and isolable. Sterics play a role in controlling the formed olefin conjugation and electronic donation make them less reactive counterparts, Compared with their isomeric manifolds or a geometry, which in turn command the subsequent reaction of structural and electronic effects. 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, then they undergo the usual reactions associated with a reactive unsaturated ketone or π-allyl species, including catalyzed asymmetric reactions. 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 and subsequent spectroscopic investigation and crystallographic studies, o-QMs have chiefly remained of interest to physical organic chemists.

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

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**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 of structural and electronic effects. 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

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**Figure 1.** Plausible canonical representation of o-QMs.
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 β-elimination11 and to a lesser extent tautomerization,12 photolysis,13 and base promoted β-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.](image)

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 stawlart 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 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 tautomeration 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 benzo furan-2-one yielded an o-QM that participated in an oxo-6π-cyclization and a 1,3-sigmatropic shift to a xanthene (Figure 3D).18 Acid and base promoted β-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.

![Figure 3. Applications of o-QM generation protocols.](image)

### 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
During the following years, precursor developments and synthetic applications. Herein, we reported our method in 2000 and disclosed a comprehensive review of what might be both generated and intercepted by an intermediate. β-reduction, the resulting nonisolable acyl protecting group. They proposed that an acyl transfer by the addition of two hydrides resulting in cleavage of the sodium borohydride, whereby the carbonyl was fully reduced in acetate (Figure 4, inset). They independently observed that the corresponding -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 salicylaldehyde, then after the first hydride reduction, the resulting nonisolable β-unsubstituted o-QM intermediate might be 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 and disclosed a comprehensive review of o-QMs from a synthetic and precursor perspective in 2002. During the following years, o-QM chemistry had received more attention from synthetic chemists with respect to precursor developments and synthetic applications. 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 = –NMe2, –NEt2) 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 and subsequent acidification employed by Dani-shesky and co-workers.

In our hands, formate, methyl carbonate, and acetate phenolic derivatives (R = –H, –OMe, –CH3) 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 (R2 = –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/CH2Cl2, H2O/1,4-dioxane, or ZnBr2/CH3NO2).

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 protocol was initiated with a reduction with LiAl(OBu)3 or NaBH4/H2O. However, LiAl(OBu)3/H2O rarely provided a complete reaction, and NaBH4/H2O required very fast quenching with acid to thwart over-reduction. A more reliable protocol was implemented whereby BH3·Me2S 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. 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 Bu4NCN, or a less hindered magnesium nucleophile could be introduced in the following 1,4-addition.
The one-pot procedure started with the 1,2-addition of the corresponding sodium or lithium nucleophile. From concurrent mechanistic studies, it appeared that sodium or lithium nucleophiles entered the cascade as far as the corresponding phenoxide, whereupon the sequence paused. If a combination of NaBH₄−THF−H₂O was introduced, then the o-QM formed and was immediately reduced. Our experiments therefore showed that NaBH₄−THF−H₂O 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). 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 stable, nonisolable π-metal stabilized surrogate. The catalytic protocol was capable of activating our unstable, nonisolable o-QMs or their organometallic surrogates. However, the catalysts that activated our unstable, nonisolable o-QMs usually led to their destruction. Better experience with the organomagnesium or organolithium reagents became interested in developing asymmetric protocols. We therefore showed that NaBH₄−THF−H₂O or an organomagnesium reagent to incorporate two diketone differentiation to afford the natural product. 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. 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. The tricylic nitronate propellane 29 emerged from application of a similar sequence with the phenol. The N-β-Me phenol 15 after olefin dihydroxylation and cleavage of the phenolic OBoc with ZnBr₂. Analogously, Lee prepared phenol 25 and completed the synthesis of moracin O (31).

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 MgX₂ is present. However, we speculate that in these conjugated phenyl o-QM instances, the o-QMs are more stable and we 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 ICH₂MgI and warming to room temperature. Yields were similar if the organolithium was employed as the starting organolithium.

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). 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. 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-QOMs with Some Applications

| Compound | Structure | Application |
|----------|-----------|-------------|
| 1        | ![Structure 1](image1) | ![Application 1](image2) |
| 2        | ![Structure 2](image3) | ![Application 2](image4) |
| 3        | ![Structure 3](image5) | ![Application 3](image6) |
| 4        | ![Structure 4](image7) | ![Application 4](image8) |
| 5        | ![Structure 5](image9) | ![Application 5](image10) |
| 6        | ![Structure 6](image11) | ![Application 6](image12) |
| 7        | ![Structure 7](image13) | ![Application 7](image14) |
| 8        | ![Structure 8](image15) | ![Application 8](image16) |
| 9        | ![Structure 9](image17) | ![Application 9](image18) |
| 10       | ![Structure 10](image19) | ![Application 10](image20) |
| 11       | ![Structure 11](image21) | ![Application 11](image22) |
| 12       | ![Structure 12](image23) | ![Application 12](image24) |
| 13       | ![Structure 13](image25) | ![Application 13](image26) |
| 14       | ![Structure 14](image27) | ![Application 14](image28) |
| 15       | ![Structure 15](image29) | ![Application 15](image30) |
| 16       | ![Structure 16](image31) | ![Application 16](image32) |
| 17       | ![Structure 17](image33) | ![Application 17](image34) |
| 18       | ![Structure 18](image35) | ![Application 18](image36) |
| 19       | ![Structure 19](image37) | ![Application 19](image38) |
| 20       | ![Structure 20](image39) | ![Application 20](image40) |
| 21       | ![Structure 21](image41) | ![Application 21](image42) |
| 22       | ![Structure 22](image43) | ![Application 22](image44) |
| 23       | ![Structure 23](image45) | ![Application 23](image46) |
| 24       | ![Structure 24](image47) | ![Application 24](image48) |
| 25       | ![Structure 25](image49) | ![Application 25](image50) |
| 26       | ![Structure 26](image51) | ![Application 26](image52) |
| 27       | ![Structure 27](image53) | ![Application 27](image54) |
| 28       | ![Structure 28](image55) | ![Application 28](image56) |
| 29       | ![Structure 29](image57) | ![Application 29](image58) |
| 30       | ![Structure 30](image59) | ![Application 30](image60) |

Scheme 2. Construction of Branched ortho-Aliphatic Phenols

![Scheme 2](image61)
OBoc acylation, 1,4-addition of the o-QM to give compound 45, in situ methylation, and finally acidic cleavage of the Boc residue. The tricycle 51, a precursor to (±)-cedrene, was accessed in one pot from phenol 48 by oxidation with lead tetraacetate. 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.

The corresponding reactions of ortho-OBoc aryl ketones and their esters were not extensively studied. However, it would appear that various ortho-OBoc acetophenones undergo addition of 2 equiv of MeMgBr to 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 phenoxy 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 S6–S8 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.

### BENVZOPYRANS 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.

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. More electron-rich alkenes gave improved yields. For example, 1-(tert-butoxy)-4-vinylbenzene afforded the corresponding tert-butoxy analog 60 in 80% yield. 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

### Table 2. Ortho-Branching Alkyl Substituted Phenols via o-QMs with Some Applications

| Structure | Application |
|-----------|-------------|
| ![Structure](image1) | ![Application](image2) |

### Table 3. Related Reactions of Ortho-OBoc Ketones and Esters

| Structure | Reaction |
|-----------|----------|
| ![Structure](image3) | ![Reaction](image4) |
followed by the addition of MgBr₂. This benzopyran was subsequently oxidized to a flavone and its protecting residues were concurrently cleaved by treatment with ZnBr₂. Its further reaction with a benzopyrylium salt yielded diinsininone (63), which was subsequently converted to the respective spiroketal. We are presently investigating the stereochemistry between the vicinal oxygen and alkyl residues of the cycloadduct. For example, the phenyl residue in the endo-transition state. The methyl residue of the spiroketal 65 is secured by the reaction proceeding nearly exclusively through the corresponding vicinal oxygen and allyl residues in the respective spiroketal. We are presently investigating the conversion of 64 into paecilospirone (71) by regioselective benzyl 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 2r-enol ether controls the stereochemistry of the cycloadduct. For example, the phenyl residue in the benzylidine ketal 6$′$ 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. 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 MgBr₂, undergoes a stereoselective reaction to produce pyran 67 as a single diastereomer.

Based on these diastereoselectivities, we designed, synthesized, and investigated a number of chiral enol ethers that fulfilled the role of a chiral auxiliary. Enol ethers derived from 2-phenylcyclohexanol are the culmination of these studies.

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

| Compound | Structure |
|----------|-----------|
| Diinsininone (70) | ![Structure](image) |
| Sophoracarpan-A (73) | ![Structure](image) |
| Medicarpin (74) | ![Structure](image) |

For example, the chroman acetal was reductively cleaved with BF₃·Et₂O 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). These stereoselective sequences demonstrated that the Y-residue serves as a diastereoselective element for subsequent kinetic reactions at the corresponding vicinal oxonium intermediate. This finding is not altogether surprising because there are four sp²-configured atoms within the pyran ring of the oxonium intermediate and the Y substituent usually occupies a pseudo-axial position because there are no steric interactions to prevent it. Thus, nucleophiles add to the oxonium opposite the Y substituent. For example, the chroman acetal was reductively cleaved with BF₃·Et₂O 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).

Chromans displaying aliphatic, aryl, vinyl, or silicon substituents at their benzylic sites (4-position) could be prepared by the different chroman methyl acetal in diastereoselective fashion via a mixed thioacetal as seen in the synthesis of kushecarpin (72). These stereoselective sequences demonstrated that the Y-residue serves as a diastereoselective element for subsequent kinetic reactions at the corresponding vicinal oxonium intermediate. This finding is not altogether surprising because there are four sp²-configured atoms within the pyran ring of the oxonium intermediate and the Y substituent usually 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 4–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 4. Stereoecontrol Emanating from Y Substituent at the C3-Position

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

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). 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).
sequential addition of organolithium, intended enol ether, and MgBr₂. 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 Boc₂O. Upon warming, the cycloaddition occurred for most systems.46

Electron-rich 2π 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 β-Substituted o-QMs also reacted with nonracemic enol ethers to yield chiral adducts with outstanding diasterecontrol (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 α-cedrene.24 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 used with BF₃·Et₂O/TESH and elaborated into ent-(+)-heliespirone A (91).47

Chiral chromans containing a benzylic R¹ substituent underwent several useful transformations (Scheme 6). For 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 R² 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 R² residue serves as a diastereocenteric element for building various chiral ortho-aliphatic α-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 β-elimination requires that the leaving O-acyl bond have partial coplanarity with the aromatic π-orbitals. As a result, the five-membered γ-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 δ-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 OBC δ-lactone 104 also underwent addition of organocerium and subsequent cycloaddition with enol ether.

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

| Position | R² | Chroman Example | Application |
|----------|----|----------------|-------------|
| α        | R² | Chroman Example | Application |
| β        | R² | Chroman Example | Application |
| γ        | R² | Chroman Example | Application |

β-substituted o-QMs also reacted with nonracemic enol ethers to yield chiral adducts with outstanding diasterecontrol (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 α-cedrene.24 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 used with BF₃·Et₂O/TESH and elaborated into ent-(+)-heliespirone A (91).47

Chiral chromans containing a benzylic R¹ substituent underwent several useful transformations (Scheme 6). For 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 R² 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 R² residue serves as a diastereocenteric element for building various chiral ortho-aliphatic α-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 β-elimination requires that the leaving O-acyl bond have partial coplanarity with the aromatic π-orbitals. As a result, the five-membered γ-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 δ-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 OBC δ-lactone 104 also underwent addition of organocerium and subsequent cycloaddition with enol ether.
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 R1 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.

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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