Mg^{+}, continues the cascade to form the *o*-QM, which undergoes subsequent 1,4-conjugate addition. It is in this manner that adducts **140**-**142** are formulated in 50-86% yield. The procedure has also been used for salicyl alcohol and *o*-hydroxyacetophenone precursors.[37a,b]

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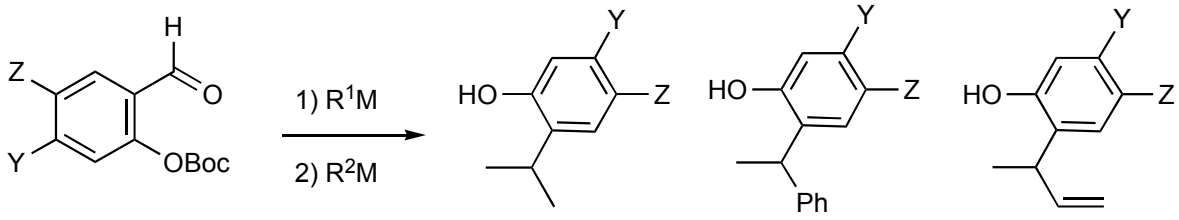
Scheme 31



5: Y=Z=H
132: Y=OBoc, Z=H
133: Y=H, Z=OBoc

134 **135** **136** **137** **138** **139** **140** **141** **142**

SM	R^1M	R^2M	Product	Yield (%)
5	2.5 equiv MeMgCl		**134**	86
132	2.5 equiv MeMgCl		**135**	97
133	2.5 equiv MeMgCl		**136**	57
5	PhMgCl	MeMgCl	**137**	71
132	PhMgCl	MeMgCl	**138**	74
133	PhMgCl	MeMgCl	**139**	50
5	MeLi	$CH_2CHMgBr$	**140**	56
132	MeLi	$CH_2CHMgBr$	**141**	86
133	MeLi	$CH_2CHMgBr$	**142**	65

2-Isopropylphenols (134-136); **General Procedure**: [37a]

To a stirred soln of the *o*-OBoc aldehyde (1 equiv) in Et_2O (0.2 M) at 0°C was added the Grignard reagent (2.5 equiv) drop-wise. The reaction was stirred at 0°C until complete consumption of the starting material was observed by TLC. 0.5N HCl was then added while the reaction was still cold. After warming to rt, the mixture was extracted with Et_2O, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel using EtOAc/ petroleum ether (1:9).

2-(1-Phenylethyl)phenols (137-139); **General Procedure**: [37a]

The first Grignard reagent (1.05 equiv) was added drop-wise to a stirred soln of the aldehyde (1 equiv) in Et_2O (0.2 M) at –78°C. When the starting material was **4**, the second Grignard reagent (2 equiv) was added immediately; otherwise, the reaction was stirred for 20 min and the second Grignard reagent was subsequently added. The reaction was warmed to rt and stirred for three hours. The reaction was

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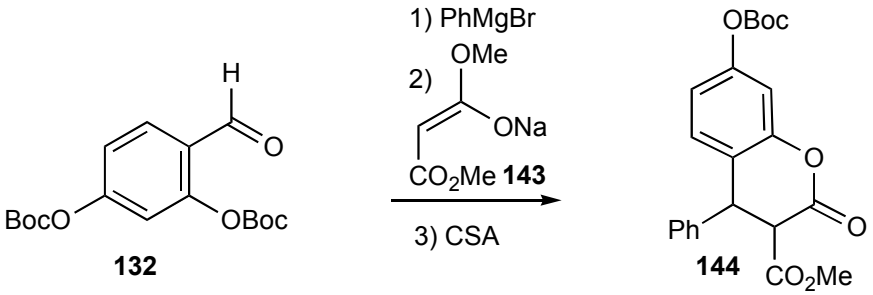
quenched with 0.5N HCl, extracted with Et_2O, washed with brine, dried with Na_2SO_4, and concentrated in vacuo. Flash chromatography on silica gel using petroleum ether/ EtOAc (95:5) yielded clean product.

2-(But-3-en-2-yl)phenols (140-142); **General Procedure**: [37a]

The organolithium reagent (1.05 equiv) was added drop-wise to a stirred soln of the aldehyde (1 equiv) in THF (0.2 M) at –78°C. After 25 min, the cold bath was removed. After an additional 10 min, the Grignard reagent was added and the reaction was stirred at rt until complete. After warming to rt, the mixture was extracted with Et_2O, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography on silica gel using petroleum ether/EtOAc (95:5) yielded the product.

The δ-lactone **144** is constructed by the sequential addition of phenylmagnesium bromide to the aldehyde **132** followed by the addition of the sodium enolate of dimethyl malonate **143** in 73% (Scheme 32).[37b]

Scheme 32



Chroman-2-one (144); **Typical Procedure**: [37b]

The phenylmagnesium bromide (1.1 equiv) was added to the aldehyde (1 equiv, 0.1 M Et_2O) at -78°C. In a separate flask, NaH (2 equiv) was dissolved in THF (0.1 M) and dimethyl malonate (2 equiv) was added. This enolate soln was then added to the aldehyde soln at -78°C. The mixture was stirred at rt until complete. 0.5 N HCl was added while the reaction was still cold. After warming the reaction to rt, the mixture was extracted with Et_2O, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. To complete the ring closure, the product was dissolved in THF and stirred in the presence of camphorsulfonic acid (5 equiv) for 8 h. Flash chromatography on silica gel with petroleum ether/EtOAc (95:5) yielded the product.

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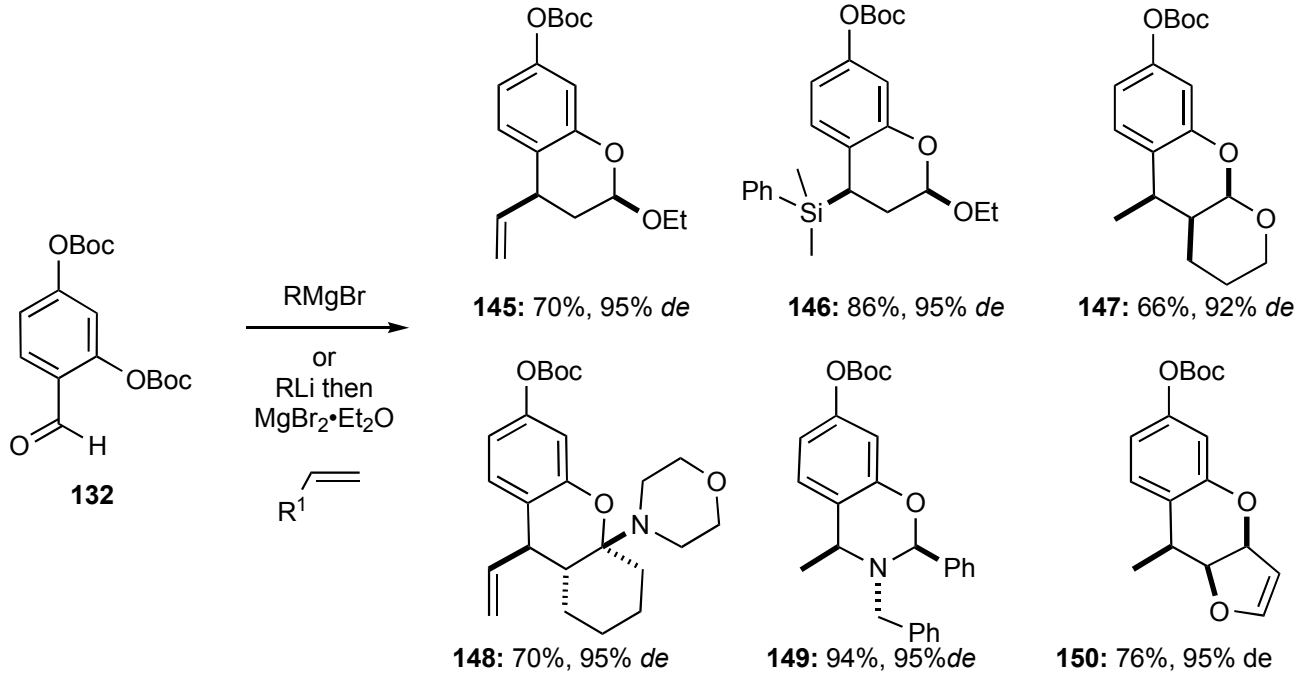
A three-component, one-pot benzopyran synthesis also uses mild, anionic conditions for *o*-QM generation (Scheme 33). The addition of Grignard reagents to *o*-Boc salicylaldehydes such as **132** in the presence of assorted enols, enamines, and imines results in the formation of various chroman derivatives (**145-150**) with excellent diastereoselectivities. The impressive selectivity is due in part to the low temperature (-78°C) conditions at which the *o*-QM is generated. Alternatively, organolithium reagents can be used if $MgBr_2 \bullet Et_2O$ is subsequently added to induce the formation of the corresponding *o*-QM. The straightforward procedure leads to a structurally diverse array of benzopyrans in a single pot with good yields (66-94%). The strategy was also extended to *o*-Boc salicyl alcohol precursors.[37a,c]

Scheme 33



Chromans (145**,** 147- 150**); Typical Procedure**:[37c]

To a flame-dried flask was added benzaldehyde **132** (0.23 mmol, 0.1 M Et_2O). The appropriate dienophile (5 equiv) was then added and the vial was cooled to -78°C. To this soln was added the appropriate Grignard reagent (1.05 equiv) drop-wise. The reaction was slowly warmed to rt over 3 h, quenched with 1M $NaHCO_3$, and extracted with Et_2O. The Et_2O layer was washed with brine, dried

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over $NaSO_4$, filtered, and concentrated in vacuo. The crude mixture was chromatographed through silica gel with petroleum ether/ EtOAc (98:2).

Chroman (146**)**; **Typical Procedure**: [37c]

A flame-dried flask was charged with the aldehyde **132** (30.0 mg, 0.089 mmol), ethyl vinyl ether (0.89 mL), and cooled to -78°C. Dimethylphenylsilyllithium (740 μL, 0.27 mmol, 0.36 M in THF) was added drop-wise and stirred at -78°C for 30 min. $MgBr_2{\cdot}OEt_2$ (32.2 mg, 0.125 mmol) was then added and the reaction was slowly warmed to rt. Upon completion, the reaction was quenched with 1M $NaHCO_3$, extracted with Et_2O, washed with brine, dried over $NaSO_4$, filtered, and concd in vacuo. The crude mixture was chromatographed through silica gel with petroleum ether/ EtOAc (98:2).

The first enantioselective reaction of an *o*-QM with a chiral enol ether was utilized in the synthesis of *R*-mimosifoliol (**158**) and the formal synthesis of *R*-tolterodine (**159**) (Scheme 34).[39] The three-component, one-pot benzopyran method is used to set the chiral benzylic junctions of both natural products. Aldehydes **151** and **152**, phenylmagnesium bromide, and *trans*-*2S*-phenyl-cyclohexan-*1R*-ol vinyl ether (**153**) produce benzopyrans **154** and **155** in both 95% *de* and 83% and 90% yields, respectively. The *syn* relationship between the phenyl residue of the benzopyran and the oxygen substituent of the acetal results from an *endo*-transition state. Taking into account *pseudo*-allylic strain and Houk's calculation,[40] the enol ether reacts in the s-*trans* conformation. The *o*-QMs undergo reaction opposite the 2*S*-phenyl residue in enol ether **153** and induce *R*-configuration in the resulting benzyl junctions. Benzopyran **154** was transformed into *R*-mimosifoliol (**136**) in six steps whereas benzopyran **155** was converted into *R*-tolterodine (**159**) in two steps, both utilizing malleable lactol intermediates **156** and **157**.

Scheme 34

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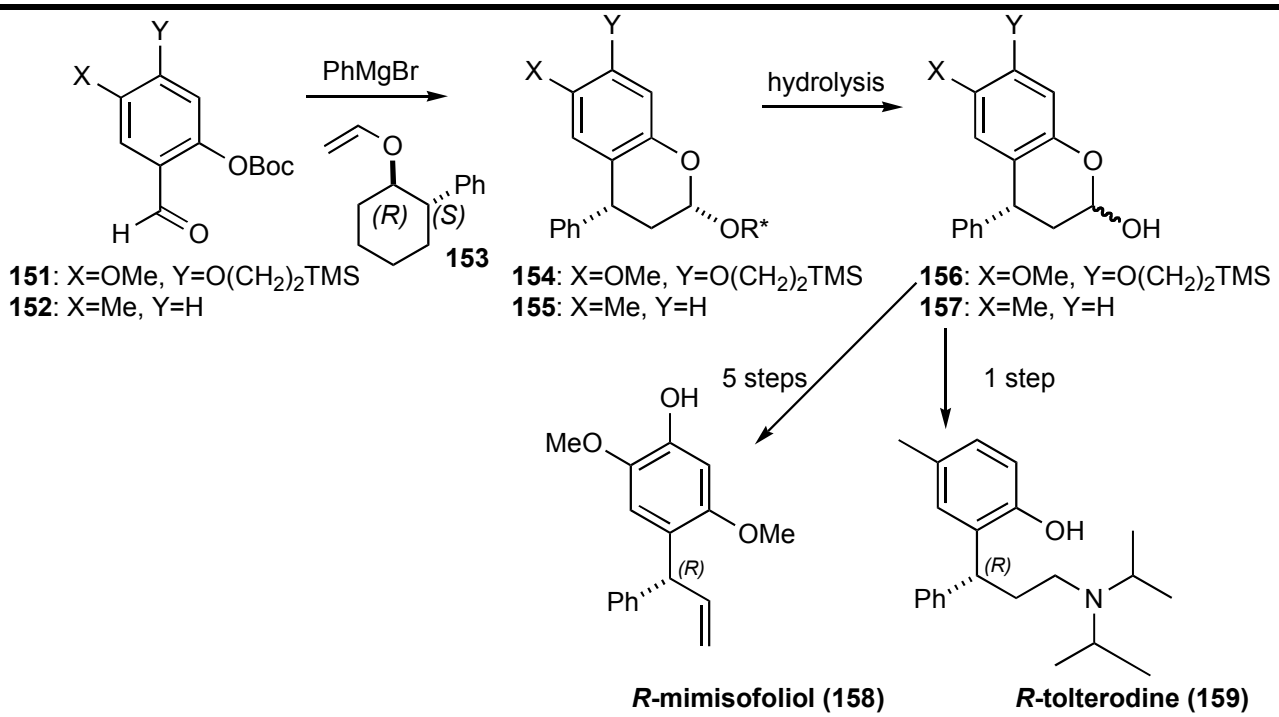

Chromans (154) and (155); **Typical Procedure**:[39]

A flame-dried flask equipped with stir-bar and nitrogen line, was charged with the aldehyde (0.1 M Et_2O) and enol ether (2 equiv) **153**. The soln was cooled to -78°C and phenylmagnesium bromide (1.05 equiv) was added drop-wise. The reaction was warmed to rt over 3 h then quenched with 1 M $NaHCO_3$ and extracted with Et_2O. The ether layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was then chromatographed through silica gel, eluting with petroleum ether/ EtOAc (95:5).

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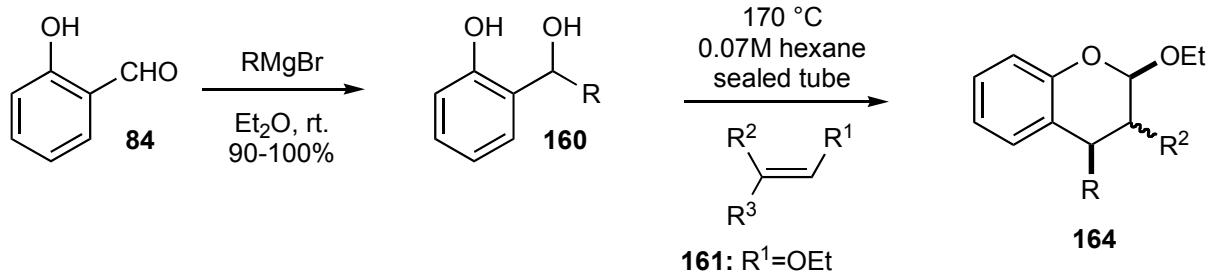
4.28.12.1.3.6 *o*-hydroxymethylphenol precursors

Variation 1: Thermal induction

The pyrolysis of *o*-hydroxybenzylalcohols such as **160** (R=H) [41,42] and 160 (R≠H)[29,2,43,42d,e] has been well examined. Thermally initiated intermolecular [4+2] reactions of *o*-QMs generated from the corresponding hydroxybenzylalcohols **160** have been investigated (Scheme 35).[**Error! Bookmark not defined.**d,e] When phenol **160** is heated to 170° C in the presence of two equivalents of a vinyl ether, a cycloaddition affords chromans like **164**. The overall yields for the cycloadducts range from 35-100% with diastereomeric ratios ranging from 9-90%. The major diastereomer results from an *endo*-transition state resulting in a *cis* relationship between the substituents at the 2- and 4-positions. Starting material **160** is prepared from salicylaldehyde (**84**) and the appropriate Grignard reagent.

Scheme 35



161: R^1=OEt
162: R^1=OEt, R^2=CH_3
163: R^1=OEt R^3=CH_3

R	Enol Ether	Yield (%)	*dr (cis:trans)*
Ph	**161**	100	3:1
Ph	**162**	100	2.3:1
Ph	**163**	100	2.3:1
Me	**161**	50	4:1
Me	**162**	35	9:1
Me	**163**	60	1.2:1
Bn	**161**	50	1.5:1
Bn	**162**	40	20:1
Bn	**163**	40	1:1.5

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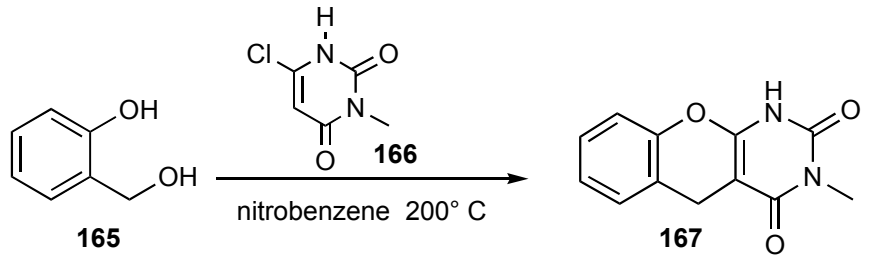
Thermally generated *o*-QMs have been harnessed for the synthesis of 5-deaza-10-oxaflavins (Scheme 36).[44] Uracil derivative **166** undergoes a [4+2] cycloaddition with the *o*-QM generated from the benzyl alcohol (**165**) (200°C) producing the chromene (**167**) in 80% yield upon HCl elimination from the initial cycloadduct.

Scheme 36



Chromene (167); **Typical Procedure**:[44]

Heating **166** with *o*-hydroxybenzyl alcohol (**165**) (3 equiv) in nitrobenzene at 200°C for 4 h afforded the 1,5-dihydro-5-deaza-10-oxaflavin **167** in 80% yield. Concentration in vacuo followed by purification by column chromatography afforded the desired product.

Variation 2: Derivatization of the *o*-hydroxymethylphenol precursor

The cycloaddition of β-substituted enamines **168** with *o*-QMs generated from benzyl alcohols such as **169** has been investigated (Scheme 37).[45] Conducted in Ac_2O, the initial chroman cycloadducts undergo a subsequent elimination of the morpholine fragment, which is then converted into its corresponding acetamide along with the respective chromenes **170**. The latter are formed in 38- 89% yield. Because the morpholine is sequestered, a potential side reaction, namely conjugate addition of morpholine to the *o*-QM intermediate is prevented. Enamines β-substituted with an ester moiety, however, afforded very little of the desired product. Surprisingly, generation of the identical *o*-QM intermediates from *o*-phenolic Mannich bases led to none of the anticipated products.

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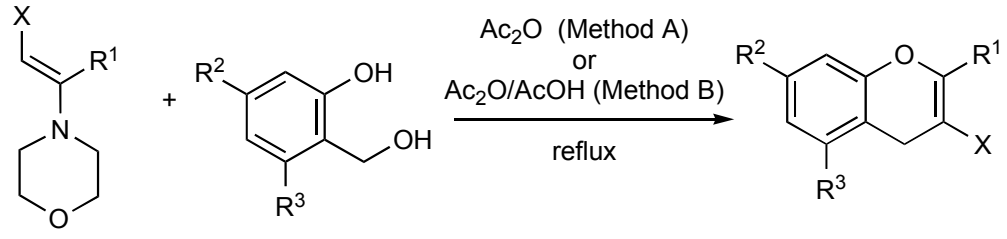
Scheme 37



168 **169** **170**

X	R^1	R^2	R^3	Method	Yield (%)
NO_2	H	H	H	A	62
Ac	H	H	H	B	89
AcPh	H	H	H	A	38
Ac	H	OMe	H	A	88
AcPh	Me	H	H	A	87
AcPh	H	H	OMe	A	78

Chromene (170); **General procedure**:[45]

A soln of β-functionalized enamine **168** (0.0125 mol), *o*-hydroxybenzyl alcohol **169** (0.0125 mol) in acetic anhydride (12 mL, Method A) or in acetic acid/acetic anhydride (12 mL/1.25 g, Method B), was heated under relux for 2 h. The mixture was concentrated in vacuo, and the crude residue was purified by column chromatography (silica gel 60, 70 g, CH_2Cl_2). The final product was either recrystallized (EtOH) or distilled.

Variation 3: Photochemical

The laser flash photolysis of various *o*-hydroxybenzyl alcohols **160** in the presence of vinyl ethers results in a [4+2] cycloaddition at room temperature affording adducts **171**-**176** in greater then 90% yields (Scheme 38).[46] Less electron-rich olefins, such as terminal olefins, do not undergo this reaction. Instead the *o*-QM intermediate undergoes the addition of water to regenerate the starting material. The product distribution for **176** was initially misconstrued as favoring the *trans*-diastereomer. This mistake was corrected and reported in a subsequent review.[47]

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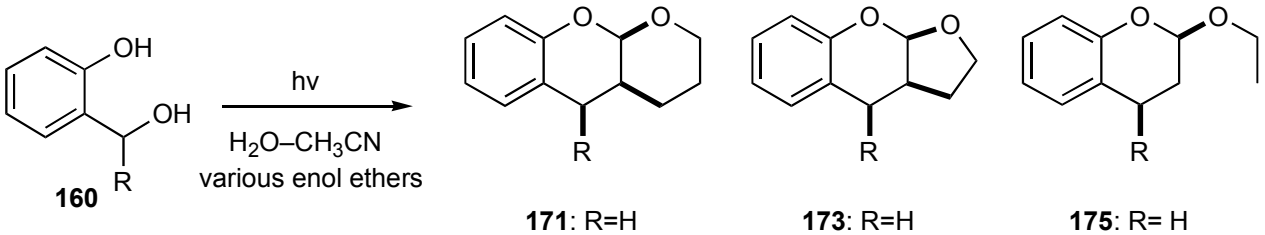
Scheme 38



Chromans (171-176**)**; **General Procedure**:[46]

Photolysis (10^{-3} M; Rayonet photoreactor; 254 nm; ~15°C; argon) of **160** in H_2O/CH_3CN (1:1) with 0.1 M of the appropriate enol ether gave the corresponding cycloadducts in >90% yield.

Variation 4: Lewis acid induction

Chiba reports that $LiClO_4$ and wet montmorillonite in CH_3NO_2 induces *o*-QM formation from the *o*-hydroxybenzyl alcohol **160** (Scheme 39). [48] *o*-QMs generated in this fashion undergo reaction with alkenes, even unactivated alkenes, to produce chromans **178** and **179**. It is believed the wide surface of the montmorillonite may accelerate this dehydration reaction and the addition of water might regulate the acidic decomposition and polymerization of the starting materials. $LiClO_4$ is expected to stabilize the zwitterion **177**, which is equivalent to *o*-QM **112**. However, due to its ionic nature a 2:1 ratio of diastereosomers is obtained in **179**.

Scheme 39

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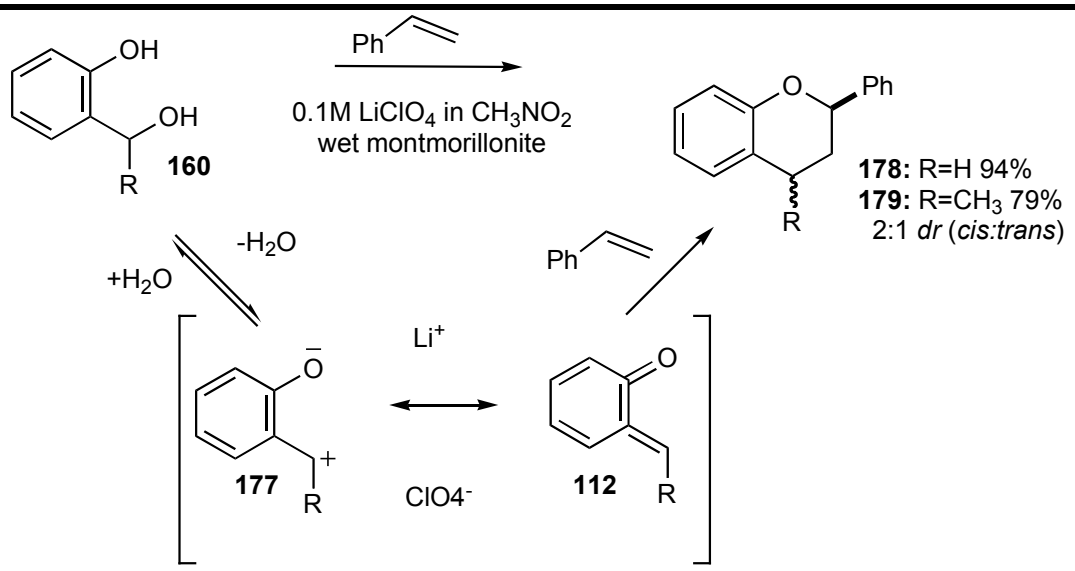

Chromans (178-179); **General Procedure**:[48]

Montmorillonite K 10 (50 mg) and water (90 μL) were dispersed in $MeNO_2$ (5 mL), then salicyl alcohol (25 mg), styrene (63 mg), and $LiClO_4$ (50 mg) were added to the soln. The reaction mixture stood at rt for 48 h. After the reaction was completed, the products were extracted with *n*-hexane. The solvent was removed in vacuo after drying over $MgSO_4$, and the crude residue was then purified by silica gel chromatography (*n*-hexane/EtOAc) to give the cycloadduct.

Variation 5: Lewis base induction

Intramolecular cyclizations of *o*-hydroxybenzyl alcohols, like **180**, with Grignard reagents probably involve *o*-QMs (Scheme 40).[49] Treatment of triol **180** (R=OH) with ethylmagnesium bromide results in the formation of **181** in 71% yield. Less then 1% of the regioisomer **182** is observed. The high regioselectivity may result from chelation between the magnesium phenoxide and the oxygen of the *o*-QM intermediate **185**. Regioselective closure has also been observed during the formation of larger rings, however, to a lesser extent. Lithium and sodium bases are ineffective for initiating this type of intramolecular cyclization. Proof for the intermediacy of an *o*-QM was demonstrated by a trapping experiment with ethyl vinyl ether (EVE) to produce **183**, however, the relative stereochemistry in this cycloadduct was not assigned.

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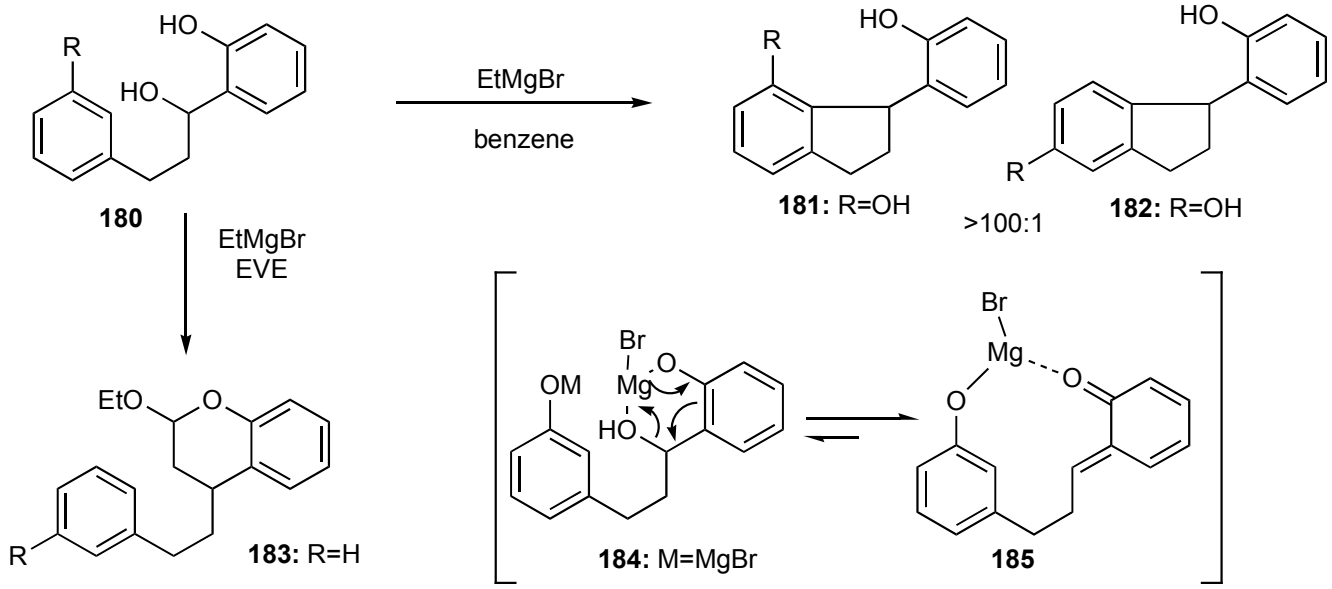
Scheme 40



2,3-Dihyrdo-1H-indene (181); **General Procedure**:[49b]

Ethylmagnesium bromide (1.5 mmol) and the alcohol (0.70 mmol) were refluxed in benzene (15 mL) for 20 h.

Chroman (183); **General Procedure**:[49b]

A soln of the alcohol (0.79 mmol) in Et_2O (5 mL) was treated with ethylmagnesium bromide (0.94 mmol). The mixture was stirred for 10 min and the solvent was removed in vacuo under nitrogen. Benzene (15 mL) was addded, followed by ethyl vinyl ether (1.39 mmol) in benzene (2 mL), and the mixture was refluxed for 20 h.

Corey reports that acylation of **186** with *p*-nitrobenzoyl chloride and pyridine affords the acylated benzyloxy compound **187** (Scheme 41). Exposure of this material to 2 equivalents of N-methyl ephedrine (**188**) produced the amine **189** in 77% yield, which can serve as a chiral ligand for the addition of dialkyl zinc reagents to some aromatic aldehydes.[50]

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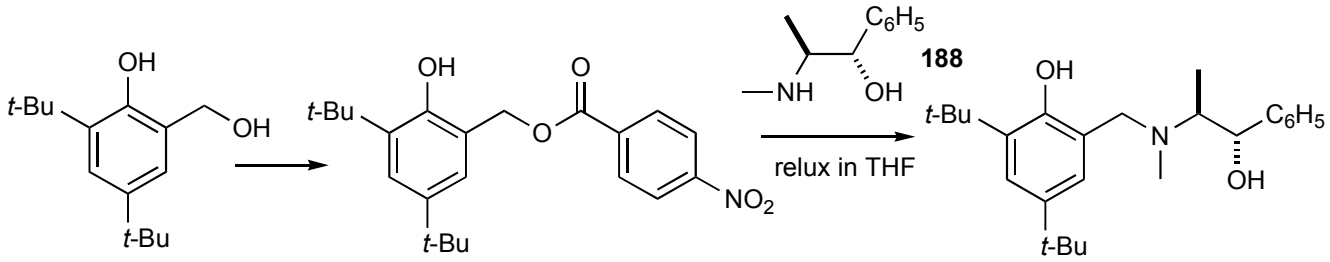
Scheme 41



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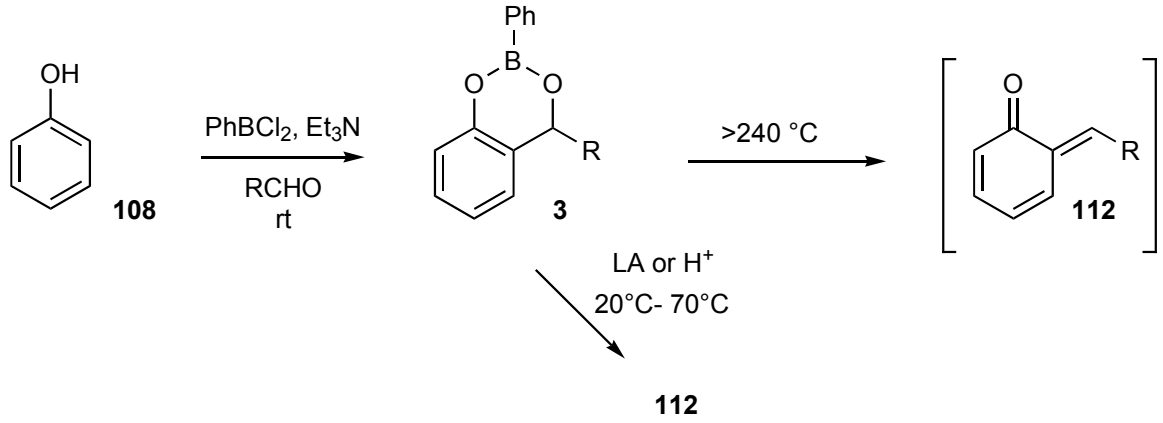
4.28.12.1.3.6 Benzodioxoborin precursors

Benzodioxaborins, like **3**, have been developed as *o*-QM precursors (Scheme 42).[51] The procedure proves quite useful for both intramolecular and intermolecular applications. However, it has two limitations: 1) the reactants must withstand acidic conditions, and 2) the high temperature requirements cause low diastereoselectivity in some reactions. Cycloadditions using thermal conditions lead to cycloadducts in 0% *de*. It was found Lewis acids greatly enhance the ability of 2-phenyl-4H-1,3,2-benzodioxaborins **3** to form *o*-QMs, such as **110**, at temperatures < 70°C.[51a]

Scheme 42



Variation 2: Lewis Acid Induction

The reactions of benzodioxaborin **190** with toluene (**191**), phenol (**108**), and thiophene (**193**) form aryl methylphenols **192**, and **194-196** in respectable yields, 56-76%, under low temperature, Lewis acidic conditions (Scheme 43). With less reactive substrates, such as toluene (**178**), a stronger Lewis acid, titanium tetrachloride, is needed.

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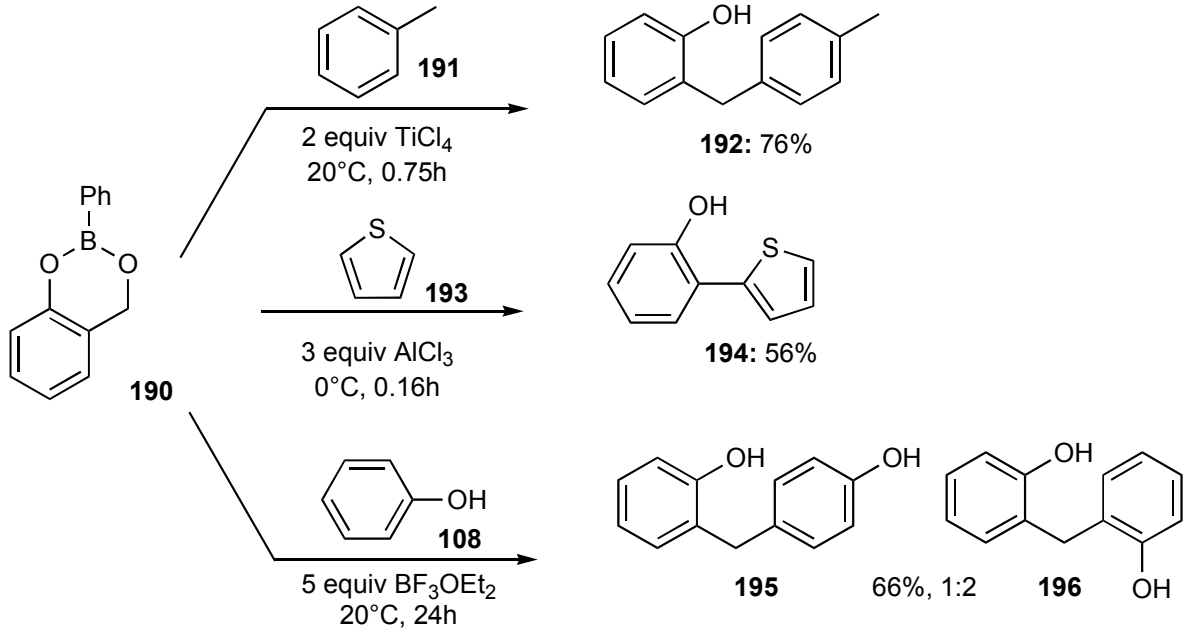
Scheme 43

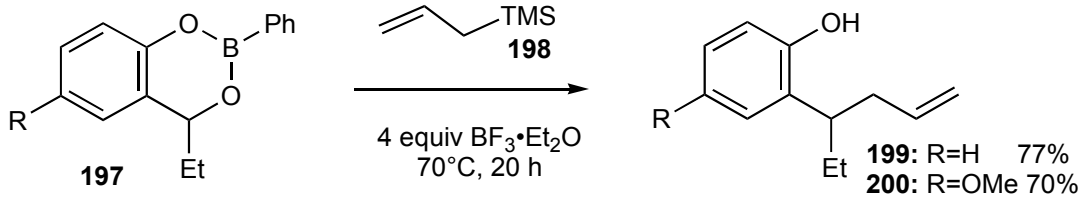


Conjugate addition products (192, 194-196**);Typical Procedure**: [51a]

$TiCl_4$ (2 equiv), boron trifluoride-diethyl ether complex (5 equiv), or $AlCl_3$ (3 equiv) was added to a soln of **177** (5 mmol) in toluene (15 mL), **177** (5 mmol) in 1,2-dichloroethane (15 mL) and phenol (3 equiv), or **177** (4 mmol) in CH_2Cl_2 (12 mL) and thiophene **182** (3 equiv) at 0°C and the resulting soln was stirred at rt for 45 min, 24 h, or 10 min, respectively,

Allyltrimethylsilane (**198**) reacts with *o*-QMs generated from **197** under these conditions to produce *o*-homo allylated phenols, **199** and **200**, in good yields (Scheme 44).

Scheme 44



2-(Hex-5-en-3-yl)phenol (199**)** and **(**200**)**; **Typical Procedure**: [51a]

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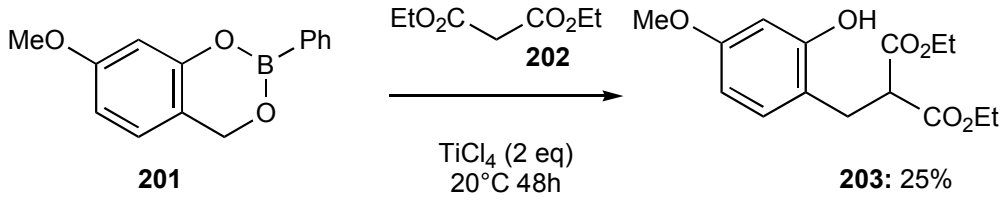
To a soln of **197** (1 mmol) and allyltrimethylsilane (**198**) (4 equiv) in dichloroethane (10 mL) was added boron trifluoride-diethyl etherate complex (4 equiv). The mixture was warmed to 70°C for 20 h.

o-QM generated from **201** under Lewis acidic conditions reacts with diethyl malonate (**202**) to yield adduct **203** in 25% (Scheme 45) .

Scheme 45



Diethyl 2-(2-hydroxybenzyl)malonate (203**)**; **Typical Procedure**: [51a]

To a cooled (0°C) soln of $TiCl_4$ (0.82 mmol) in CH_2Cl_2 (10 mL) was added diethylmalonate (**202**) (0.746 mmol). The mixture was stirred for 10 min then **201** was added. After stirring for another 5 min, triethylamine (0.858 mmol) was added and the reaction was stirred overnight at rt. Another equiv of $TiCl_4$ was added and the reaction was stirred for another night.

This methodology was extended to tricyclic benzodioxaborins, such as **204** (Scheme 46).[51e] The starting materials are prepared by an annulation reaction, heating a phenol bearing a *m*-alkyl aldehyde of various chain lengths with phenylboronic acid. These tricyclic benzodioxaborins are useful *o*-QM precursors and upon treatment with boron trifluoride undergo reactions with various allyl silanes **205** to form adducts **207** and **209** (n=1) and **206** and **208** (n=2), all in respectable yields.

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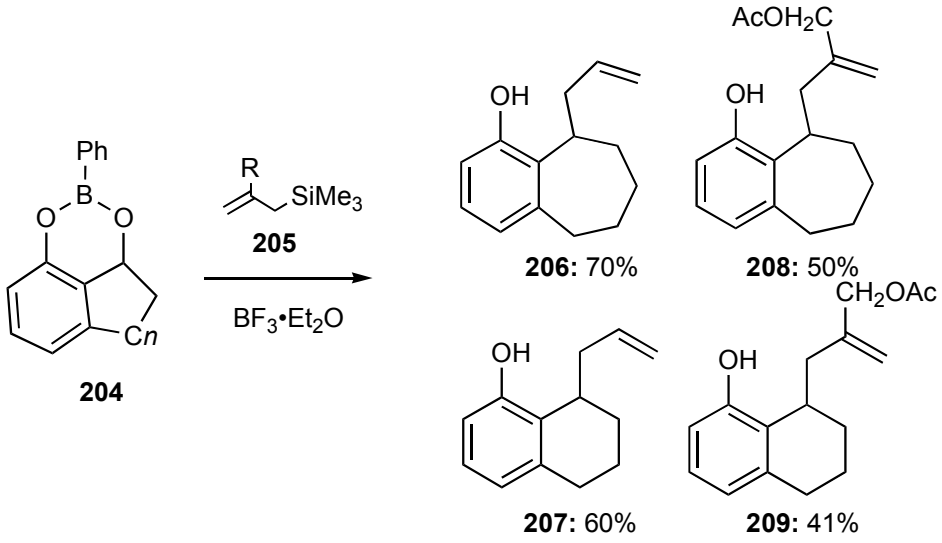
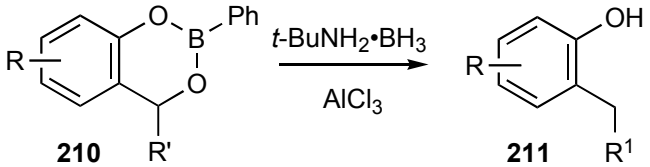
Scheme 46



The ability to reduce *o*-QMs generated from benzodioxaborins **210** under Lewis acid conditions has been studied (Scheme 47).[51b] In this manner, *o*-alkylated phenols **211** are produced in yields of 50-98%. Unfortunately, the use of *t*-butyl amine borane complex precludes unsaturation in the side-chain and the Lewis acid conditions limit the functional groups of the starting materials.

Scheme 47



R	R^1	Temp (°C)	Time (h)	Yield (%)
3-CH_3	H	20	20	50
H	Ph	0	0.75	97
H	Bn	20	20	71
H	$(CH_2)_4Ph$	20	20	98

***o*-Alkylphenol (**211**); General Procedure**:[51b]

To a suspension of anhyd $AlCl_3$ (3 mmol) in CH_2Cl_2 (15 mL) at 0°C was added *t*-butylamine borane (6 mmol). The resulting mixture was allowed to react at 0°C for 20 min. A soln of the appropriate

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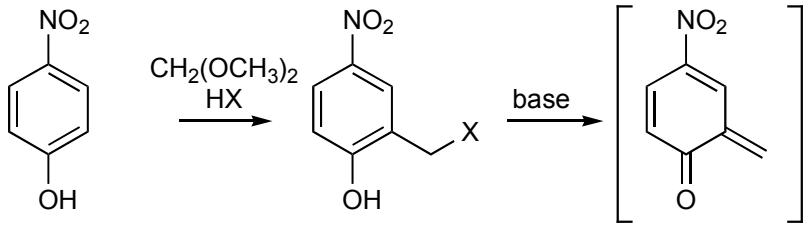
dioxaborin (1 mmol) in CH_2Cl_2 (2mL) was added. The mixture was warmed to rt and stirred for 20 h, at which time, cold dilute (1 N) HCl was added. The product was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated in vacuo. Silica gel chromatography EtOAc/ hexane (1:9) afforded the products.

4.28.12.1.3.7 *o*-halomethyl phenol precursors

It has been shown that *o*-halomethyl phenols are also *o*-QM precursors. Precursor **213** can be produced by halomethylation of a phenol **214** with dimethoxymethane and HX, however, this is only controllable if the *para*-position is blocked with an electron-withdrawing group (Scheme 48).[52] Under acidic or neutral conditions, the *o*-hydroxybenzyl bromide **213** (X=Br) displays selectivity for N-alkylation of tryptophan.[53] Under basic conditions, however, **213** displays no selectivity in its reaction with amino acids, suggesting that base accelerates formation of the corresponding *o*-QM. Base in conjunction with **213** (X=Cl) is also inappropriate for subsequent [4+2] cycloaddition. However, these conditions were useful for the preparation of dimers and trimers of the corresponding *o*-QM.[54] The action of base on unsubstituted **213** (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 SN_2 displacement of the chloride is also possible). The kinetics for the formation of **214** from **213** (X=Cl) with various anilines as well as the subsequent addition reaction of the anilines with the *o*-QM has been studied.[55]

Scheme 48



212 **213** **214**

Variation 1: Neutral Conditions

2-hydroxy-5-nitrobenzyl bromide (**213**) undergoes reaction with tryptophan (**214**) to produce the tricycle compound **215** in 70% (Scheme 49).[56] The indole, which is fairly basic, likely facilitates the

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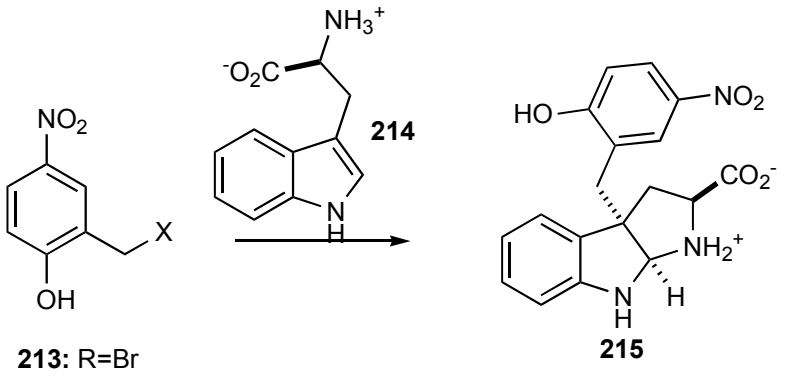
formation of the *o*-QM by β–elmination of the bromide and then intercepts it by undergoing reaction as an enamine. Cyclization of the primary amine on the resulting iminium ion affords the third ring.

Scheme 49



Tricyclic product (204**); General Procedure**:[56]

A dry acetone soln (4 MM) of **213** was added to a soln ($2x10^{-2}$ M) of tryptophan (**214**) in water. The resulting reaction was extracted repeatedly with Et_2O. The remaining soln was evaporated to a small volume and neutralized to pH 4, whereupon, the mixture of reaction products precipitated. The products were collected, washed by centrifugation, and dried.

Variation 2: Basic Conditions

One method generates an *o*-QM **218** from the corresponding silyl ether **217** with fluoride ions (Scheme 50).[57] The bromide **217** is available from silylation, followed by free radical halogenation of **216**. The dibromide (**218**: R=CH_2Br) has been used to crosslink strands of DNA and form **219**. The mono-bromide (**218**: R=H) has been investigated for its ability to alkylate deoxynucleosides and form **220** upon the introduction of fluoride. Their site of alkylation was determined through NMR studies of the isolated adducts. 2′-Deoxyribose derived adenine, guanine, cytosine, and thiamine were used for the experiment.

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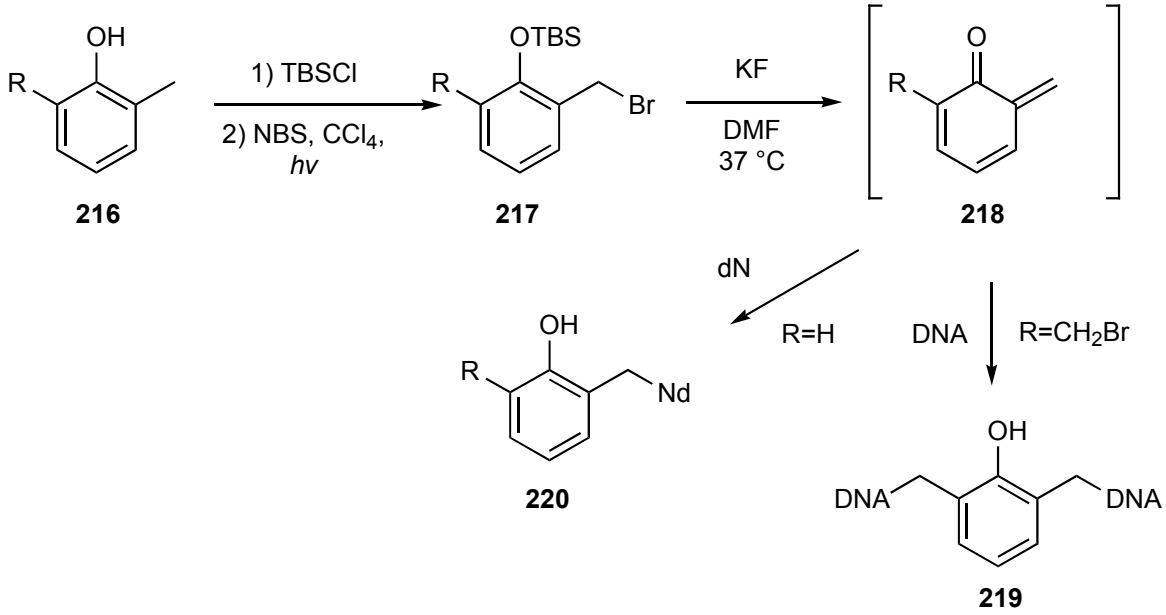
Scheme 50



216 **217** **218** **220** **219**

DNA cross-linking Procedure:[57b]

Duplex DNA (3 μm) formed by (oligodeoxynucleotides) OD1, ODN2, or ODN3 was annealed in MES-NaOH buffer (2 mM, pH 7.0) by placing the mixture (total volume 100 μL) in a microfuge tube. The tube was heated in a water bath to 90°C, and the bath and tube were allowed to cool to rt over 2 h. Typically, 5 μL of the above soln was mixed with 3 μL of the alkylating agents (1.5 mM in CH_3CN). Reactions were initiated by addition of 2 μL aq KF. The mixture was incubated at 20°C for 24 h, and then dialyzed against water for 12 h, dried, resuspended in gel loading buffer (5 μL) and analyzed by denaturing PAGE (20%, 7 M urea).

Nucleic acid Procedure:[57d]

The appropriate nucleic acid (1.5 mmol) and *O*-(*tert*-butyldimethylsily)-2-bromomethylphenol (2.2 mmol) were dissolved in DMF (1 mL) and combined with an aq soln of KF (2.64 M, 1.5 mL). The reaction was heated at 50°C for 14 h, cooled, and then directly subjected to silica gel chromatography with $CHCl_3/CH_3OH$ (4:1) to yield the appropriate adducts.

Variation 3: Lewis Acidic Conditions

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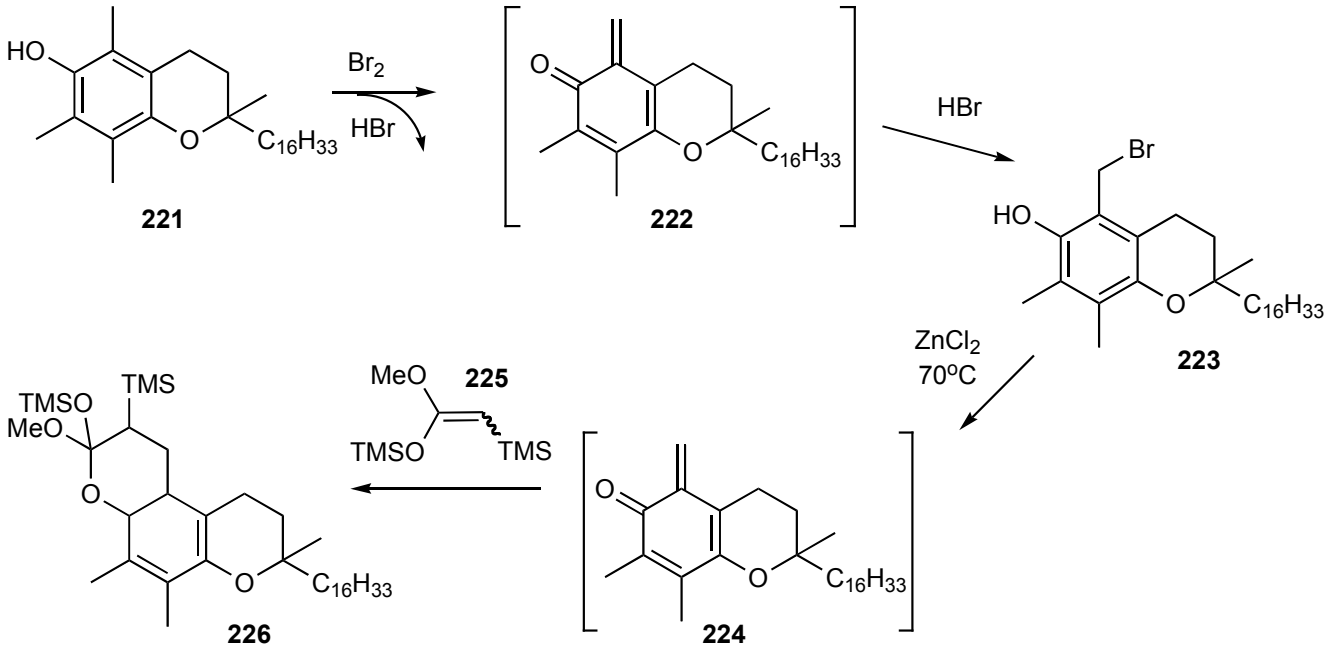
Bromination of α-tocopherol (**221**) with bromine has shown to proceed as a two-step process including the occurrence of an *o*-QM, not as a radical-chain reaction, contrary to earlier reports (Scheme 51). The first step in the mechanism is an oxidation of **221** to the *o*-QM **222**, which adds hydrogen bromide that was formed in the first step. [20a] *o*-QM **224** is readily formed from **223** by elimination of hydrogen bromide at temperatures above 50°C. When the reaction takes place in the presence of the silyl enol ether **225** cycloaddition ensues producing **226**.

Scheme 51



5a-bromo-α-tocopherol (222**); Typical Procedure:**[20a]

A soln of α-tocopherol (1.29g, 3.00 mmol) in *n*-hexane (50mL) was placed into a 250 mL flask equipped with a dropping funnel, magnetic stirrer, and a drying tube filled with $CaCl_2$. A soln of Br_2 (0.50g, 3.13 mmol) in *n*- hexane (20 mL) was quickly added at rt. The solution was stirred for 2 h and the solvent was removed in vacuo.

Chroman (226**); Procedure**:[20e]

In a 100 mL flask, a mixture of anhyd zinc chloride (0.220 mmol), silyl enol ether (20.80 mmol), and CH_3CN (10mL) was heated to 70°C. A soln of 5a-bromo-α-tocopherol (6.0 mmol) in 10 mL of

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CH_3CN was slowly added over 15 min under constant stirring, and the reaction was heated for 1 h, then 10 min at 85°C, and cooled to rt.

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4.28.12.1.4 Conclusion

The most prevalent course of reaction for *o*-QMs 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 as it is formed usually through an intramolecular or intermolecular reaction. Indeed, *o*-QMs used in this capacity have proven to be very useful. Undoubtedly as more techniques evolve this venerable intermediate will find greater use in synthesis.

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