### Title

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# The Domestication of *ortho*-Quinone Methides

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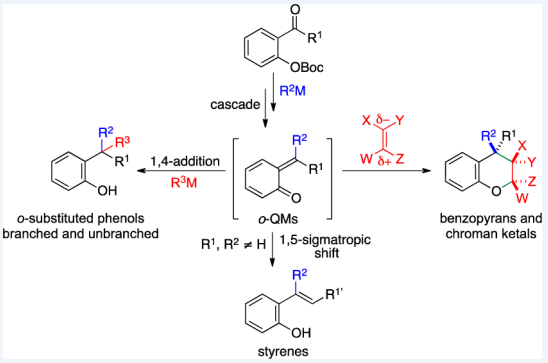
**CONSPECTUS:** An *ortho*-quinone methide (*o*-QM) is a highly reactive chemical motif harnessed by nature for a variety of purposes. Given its extraordinary reactivity and biological importance, it is surprising how few applications within organic synthesis exist. We speculate that their widespread use has been slowed by the complications that surround the preparation of their precursors, the harsh generation methods, and the omission of this stratagem from computer databases due to its ephemeral nature.




About a decade ago, we discovered a mild anionic triggering procedure to generate transitory *o*-QMs at low temperature from readily available salicylaldehydes, particularly OBoc derivatives. This novel reaction cascade included both the *o*-QM formation and the subsequent consumption reaction. The overall transformation was initiated by the addition of the organometallic reagent, usually a Grignard reagent, which resulted in the formation of a benzyloxy alkoxide. Boc migration from the neighboring phenol produced a magnesium phenoxide that we supposed underwent $\beta$-elimination of the transferred Boc residue to form an *o*-QM for immediate further reactions. Moreover, the cascade proved controllable through careful manipulation of metallic and temperature levers so that it could be paused, stopped, or restarted at various intermediates and stages. This new level of domestication enabled us to deploy *o*-QMs for the first time in a range of applications including diastereocontrolled reactions.

This sequence ultimately could be performed in either multipot or single pot processes. The subsequent reaction of the fleeting *o*-QM intermediates included the 1,4-conjugate additions that led to unbranched or branched *ortho*-alkyl substituted phenols and Diels–Alder reactions that provided 4-unsubstituted or 4-substituted benzopyrans and chroman ketals. The latter cycloadducts were obtained for the first time with outstanding diastereocontrol. In addition, the steric effects of the newly created stereocenters in subsequent reactions of chroman ketals and acetals were studied and proved predictable. Through the use of a chiral auxiliary, Diels–Alder products were deployed in numerous enantioselective reactions including several complex natural products syntheses. In this Account, we summarize our efforts, which we hope have contributed to the synthetic renaissance for this venerable species.

## INTRODUCTION AND MOTIVATIONS

*o*-QMs display a cyclohexadiene core affixed with an exocyclic methylene and a carbonyl residue disposed in *ortho* fashion (Figure 1). Their overall stability depends upon a combination

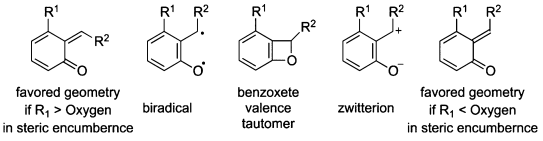



**Figure 1.** Plausible canonical representation of *o*-QMs.

of structural and electronic effects.[1] In general, extended conjugation and electronic donation make them less reactive and isolable. Sterics play a role in controlling the formed olefin geometry, which in turn command the subsequent reaction manifolds or affect the stereochemistry of the products. Compared with their isomeric *para*-quinone methide (*p*-QM) counterparts, *o*-QMs display a greater charge dipole and prove less stable and more reactive. Most are *nonisolable* and tend to self-destruct through dimerization or reactions with unintended nucleophiles. When they are stable and isolable or masked by metal complexation,[2] then they undergo the usual reactions associated with a reactive unsaturated ketone or $\pi$-allyl species,[3] including catalyzed asymmetric reactions.[4] However, when they are *nonisolable*, chiral catalysts aimed at enhancing their reactivity usually lead to more rapid self-destruction than to favorable asymmetric induction.

When we began working with *o*-QMs in 1999, a comprehensive review logically organized around their precursor preparations and generation methods had been wanting. Largely overlooked by synthetic chemists since their first supposition by Fries in 1907[5] and subsequent spectroscopic investigation[6] and crystallographic studies,[7] *o*-QMs have chiefly remained of interest to physical organic chemists.[8]

Among the unstable nonisolable examples, the canonical representations indicate some of their characteristics and

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reactivities (Figure 1). They display both biradical and zwitterionic characteristics. Their ensuing products along with the favored stereoisomers can be determined by the method used to access them.

Past *o*-QM generation methods can be categorized as thermolysis,[9] oxidation,[10] and acid promoted $\beta$-elimination[11] and to a lesser extent tautomerization,[12] photolysis,[13] and base promoted $\beta$-elimination.[14] These methods can be used exclusive of one another or in some combination, if compatible (Figure 2).

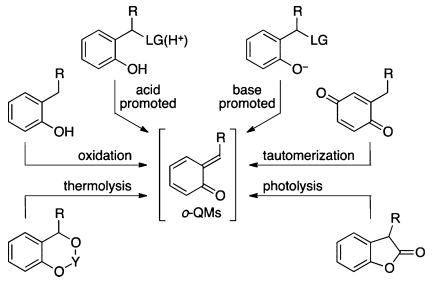


**Figure 2.** Synthetic methods to generate *o*-QMs.

Some more recent examples of these venerable protocols are shown in Figure 3, illuminating the synthetic effectiveness and the complications surrounding precursor preparation and *o*-QM reactivity. Thermolysis reactions require prior construction of a challenging *o*-QM precursor and mandate thermally stalwart functional groups. However, thermal generation proves very useful for intramolecular Diels–Alder reactions (IMDA) leading to thermodynamic products. For example, Funk reported that the benzodioxin underwent thermolysis to produce the desired *N*,*O*-acetal cycloadduct (Figure 3A).[15]

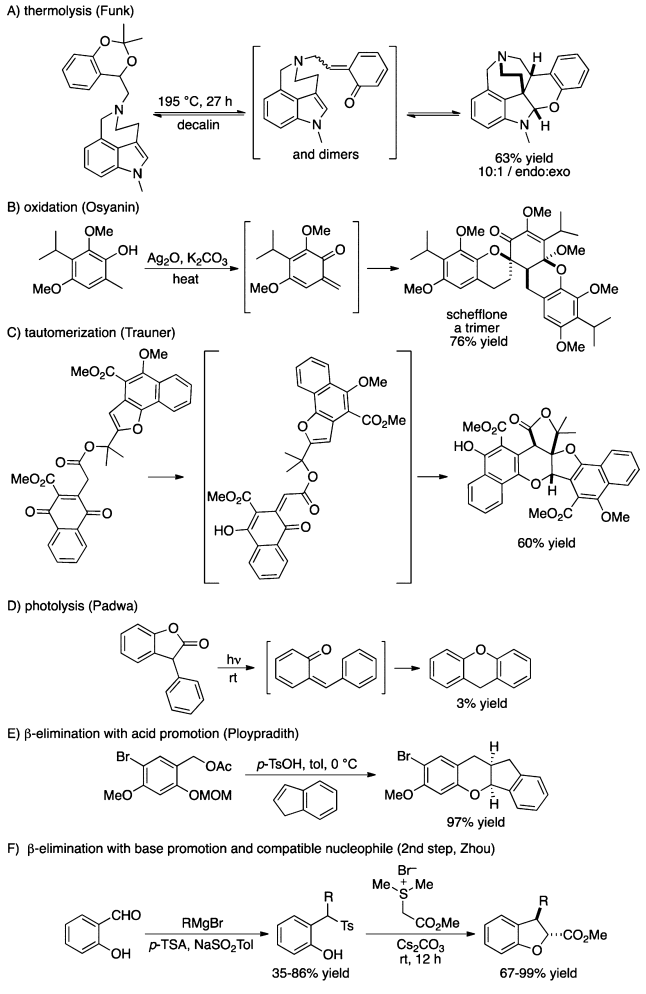


**Figure 3.** Applications of *o*-QM generation protocols.

Oxidative formation usually enables straightforward *o*-QM preparation from simple and stable precursors. However, this category excludes further applications with oxidatively reactive nucleophiles. For example, after thermolytic and acidic *o*-QM generation procedures had failed, Osyanin and co-workers demonstrated that 3-isopropyl-2,4-dimethoxyphenol underwent oxidation and trimerization to afford (±)-schefflone (Figure 3B).[16]

Tautomerization usually commences with oxidation of a *para* hydroquinone precursor to the corresponding *p*-QM. Thermal or basic equilibration results in an *o*-QM for further reaction. For example, Trauner oxidized a *p*-naphthoquinol with $PhI(OAc)_2$ and the resulting *p*-naphthoquinone then tautomerized and underwent an IMDA reaction to afford a rubioncolin B intermediate (-Figure 3C).[17]

Photolytic methods present limitations regarding precursor preparation, triggering residues, and functional group tolerance. These issues can be avoided in an intramolecular reaction. For example, Padwa noted that photo-decarbonylation of benzofuran-2-one yielded an *o*-QM that participated in an oxo-6$\pi$-cyclization and a 1,3-sigmatropic shift to afford the corresponding xanthene (Figure 3D).[18]

Acid and base promoted $\beta$-eliminations leading to *o*-QMs are among the most powerful categories, because they usually proceed at low temperature and permit simultaneous introduction of separate nucleophiles. However, these pH-dependent methods are frequently complicated by lengthy precursor preparations and poor functional group tolerance. Moreover, nucleophile reactivity diminishes under acidic conditions. Ploypradith found that immobilized *p*-TsOH catalyzed the reaction of MOM-protected benzylacetate derivatives with indene to secure the *cis*-substituted chroman (Figure 3E).[19] Using an acidic method, Zhou first prepared the *ortho*-sulfone phenols that were subsequently used to release *o*-QMs under basic conditions (step 2, Figure 3F).[20] We speculate that only basic methods are compatible with the intended sulfur ylide that provides the respective *trans*-2,3-dihydrobenzofuran.

## ■ FULFILLING A *PHENOLIC* NEED

Ortho-alkylated polyhydric phenolic motifs are prevalent among natural products and display interesting biological activities (Figure 4III). They are often constructed by rearrangement, halogenation followed by some metal-mediated coupling reaction, electrophilic substitution, or directed-*ortho*-metalation (DoM) and alkylation event.[21] However, these strategies can not address all types of *ortho* alkylated phenols. The construction of *ortho* alkylated hydroquinone, catechol, and resorcinol derivatives with differentially protected hydroxyl residues is particularly challenging.[22] The combination of regioselectively installing alkyl moieties and chemically distinguishing between the phenolic residues is not straightforward.[23] We required access to differentially phenol protected resorcinol derivatives with differing 4-alkyl residues for our dearomatization research.[24] We imagined a solution by separating the issues of selective phenol protection from


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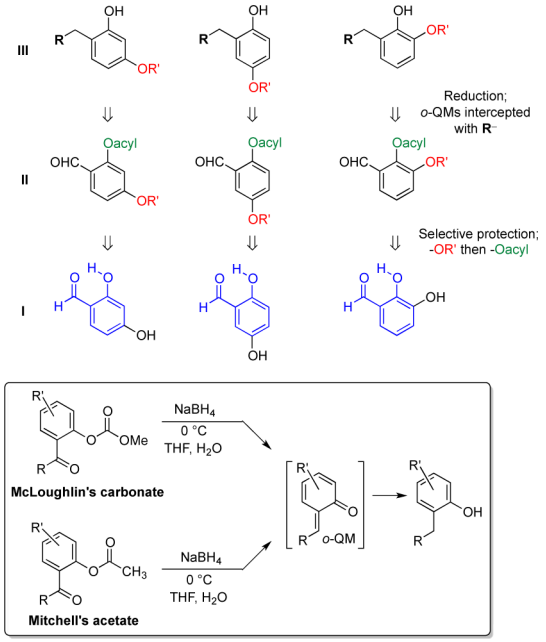



**Figure 4.** *ortho*-Alkylated polyhydridic phenolic motifs.

bond construction. The selective protection in a salicylaldehyde motif was achieved because of its internal hydrogen bond that would facilitate protection of the non-hydrogen bonding phenolic residue via acylation or alkylation (Figure 4I). The answer to access various alkyl derivatives via an *O*-acyl derivative (Figure 4II) was inspired by the reduction of McLoughin's carbonate[25] and Mitchell's acetate[26] (Figure 4, inset). They independently observed that the corresponding *ortho O*-acylated ketonic systems underwent reduction with sodium borohydride, whereby the carbonyl was fully reduced by the addition of two hydrides resulting in cleavage of the *O*-acyl protecting group. They proposed that an acyl transfer occurred and the formed *o*-QM intermediate underwent a subsequent 1,4-reduction. We reasoned that should the starting material be a salicylicaldehyde, then after the first hydride reduction, the resulting nonisolable *β*-unsubstituted *o*-QM intermediate might be both generated and intercepted by an organometallic reagent. Thus, assorted *ortho* alkylated hydroquinone, catechol, or resorcinol derivatives could be constructed with differentially protected phenolic functionality. However, this notion presented some unanswered questions as to what *O*-acyl protecting groups might be best utilized for this process and how the cascade might be controlled to incorporate two different nucleophiles. We subsequently reported our method in 2000[27] and disclosed a comprehensive review of *o*-QMs from a synthetic and precursor perspective in 2002.[28] During the following years, *o*-QM chemistry had received more attention from synthetic chemists with respect to precursor developments and synthetic applications.[29] Herein, we account for the products that we have made and used.

## ■ *ortho*-ALIPHATIC PHENOLS FROM *o*-QMs

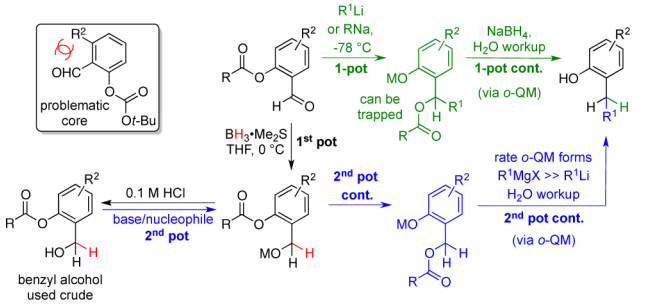
The movement of substrates through our proposed cascade depended upon a combination of factors, including temperature, strength of various oxygen−metal bonds, phenol and alcohol acidity, migratory aptitude of phenol protecting groups, its inclination toward *β*-elimination, and the propensity for the *o*-QM intermediate to undergo the subsequent 1,4-conjugate addition.

We found that *ortho* carbamate salicylaldehyde derivatives (R = $-NMe_2$, $-NEt_2$) only underwent a 1,2-addition. However, their subsequent migration and elimination can be encouraged under acidic conditions. Further carbamate studies were outside of our interest because they mandated two pot processes. However, our early findings agreed with observations regarding carbamate DoM additions to aldehydes popularized by Snieckus,[30] and subsequent acidification employed by Danishefsky and co-workers.[31]

In our hands, formate, methyl carbonate, and acetate phenolic derivatives (R = −H, −OMe, $-CH_3$) failed to survive the addition of various organometallic reagents and suffered cleavage before 1,2-aldehyde addition. *ortho-t*-Butyl carbonate (Boc) and pivalate (Piv) salicylic derivatives displayed a desirable reactivity profile over the greatest range of starting substrates and organometallic reagents. Moreover, if other phenolic residues among bis-phenolic materials ($R^2$ = −OH) were Boc protected, then the *t*-butyl carbonate derivatives proved to be more easily freed with several conditions, including reduction (LAH), saponification (LiOH), and acidic treatment (TFA/$CH_2Cl_2$,[32] $H_3O^+$/1,4-dioxane, or $ZnBr_2$/$CH_3NO_2$[27]).

Syntheses of unbranched *ortho*-alkylated phenols were accomplished through a two-pot protocol without chromatography or a one-pot procedure (Scheme 1). The two-pot

**Scheme 1. Construction of Unbranched *ortho*-Aliphatic Phenols**




protocol was initiated by a reduction with $LiAl(OtBu)_3H$ or $NaBH_4/H_2O$. However, $LiAl(OtBu)_3H$ rarely provided a complete reaction, and $NaBH_4/H_2O$ required very fast quenching with acid (12 s to 5 min) to thwart over-reduction. A more reliable protocol was implemented[33] whereby $BH_3$·$Me_2S$ was used followed by an aqueous acidic workup to smoothly yield the benzylic alcohol without over-reduction. When this crude alcohol was submitted in a second-pot to an excess of Grignard reagent (3−4 equiv), redeprotonation ensued, and it was followed by acyl group migration and elimination to form the *o*-QM, which underwent near instantaneous 1,4-conjugate addition with any remaining Grignard reagent. The amount of the organomagnesium reagent could be reduced, if NaH was first used to initiate the deprotonation.[24c] Alternatively, a sterically hindered *t*-butyl magnesium bromide could serve to deprotonate the alcohol and trigger formation of the *o*-QM, so that a non-magnesium nucleophile, such as Na-methyl malonate or $Bu_4NCN$, or a less hindered magnesium nucleophile could be introduced in the following 1,4-addtion.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The one-pot procedure started with the 1,2-addition of the corresponding sodium or lithium nucleophile.[24e,f] From concurrent mechanistic studies,[34] it appeared that sodium or lithium nucleophiles entered the cascade as far as the corresponding phenoxide, whereupon the sequence paused. If a combination of $NaBH_4$−THF−$H_2O$ was introduced, then the *o*-QM formed and was immediately reduced. Our experiments therefore showed that $NaBH_4$−THF−$H_2O$ or an organomagnesium reagent was necessary to cause the formation of the *o*-QM whereupon the strongest available nucleophile consumed it. These two processes and their modifications proved general for all the salicylaldehydes that we examined. Only those benzaldehydes flanked on either side of the aldehyde motif with a substituent (-halogen, -OR, or -alkyl) proceeded in marginal yields (Scheme 1, inset).

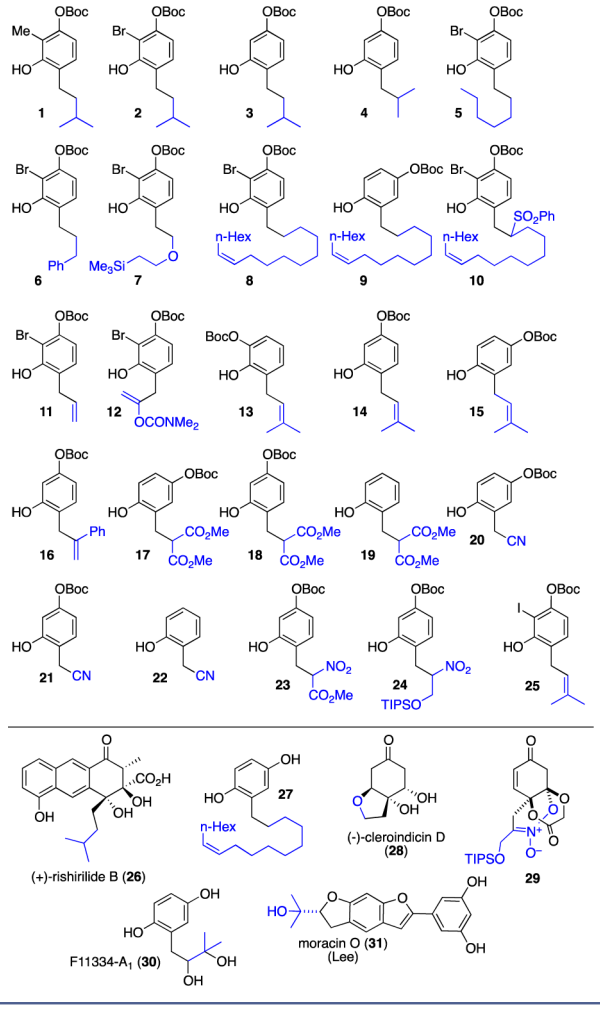
Using the above procedures, the corresponding *o*-unbranched alkyl phenols **1**−**25** were constructed in 52−97% yields (Table 1).[24b,27,35] Several compounds among these have been carried forward to complex products, **26**−**31**. For example, (+)-rishirilide B (**26**) was assembled from phenol **1** in 11 pots via addition of a chiral tether, Boc deprotection, and diastereoselective dearomatization, which led to an elaborate chiral cyclohexadienone. This substrate underwent a regioselective Diels−Alder reaction with an isobenzofuran, followed by cleavage of the chiral tether, then *β*-diketone differentiation to afford the natural product.[24d] The anticancer *p*-hydroquinone **27** was constructed by acidic cleavage of the OBoc substituent from the phenol **9**. This phenol was prepared from a modified two-pot protocol, whereby NaH was used to reinitiate the cascade so that a lesser amount of the precious carbon nucleophile could be deployed.[24c] Similar to synthesis of (+)-rishirilide B, cleroindicin D (**28**), along with all known chiral cleroindicins were prepared from the phenol **7** through chiral tether introduction, diastereoselective dearomatization, regioselective enone reduction, dehalogenation of the resulting *α*-keto aliphatic bromide, TMSE deprotection, conjugate addition, and chiral tether cleavage.[24f] The tricyclic nitronate propellerane **29** emerged from application of a similar sequence with the phenol **24**.[24c] The *N*-SMase inhibitor F11334-A1 (**30**) arose from phenol **15** after olefin dihydroxylation and cleavage of the phenolic OBoc with $ZnBr_2$.[36] Analogously, Lee prepared phenol **25** and completed the synthesis of moracin O (**31**).[37]

Our chemistry also produced branched *ortho*-aliphatic phenols (Scheme 2). For example, if the starting OBoc salicylaldehyde was treated with 2 equiv of a Grignard reagent, then the corresponding aliphatic substituent was doubly incorporated. Besides, the reaction could be initiated by addition of 1 equiv of an organolithium or sodium reagent and then followed sometime thereafter by the addition of an organomagnesium reagent to incorporate two different aliphatic groups.

For example, compounds **32**−**35** were constructed by addition of 2 equiv of organomagnesium reagents, whereas compounds **36**−**40** and **45**−**49** arose by sequential addition of organolithium reagents and Grignard reagents (Table 2). The lactones **41**−**43** were prepared by sequential addition of PhMgBr and the sodium enolate of methyl malonate. In our experience *o*-QMs rapidly form if $MgX_2$ is present. However, we speculate that in these conjugated phenyl *o*-QM instances, the *o*-QMs are more stable and do not undergo reaction until the temperature is raised. The dihydrofuran **44** arose from treatment of the starting salicylaldehyde with PhLi followed by addition of $ICH_2MgI$ and warming to room temperature. Yields were similar if the organolithium was employed as the starting organomagnesium or *vice versa*.

Since compounds **36**−**49** contained stereocenters, we became interested in developing asymmetric protocols. We examined the introduction of the second organometallic in a chiral environment and achieved some limited successes (20−40% ee).[38] However, the catalysts that activated our unstable, nonisolable *o*-QMs usually led to their destruction. Better enantiocontrol has been obtained by others who work with stable *o*-QMs or their *π*-metal stabilized surrogates.[3a,4] Nevertheless, our *racemic* protocols prove very direct, efficient, and robust. Mimosifoliol (**50**) was prepared from trimethoxybenzaldehyde through regioselective bis-deprotection, bis-

**Table 1. *ortho*-Unbranched Alkyl Substituted Phenols via *o*-OMs with Some Applications**




**Scheme 2. Construction of Branched *ortho*-Aliphatic Phenols**

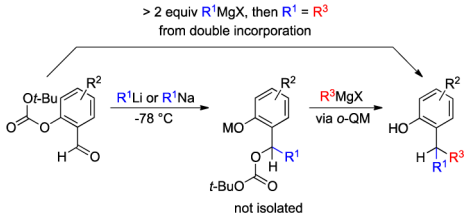




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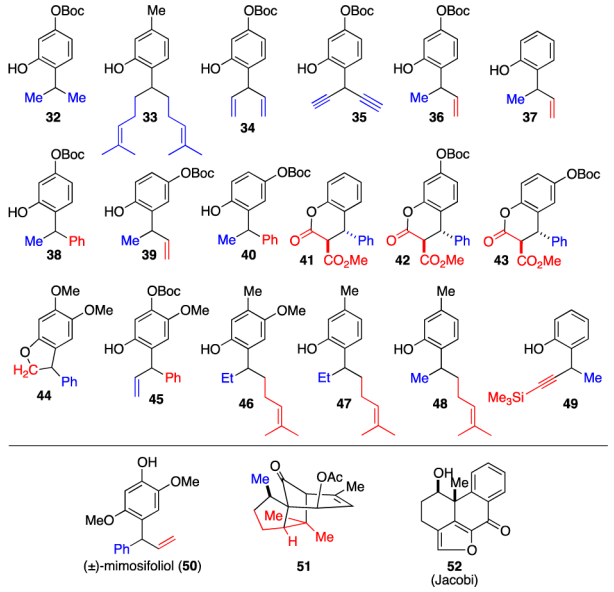
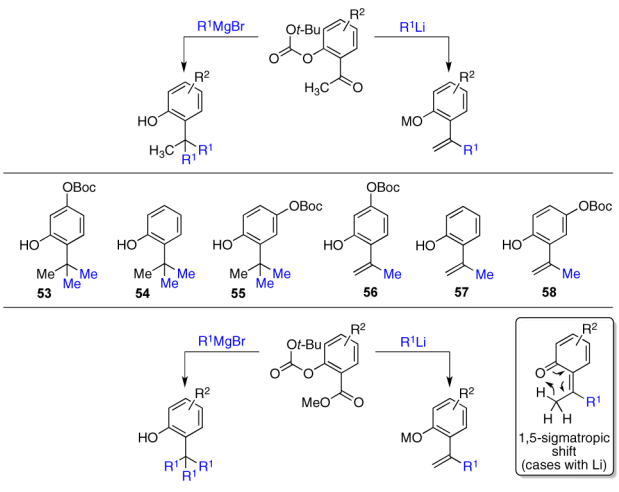
**Table 2. *ortho*-Branched Alkyl Substituted Phenols via *o*-OMs with Some Applications**




OBoc acylation, 1,4-addition of the *o*-QM to give compound **45**, *in situ* methylation, and finally acidic cleavage of the Boc residue.[39] The tricycle **51**, a precursor to (±)-cedrene, was accessed in one pot from phenol **48** by oxidation with lead tetraacetate.[24g] Due to the ease of implementation, we assembled analogs **46** and **47** and examined both aryl and aliphatic substituent effects upon the subsequent oxidative dearomatization. Sessions and Jacobi reported that treatment of the respective OBoc salicylaldehyde with MeLi followed by exposure to trimethylsilylacetylene (TMSA) magnesium bromide yielded the phenol **49**. This phenol underwent further reactions to produce the tetracycle **52**, a model system for an approach toward wortmannin.[40]

The corresponding reactions of *ortho*-OBoc aryl ketones and their esters were not extensively studied (Table 3).[27,35] However, it would appear that various *ortho*-OBoc acetophenones undergo addition of 2 equiv of MeMgBr to afford *ortho t*-butyl phenols in outstanding yields. To our surprise, we could not introduce two different alkyl groups when initiating the reaction with organolithium reagents. In this case, a styrenyl product emerged. The cascade does not pause at the lithium phenoxide as previously noted for the corresponding *ortho*-OBoc salicylaldehydes. We speculate that the *o*-QM may form more readily but proves unstable or that perhaps the MeLi is less nucleophilic. We presume that the styrenes **56**–**58** arise from a facile 1,5-sigmatropic shift of the *o*-QM intermediates instead of the desired 1,4-addition. Similar outcomes were gained regarding the corresponding OBoc aryl esters.

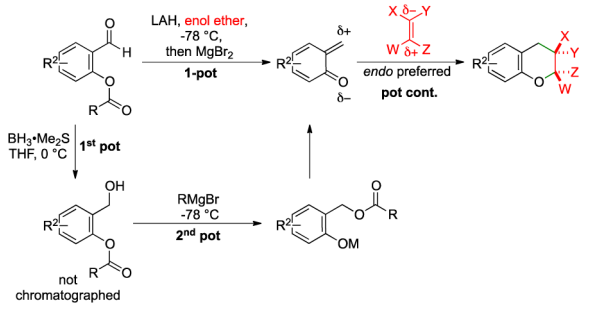
**Table 3. Related Reactions of *ortho*-OBoc Ketones and Esters**




## BENZOPYRANS AND CHROMAN KETALS FROM *o*-QMs

Besides 1,4-addition, the *β*-unsubstituted *o*-QMs could also be intercepted in an inverse demand Diels–Alder reaction with alkenes to give the benzopyrans and chroman ketals, which prevalently exist in natural products and therapeutic drugs (Scheme 3). Prior to our work, the conditions to form *o*-QMs had most often relied upon high temperatures or strong Lewis acids resulting in poor diastereoselectivity due to epimerization or equilibration. Our mild anionic procedures enabled this ephemeral species to undergo controlled reaction at low temperatures for the first time. Polarized alkenes, including an assortment of enol ethers and enamines, participated in this reaction (Table 4). In head-to-head comparisons between excess MeMgBr and ethoxyvinyl ether (EVE), the cycloaddition nearly always superseded the 1,4-conjugate addition. Furans, imines, and amino-oxazoles also participated in these cycloadditions.

**Scheme 3. Construction of 4-Unsubstituted Benzopyrans and Chroman Ketals from *β*-Unsubstituted *o*-QMs**




We fortuitously isolated our first aliphatic benzopyran motif **59** during our planned preparation of an *ortho*-aliphatic phenol (Table 4). Adding an excess of (2-methylprop-1-en-1-yl) magnesium bromide to the corresponding OBoc salicyclic alcohol resulted in an *o*-QM intermediate and 2-methylprop-1-ene, formed upon protonation of the Grignard reagent. These two entities then combined to form the benzopyran rather than the intended *ortho* C-prenylated phenol (**14**, Table 1). This undesired cycloaddition could be avoided by inverse addition of the starting alcohol to the organomagnesium reagent. However, we decided to examine the scope of this cycloaddition. While aliphatic alkenes proved unreactive, styrene merged with our *o*-QM to give benzopyran **60** in 50% yield.[41] More electron-rich alkenes gave improved yields. For example, 1-(*tert*-butoxy)-4-vinylbenzene afforded the corresponding *tert*-butoxy analog **60** in 80% yield.[41] The benzopyran **61**, arising from the troublesome salicylalcohol core (Scheme 1, inset), was obtained in 45% yield by a modified single-pot protocol, whereby the reduction of the preceding salicylaldehyde was achieved with LAH in the presence of 1-(*tert*-butoxy)-4-vinylbenzene and


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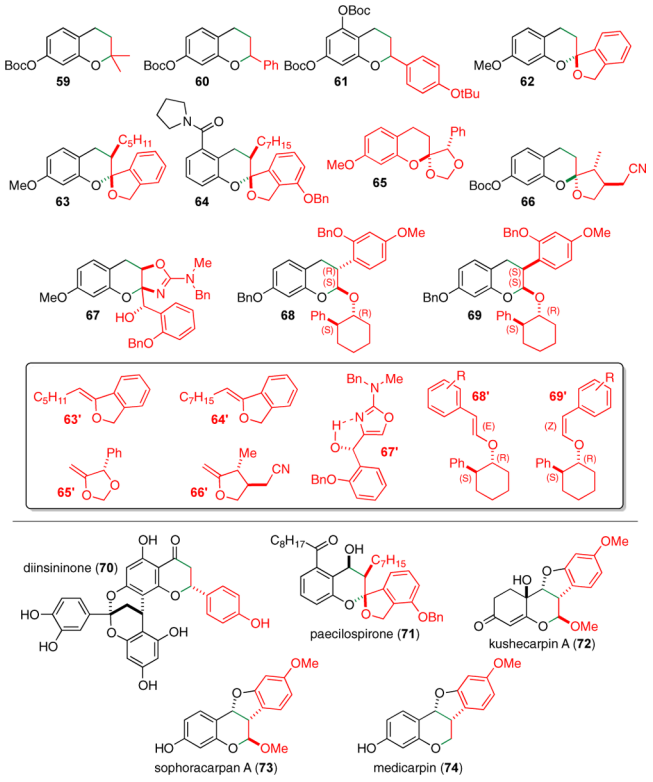
**Table 4. Some 4-Unsubstituted Benzopyrans and Chroman Ketals, Complex Enol Ethers, and Their Applications**




followed by the addition of $MgBr_2$.[42] This benzopyran was subsequently oxidized to a flavone and its protecting residues were concurrently cleaved by treatment with $ZnBr_2$. Its further reaction with a benzopyrylium salt yielded diinsininone (**70**).

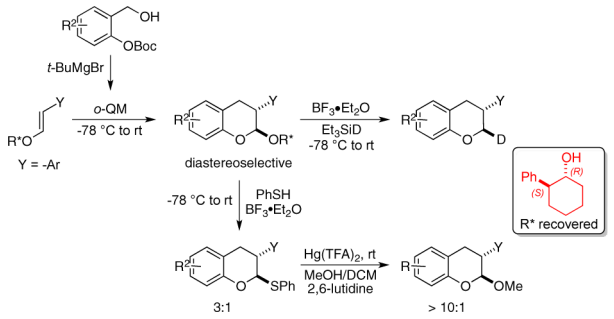
Various complex enol ethers had been examined in the cycloaddition. Enol ethers **63′** and **64′**, obtained from isobenzofuran-1(3*H*)-one, underwent reaction with various *β*-unsubstituted *o*-QMs to produce spiroketals **62**–**64**.[33b] The *Z*-geometry within the starting enol ether was retained as the *syn* stereochemistry between the vicinal oxygen and alkyl residues in the respective spiroketal. We are presently investigating the conversion of **64** into paecilospirone (**71**) by regioselective benzylic oxidation, followed by stereoselective reduction of the resulting flavone carbonyl and elaboration of the amide into the desired aliphatic ketone.

X-ray analysis of the respective products reveals that the chirality within the 2*π* enol ether controls the stereochemistry of the cycloadduct. For example, the phenyl residue in the benzylidene ketal **65′** causes the enol ether to undergo reaction on its *Re*-face. The stereochemistry of the spiroketal **65** is secured by the reaction proceeding nearly exclusively through an *endo* transition state.[33b] The methyl residue of the tetrahydrofuran **66′** directs the reaction of the enol ether from *Re*-face with the *Si* face of the methylene of the *o*-QM to provide the spiroketal **66** as the major diastereomer (5:1). Similarly, the corresponding amino-oxazole, containing the hydroxyl stereocenter and likely forming a tridentate chelate with $MgBr_2$, undergoes a stereoselective reaction to produce pyran **67** as a single diastereomer.[43]

Based on these diastereoselectivities, we designed, synthesized, and investigated a number of chiral enol ethers that fulfilled the role of a chiral auxiliary.[34,44] Enol ethers derived from 2-phenylcyclohexanol are the culmination of these studies. The *E*-enol ether **68′** was shown to undergo a cycloaddition to form the chroman ketal **68** (>10:1 dr) in 90% yield. On the other hand, the *Z*-enol ether **69′** afforded the chroman ketal **69** (>20:1 dr) in 93% yield. These two diastereomers emerge from the same chiral alcohol yet led to opposite enantiomers of kushecarpin-A (**72**), sophoracarpan-A (**73**), and medicarpin (**74**).[45] In other words, the absolute configuration of the C3-position is controlled by a combination of the absolute configuration of the starting chiral alcohols and the geometry of the enol ethers.

Chiral chromans containing a Y substituent at the C3-position underwent several useful transformations (Scheme 4).

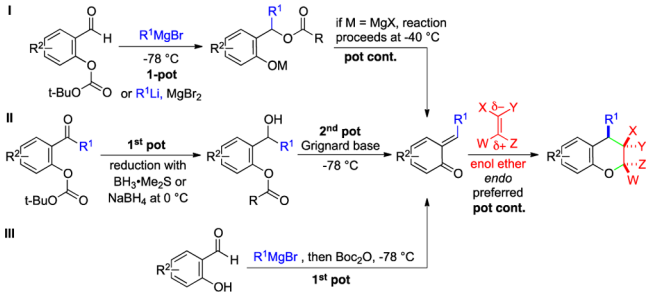
**Scheme 4. Stereocontrol Emanating from Y Substituent at the C3-Position**




For example, the chroman acetal was reductively cleaved with $BF_3{\cdot}Et_2O$ and deuterated triethyl silane to afford the corresponding *anti* configured benzopyran, together with the recovered chiral alcohol. In addition, the chroman acetal was converted into a different chroman methyl acetal in diastereoselective fashion via a mixed thioacetal as seen in the synthesis of kushecarpin (**72**).[45] These stereoselective sequences demonstrated that the Y-residue serves as a diastereocontrol element for subsequent kinetic reactions at the corresponding vicinal oxonium intermediate. This finding is not altogether surprising because there are four $sp^2$ configured atoms within the pyran ring of the oxonium intermediate and the Y substituent likely occupies a pseudo-axial position because there are no steric interactions to prevent it. Thus, nucleophiles add to the oxonium opposite the Y substituent.

Chromans displaying aliphatic, aryl, vinyl, or silicon substituents at their benzylic sites (4-position) could be prepared by three separate methods (Scheme 5I–III). In the first procedure, we combined the aldehyde with a Grignard reagent in the presence of the enol ether at −78 °C. Alternatively, this one pot protocol could be initiated by

**Scheme 5. Construction of 4-Substituted Benzopyrans and Chroman Ketals from *β*-Substituted *o*-QMs**





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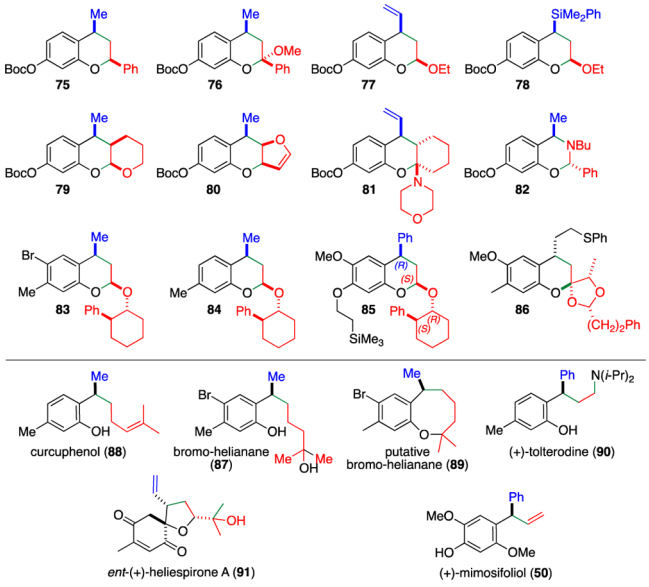
sequential addition of organolithium, intended enol ether, and $MgBr_2$. In the two-pot procedure (II), a starting ketone was first reduced to the salicylalcohol, which was deprotonated with a Grignard reagent in the presence of the enol ether to initiate the cycloaddition and afford the corresponding benzopyran. More recently, we have begun to combine the Boc acylation during the generation of the *o*-QMs for the ensuing cycloaddition. For this protocol (III), excess of the Grignard reagents (>2 equiv) was added at −78 °C, followed by addition of enol ethers and $Boc_2O$. Upon warming, the cycloaddition occurred for most systems.[24g]

Electron-rich 2$\pi$ dienophiles, including styrenes, enol ethers, furans, enamines, and imines, underwent this cycloaddition to produce the desired chromans **75**−**86** with >20:1 diastereoselectivity, unless noted otherwise (Table 5).[41] $\beta$-Substituted

**Table 5. Some 4-Substituted Benzopyrans and Chroman Ketals and Their Applications**

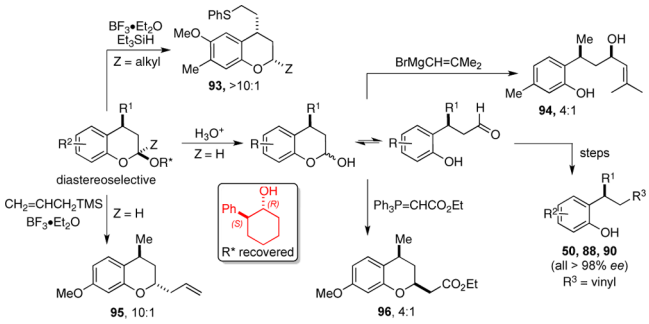



*o*-QMs appear less reactive than their $\beta$-unsubstituted counterparts, particularly in regards to their reactions with less polarized olefins. For example, the benzopyran **75** was isolated in a paltry 27% yield and 6:1 dr compared with the 50% yield for its analog **60**. On the other hand, more electron rich $\alpha$-methoxystyrene underwent reaction with the $\beta$-methylated *o*-QM to afford the chroman **76** in a 55% yield and 4:1 dr. The combination of EVE and the respective *o*-QM yielded the chroman **77** in 70%. The analogous reaction initiated with $PhMe_2SiLi$ and $MgBr_2$ yielded the chroman **78** in 70% yield. Similarly, the combination of MeMgBr and the corresponding OBoc salicylaldehyde in the presence of dihydropyran afforded tricycle **79** in 66% yield. Furan also underwent the cycloaddition smoothly to afford tricycle **80** in a 76% yield. Enamines were also reactive and afforded tricycle **81** in 70% yield. Mixed aminal adducts were readily converted into the corresponding ketone upon acidic treatment. $\beta$-Methylated *o*-QMs also underwent reaction with imines to afford the corresponding aminals, such as **82** in 94% yield, the highest yield recorded among all 2$\pi$ dienophiles. The *anti* stereochemistry for this adduct suggests either an *exo*-oriented combination of reactants or equilibration.

$\beta$-substituted *o*-QMs also reacted with *nonracemic* enol ethers to yield chiral adducts with outstanding diastereocontrol (**83**−**86**). For example, the unprotected salicylaldehydes produced the chroman **83** (71%) and **84** (69%, 16:1) via procedure III.[46] These chiral materials were then used to repudiate the existence of the helianane family. Spectral comparisons, between the synthetic (**87**) and proposed natural compound (**89**), revealed a misassignment of the eight-membered ring. Chroman **84** was carried onto (+)-curcuphenol (**88**) and $\alpha$-cedrene.[24g] Chroman **85**, obtained in 83% yield, was then used to prepare (+)-mimosifoliol (**50**) and (+)-tolterodine (**90**).[44] Adduct **86**, prepared in 61% yield via procedure II, was reduced with $BF_3$·$Et_2O$/TESH and elaborated into *ent*-(+)-heliespirone A (**91**).[47]

Chiral chromans containing a benzylic $R^1$ substituent underwent several useful transformations (Scheme 6). For

**Scheme 6. Stereocontrol Emanating from $R^1$ at the C4-Position**




example, they could be reduced in a diastereoselective fashion, as shown in the synthesis of *ent*-(+)-heliespirone A via **93**.[47] The chroman ketal could also be hydrolyzed into an epimeric hemiketal that upon addition of a Grignard reagent provided the alcohol **94** in 4:1 dr, presumably the result of allylic strain.[46] Hemiketals were also converted into several *ortho*-branched aliphatic phenols, as shown in the syntheses of (+)-mimosifoliol (**50**), (+)-curcuphenol (**88**), and (+)-tolterodine (**90**).[44] In addition, the stereochemistry of the $R^1$ residue controls the reaction of the oxonium intermediate, as seen in the allylation leading to compound **95** and the Wittig olefination and subsequent conjugate addition resulting in benzopyran **96**. These transformations demonstrate that the $R^1$ residue serves as a diastereocontrol element for building various chiral *ortho*-aliphatic $\alpha$-branched phenols and the subsequent reactions within the benzopyran ring.

Other acyl triggers in conjunction with organomagnesium and organocerium reagents prove effective (Scheme 7). However, the intervening $\beta$-elimination requires that the leaving *O*-acyl bond have partial coplanarity with the aromatic $\pi$-orbitals. As a result, the five-membered $\gamma$-lactone **97** failed to form a detectable *o*-QM upon its deprotonation (Scheme 7I). Its amide analog **98** did proceed to an *o*-QM formation and interception with the enol ether **67′** leading to product **99** in 64% yield (Scheme 7II). The corresponding $\delta$-lactone **100** appeared fluxional enough to undergo the desired reaction with enol ether **65′** affording the carboxylic acid **101** in 60% yield (Scheme 7III).[48] The phenolic acetate of an unsubstituted salicylalcohol **102** underwent cycloaddition with excess dihydrofuran to give tricycle **103** in good yield (Scheme 7IV).[49] The OBoc $\delta$-lactone **104** also underwent addition of organocerium and subsequent cycloaddition with enol ether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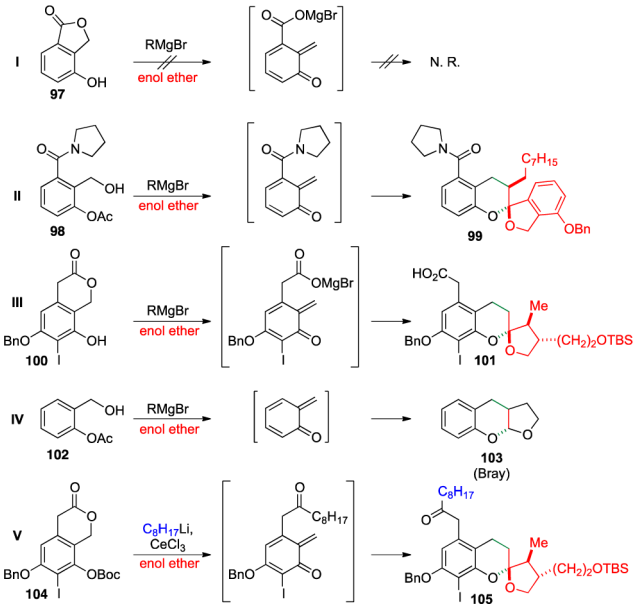
**Scheme 7. *o*-QM Production Triggered under Other Salty Conditions**

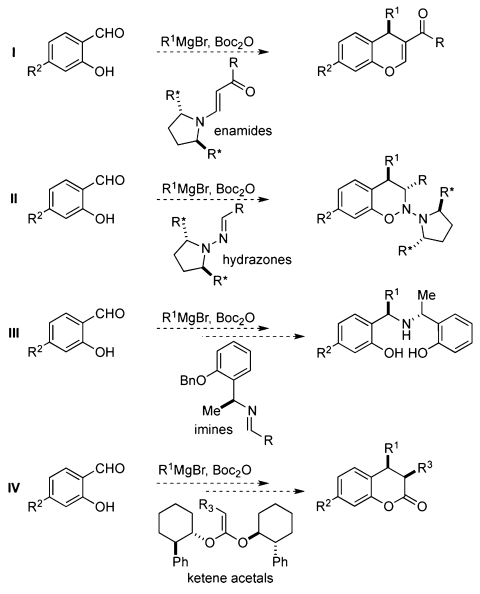



**67′** to produce the ketone **105**, thereby demonstrating formation of the C−C bond at an entirely new site (Scheme 7V).

## FUTURE EXPLORATIONS

Our past efforts suggest several applications for future studies. Chiral enamides might control the chirality of the newly formed $R^1$ substituent. Chiral hydrazones could be used to access benzo[1.2]oxazines asymmetrically (Scheme 8II). Chiral imine-derived benzo[1.3]oxazines should prove useful for asymmetric ligand development (Scheme 8III). Chiral ketene acetals may provide chiral chromanones (Scheme 8IV). The possibilities are nearly endless.

**Scheme 8. Some Future Explorations**




## CONCLUSION

In conclusion, our mild anionic strategy, using metal salts and temperature as regulators, provides access to unstable non-isolable *o*-QMs at low temperature in a manner that enables us to domesticate this previously untamed transient species. The sequence can be performed through the proper combination of metallic and temperature controls so as to be stopped, paused, or restarted. This synthetic process allows us, and others, to prepare racemic or chiral *o*-alkylated phenols, benzopyrans, and chroman ketals, which are further applied in synthesis of complex natural products. The steric effects of the newly created stereocenters in subsequent reactions are predictable. In this Account, we have summarized our past adventures, in the hope that we might accelerate the synthetic renaissance for this venerable species.

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### Notes

The authors declare no competing financial interest.

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**Thomas R. R. Pettus** received his Ph.D. from the University of Rochester in 1996 and completed a postdoctoral stint at Columbia University in 1998 before his independent career.

## REFERENCES

(1) Weinert, E. E.; Dondi, R.; Colloredo-Melz, S.; Frankenfield, K. N.; Mitchell, C. H.; Freccero, M.; Rokita, S. E. Substituents on Quinone Methides Strongly Modulate Formation and Stability of Their Nucleophilic Adducts. *J. Am. Chem. Soc.* **2006**, *128*, 11940−11947.

(2) (a) Pathak, T. P.; Sigman, M. S. Applications of *ortho*-Quinone Methide Intermediates in Catalysis and Asymmetric Synthesis. *J. Org. Chem.* **2011**, *76*, 9210−9215. (b) Stokes, S. M.; Ding, F.; Smith, P. L.; Keane, J. M.; Kopach, M. E.; Jervis, R.; Sabat, M.; Harman, W. D. Formation of *o*-Quinone Methides from Dihapto-Coordinated Phenols and Their Controlled Release from a Transition Metal to Generate Chromans. *Organometallics* **2003**, *22*, 4170−4171.

(3) (a) Alden-Danforth, E.; Scerba, M. T.; Lectka, T. Asymmetric Cycloadditions of *o*-Quinone Methides Employing Chiral Ammonium Fluoride Precatalysts. *Org. Lett.* **2008**, *10*, 4951−4953. (b) Wu, B.; Chen, M.-W.; Ye, Z.-S.; Yu, C.-B.; Zhou, Y.-G. A Streamlined Synthesis of 2,3-Dihydrobenzofurans *via* the *ortho*-Quinone Methides Generated from 2-Alkyl-Substituted Phenols. *Adv. Synth. Catal.* **2014**, *356*, 383−387.
(4) (a) Luan, Y.; Schaus, S. Enantioselective Addition of Boronates to *o*-Quinone Methides Catalyzed by Chiral Biphenols. *J. Am. Chem. Soc.* **2012**, *134*, 19965−19968. (b) Izquierdo, J.; Oreu, A.; Scheidt, K. A. A Dual Lewis Base Activation Strategy for Enantioselective Carbene-Catalyzed Annulations. *J. Am. Chem. Soc.* **2013**, *135*, 10634−10637.
(5) Fries, K.; Kann, K. I. Ueber die Einwirkung von Brom und von Chlor auf Phenole: Substitutionsproducte, Pseudobromide und Pseudochloride. Ueber *o*-Pseudohalogenide und o-Methylenchinone aus o-Oxymesitylalkohol. *Liebigs Ann. Chem.* **1907**, *353*, 335−356.
(6) Gardner, P. D.; Sarrafizadeh, H.; Brandon, R. L. *o*-Quinone Methide. *J. Am. Chem. Soc.* **1959**, *81*, 5515.
(7) Arduini, A.; Pochini, A.; Ungaro, R.; Domiano, P. *o*-Quinone Methides. Part 3. X-ray Crystal Structure and Reactivity of a Stable *o*-Quinone Methide in the *E*-Configuration. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1391−1395.
(8) (a) Diao, L.; Wan, P. Chemistry of Photogenerated α-Phenyl-Substituted *o*-, *m*-, and *p*-Quinone Methides from Phenol Derivatives in Aqueous Solution. *Can. J. Chem.* **2008**, *86*, 105−118 and references therein. (b) Rosenau, T.; Ebner, G.; Stanger, A.; Perl, S.; Nuri, L. From a Theoretical Concept to Biochemical Reactions: Strain-Induced Bond Localization (SIBL) in Oxidation of Vitamin E. *Chem.—Eur. J.* **2005**, *11*, 280−287.
(9) Spence, J. T. J.; George, J. H. Biomimetic Total Synthesis of *ent*-Penilactone A and Penilactone B. *Org. Lett.* **2013**, *15*, 3891−3893.
(10) Liao, D.; Li, H.; Lei, X. Efficient Generation of *ortho*-Quinone Methide: Application to the Biomimetic Synthesis of (±)-Schefflone and Tocopherol Trimers. *Org. Lett.* **2012**, *14*, 18−21.
(11) (a) Lawrence, A. L.; Adlington, R. M.; Baldwin, J. E.; Lee, V.; Kershaw, J. A.; Thompson, A. L. A Short Biomimetic Synthesis of the Meroterpenoids Guajadial and Psidial A. *Org. Lett.* **2010**, *12*, 1676−1679. (b) George, J. H.; Baldwin, J. E.; Adlington, R. M. Enantiospecfic, Biosynthetically Inspired Formal Synthesis of (+)-Liphagal. *Org. Lett.* **2010**, *12*, 2394−2397.
(12) Lumb, J.-P.; Trauner, D. Pericyclic Reactions of Prenylated Naphthoquinones: Biomimetic Syntheses of Mollugin and Microphyllaquinone. *Org. Lett.* **2005**, *7*, 5865−5868.
(13) Arumugam, S.; Popik, V. V. Dual Reactivity of Hydroxy- and Methoxy- Substituted *o*-Quinone Methides in Aqueous Solutions: Hydration versus Tautomerization. *J. Org. Chem.* **2010**, *75*, 7338−7346.
(14) Shaikh, A. K.; Cobb, A. J. A.; Varvounis, G. Mild and Rapid Method for the Generation of *ortho*-(Naptho)quinone Methide Intermediates. *Org. Lett.* **2012**, *14*, 584−587.
(15) Crawley, S. L.; Funk, R. L. A Synthetic Approach to Nomofungin/Communesin B. *Org. Lett.* **2003**, *5*, 3169−3171.
(16) Osipov, D. V.; Osyanin, V. A.; Klimochkin, Y. N. Easy Access to (±)-Schefflone and Espintanol. *Synlett* **2012**, *23*, 917−919.
(17) Lumb, J.-P.; Choong, K. C.; Trauner, D. *ortho*-Quinone Methides from *para*-Quinones: Total Synthesis of Rubioncolin B. *J. Am. Chem. Soc.* **2008**, *130*, 9230−9231.
(18) Padwa, A.; Dehm, D.; Oine, T.; Lee, G. A. Competitive Keto-Enolate Photochemistry in the 3-Phenylisocoumaranone System. *J. Am. Chem. Soc.* **1975**, *97*, 1837−1845.
(19) Batsomboon, P.; Phakhodee, W.; Ruchirawat, S.; Ploypradith, P. Generation of *ortho*-Quinone Methides by *p*-TsOH on Silica and Their Hetero-Diels-Alder Reactions with Styrenes. *J. Org. Chem.* **2009**, *74*, 4009−4012.
(20) Chen, M.-W.; Cao, L.-L.; Ye, Z.-S.; Jiang, G.-F.; Zhou, Y.-G. A mild method for generation of o-quinone methides under basic conditions. The facile synthesis of trans-2,3-dihydrobenzofurans. *Chem. Commun.* **2013**, *49*, 1660−1662.
(21) Marsini, M. A.; Pettus, T. R. R. Polyhydric Phenols and Corresponding Phenolates. *Sci. Synth.* **2007**, *31*, 403−468.
(22) Hoarau, C.; Pettus, T. R. R. Strategies for the Preparation of Differentially Protected *ortho*-Prenylated Phenols. *Synlett* **2003**, *1*, 127−137.
(23) Kirshenbaum, K.; Maayan, G.; Ward, M. Preparation of Peptoids for Substrate-Selective Catalysis Including Asymmetric Catalysis. PCT Int. Appl. 2009139922, 19 Nov, 2009.
(24) Our dearomatization chemistry, see: (a) Van De Water, R. W.; Hoarau, C.; Pettus, T. R. R. Oxidative Dearomatization of Resorcinol Derivatives: Useful Conditions Leading to Valuable Cyclohexa-2,5-dienones. *Tetrahedron Lett.* **2003**, *44*, 5109−5113. (b) Mejorado, L. H.; Hoarau, C.; Pettus, T. R. R. Diastereoselective Dearomatization of Resorcinols Directed by a Lactic Acid Tether: Unprecedented Enantioselective Access to *p*-Quinols. *Org. Lett.* **2004**, *6*, 1535−1538. (c) Hoarau, C.; Pettus, T. R. R. General Synthesis for Chiral 4-Alkyl-4-hydroxycyclohexenones. *Org. Lett.* **2006**, *8*, 2843−2846. (d) Mejorado, L. H.; Pettus, T. R. R. Total Synthesis of (+)-Rishirilide B: Development and Application of General Processes for Enantioselective Oxidative Dearomatization of Resorcinol Derivatives. *J. Am. Chem. Soc.* **2006**, *128*, 15625−15631. (e) Marsini, M. A.; Huang, Y.; Van De Water, R. W.; Pettus, T. R. R. Synthesis of Resorcinol Derived Spironitronates. *Org. Lett.* **2007**, *9*, 3229−3232. (f) Wenderski, T. A.; Huang, S.; Pettus, T. R. R. Enantioselective Total Synthesis of All of the Known Chiral Cleroindicins (C−F): Clarification Among Optical Rotations and Assignments. *J. Org. Chem.* **2009**, *74*, 4104−4109. (g) Green, J. C.; Pettus, T. R. R. An Oxidative Dearomatization-Induced [5 + 2] Cascade Enabling the Syntheses of α-Cedrene, α-Pipitzol, and *sec*-Cedrenol. *J. Am. Chem. Soc.* **2011**, *133*, 1603−1608.
(25) Mcloughlin, B. J. A Novel Reduction of Carbonyl to Methylene by the Action of Sodium Borohydride. *Chem. Commun.* **1969**, 540−541.
(26) Mitchell, D.; Doecke, C. W.; Hay, L. A.; Koenig, T. M.; Wirth, D. D. *Ortho*-Hydroxyl Assisted Deoxygenation of Pherones. Regiochemical Control in the Synthesis of Monoprotected Resorcinols and Related Polyphenolic Hydroxyl Systems. *Tetrahedron Lett.* **1995**, *36*, 5335−5338.
(27) Van De Water, R. W.; Magdziak, D. J.; Chau, J. N.; Pettus, T. R. R. New Construction of Ortho Ring-Alkylated Phenols via Generation and Reaction of Assorted o-Quinone Methides. *J. Am. Chem. Soc.* **2000**, *122*, 6502−6503.
(28) Van De Water, R. W.; Pettus, T. R. R. *o*-Quinone Methides: Intermediates Underdeveloped and Underutilized in Organic Synthesis. *Tetrahedron* **2002**, *58*, 5367−5405.
(29) (a) Selenski, C.; Pettus, T. R. R. Quinomethanes. *Science of Synthesis* **2006**, *28*, 4.28.12.1. (b) Rokita, S. E. *Quinone Methides*; John Wiley & Sons, Inc.: Hoboken, NJ, 2009. (c) Willis, N. J.; Bray, C. D. *ortho*-Quinone Methides in Natural Product Synthesis. *Chem.—Eur. J.* **2012**, *18*, 9160−9173.
(30) Snieckus, V. Directed Ortho Metalation. Tertiary Amide and *O*-Carbamate Directors in Synthetic Strategies for Polysubstituted Aromatics. *Chem. Rev.* **1990**, *90*, 879−933.
(31) Wang, Z.; Dai, M.; Park, P. K.; Danishefsky, S. J. Synthetic Studies toward (+)-Cortistatin A. *Tetrahedron* **2011**, *67*, 10249−10260.
(32) Cha, J. Y.; Huang, Y.; Pettus, T. R. R. Total Synthesis of TK-57−164 A, Isariotin F, and their Putative Progenitor Isariotin E. *Angew. Chem., Int. Ed.* **2009**, *48*, 9519−9521.
(33) (a) Huang, Y.; Pettus, T. R. R. A Cycloaddition Strategy for Use toward Berkelic Acid, an MMP Inhibitor and Potent Anticancer Agent Displaying a Unique Chroman Spiroketal Motif. *Synlett* **2008**, *9*, 1353−1356. (b) Marsini, M. A.; Huang, Y.; Lindsey, C. C.; Wu, K.-L.; Pettus, T. R. R. Diastereoselective Syntheses of Chroman Spiroketals via [4 + 2] Cycloaddition of Enol Ethers and *o*-Quinone Methides. *Org. Lett.* **2008**, *10*, 1477−1480.
(34) Selenski, C.; Pettus, T. R. R. Enantioselective [4 + 2] Cycloadditions of *o*-Quinone Methides: Total Synthesis of (+)-Mimosifoliol and Formal Synthesis of (+)-Tolterodine. *J. Org. Chem.* **2004**, *69*, 9196−9203.

(35) Jones, R. M.; Van De Water, R. W.; Lindsey, C. C.; Hoarau, C.; Ung, T.; Pettus, T. R. R. A Mild Anionic Method for Generating *o*-Quinone Methides: Facile Preparations of *ortho*-Functionalized Phenols. *J. Org. Chem.* **2001**, *66*, 3435−3441.
(36) Lindsey, C. C.; Gómez-Díaz, C.; Villalba, J. M.; Pettus, T. R. R. Synthesis of the F11334's from *o*-Prenylated Phenols: $\mu$M Inhibitors of Neutral Sphingomyelinase (N-SMase). *Tetrahedron* **2002**, *58*, 4559−4565.
(37) Kaur, N.; Xia, Y.; Jin, Y.; Dat, N. T.; Gajulapati, K.; Choi, Y.; Hong, Y.-S.; Lee, J. J.; Lee, K. The First Total Synthesis of Moracin O and Moracin P, and Establishment of the Absolute Configuration of Moracin O. *Chem. Commun.* **2009**, 1879−1881.
(38) Mejorado, L. H.: Development and application of non-racemic cyclohexa-2,5-dienones in the total syntheses of (+)-epoxysorbicillinal and (+)-rishirilide B. Ph.D. Thesis, UCSB, 2006.
(39) Tuttle, K.; Rodriguez, A. A.; Pettus, T. R. R. An Expeditious Synthesis of (±)Mimosifoliol Utilizing a Cascade Involving an *o*-Quinone Methide Intermediate. *Synlett* **2003**, *14*, 2234−2236.
(40) Sessions, E. H.; Jacobi, P. A. Studies of the Synthesis of Furanosteroids. I. Viridin Models. *Org. Lett.* **2006**, *8*, 4125−4128.
(41) Jones, R. M.; Selenski, C.; Pettus, T. R. R. Rapid Syntheses of Benzopyrans from *o*-OBOC Salicylaldehydes and Salicyl Alcohols: A Three-Component Reaction. *J. Org. Chem.* **2002**, *67*, 6911−6915.
(42) Selenski, C.; Pettus, T. R. R. (±)-Diinsininone: Made Nature's Way. *Tetrahedron* **2006**, *62*, 5298−5307.
(43) Lindsey, C. C.; Pettus, T. R. R. Unusual Cycloaditions of *o*-Quinone Methides with Oxazoles. *Tetrahedron Lett.* **2006**, *47*, 201−204.
(44) Selenski, C.; Mejorado, L. H.; Pettus, T. R. R. Diastereoselective [4 + 2] Reactions of *o*-Quinone Methides with a Chiral Enol Ether: Asymmetric Synthesis of (+)-*R*-Mimosifoliol. *Synlett* **2004**, *6*, 1101−1103.
(45) Feng, Z.-G.; Bai, W.-J.; Pettus, T. R. R. Unified Total Syntheses of (−)-Medicarpin, (−)-Sophoracarpan A and (±)-Kushecarpin A with Some Structural Revisions. *Angew. Chem., Int. Ed.* **2014**, DOI: 10.1002/anie.201408910.
(46) Green, J. C.; Jimenez-Alonso, S.; Brown, E. R.; Pettus, T. R. R. Total Synthesis and Repudiation of the Helianane Family. *Org. Lett.* **2011**, *13*, 5500−5503.
(47) Bai, W.-J.; Green, J. C.; Pettus, T. R. R. Total Syntheses of *ent*-Heliespirones A and C. *J. Org. Chem.* **2012**, *77*, 379−387.
(48) Wenderski, T. A.; Marsini, M. A.; Pettus, T. R. R. A Diastereoselective Formal Synthesis of Berkelic Acid. *Org. Lett.* **2011**, *13*, 118−121.
(49) Bray, C. D. Generation and *hetero*-Diels-Alder reactions of an *o*-quinone methide under mild, anionic conditions: rapid synthesis of *mono*-benzannelated spiroketals. *Org. Biomol. Chem.* **2008**, *6*, 2815−2819.