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Enantioselective Phenolic α-Oxidation Using H_2O_2 via an Unusual Double Dearomatization Mechanism

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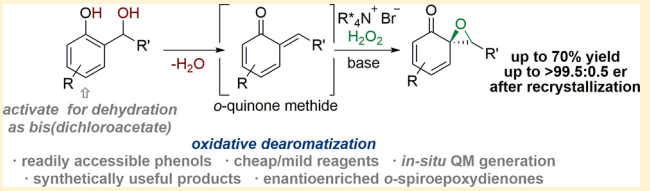
Supporting Information

ABSTRACT: Feedstock aromatic compounds are compelling low-cost starting points from which molecular complexity can be generated rapidly via oxidative dearomatization. Oxidative dearomatizations commonly rely heavily on hypervalent iodine or heavy metals to provide the requisite thermodynamic driving force for overcoming aromatic stabilization energy. This article describes oxidative dearomatizations of 2-(hydroxymethyl)phenols via their derived bis(dichloroacetates) using hydrogen peroxide as a mild oxidant that intercepts a transient quinone methide. A stereochemical study revealed that the reaction proceeds by a new mechanism relative to other phenol dearomatizations and is complementary to extant methods that rely on hypervalent iodine. Using a new chiral phase-transfer catalyst, the first asymmetric syntheses of 1-oxaspiro[2.5]octa-5,7-dien-4-ones were reported. The synthetic utility of the derived 1-oxaspiro[2.5]octadienones products is demonstrated in a downstream complexity-generating transformation.



1. INTRODUCTION

Oxidative dearomatizations of feedstock arenes, including phenols, are useful in delivering functionalized, complex organic building blocks.[1] These processes often rely on excess, and in some cases costly, hypervalent iodine or heavy metal-based (i.e., lead and bismuth) reagents which can give rise to hazardous byproducts;[2] this characteristic may counterbalance or overshadow the benefit of using inexpensive feedstock precursors. Reactions using catalytic or heavy metal-free conditions with benign oxidants, such as oxygen or hydrogen peroxide, have seldom been explored, especially in asymmetric fashion.[3] Hydrogen peroxide (H_2O_2) is especially appealing as an oxidant due to its high efficiency, abundance, and favorable byproduct profile (i.e., H_2O).[4]

A recent report from these laboratories employed the Adler−Becker oxidation as the initiating step in a cascade sequence for the synthesis of highly functionalized heterocycles.[5] The Adler−Becker oxidation utilizes stoichiometric sodium metaperiodate ($NaIO_4$), a hypervalent iodine species, to convert 2-(hydroxymethyl)phenols **1**, also referred to as salicyl alcohols, into racemic, dearomatized 1-oxaspiro[2.5]-octa-5,7-dien-4-ones **4** (spiroepoxydienones) (Scheme 1a),[6] a motif which is readily found in a number of biologically active natural products (Scheme 1c).[7] While these oxidation products have been broadly deployed due to their functionalizable dienone motif and proclivity to participate in a variety of cycloaddition reactions,[8] the lack of access to enantioenriched spiroepoxydienones limits their applicability.

The favorable attributes of the (hydroxymethyl)phenol dearomatization and the interest in enantioenriched spiroepoxydienones led to the development of the hypothesis outlined in Scheme 1b. The reaction design imagines an enabling and underexplored intersection between transient quinone methides and mechanistically validated asymmetric nucleophilic epoxidations using basic H_2O_2.[9]

ortho-Quinone methides **2** (*o*QMs) are dearomatized species that have frequently been employed in forming complex natural products and synthetically useful building blocks.[10] A strong driving force for rearomatization underlies the high reactivity of the enone toward [4 + 2]-cycloadditions[11] and 1,4-conjugate additions.[12] In almost all cases, these transformations irreversibly reset the aromaticity of the resultant system, limiting further complexity-building transformations. Reactions involving *o*QMs resulting in isolable, dearomatized products are rare.[13]

Because phenol **1** is formally related to its derived *o*QM **2** by dehydration, a key challenge to achieving the title process would be the identification of conditions that facilitate dehydrative QM formation under mild conditions: a new method of QM generation was deemed to be a prerequisite for success of the project.[14] Scheme 1 moreover postulates that the reaction of a nonstabilized,[15] ephemeral QM with H_2O_2 under basic conditions would initially re-establish aromaticity affording hydroperoxide **3** but concurrently set the stage for heterolytic O−O bond cleavage induced by engagement at the phenolic α-carbon, thereby breaking aromaticity for the second time in the sequence and creating the spiroepoxide substructure (**4**). Employing an asymmetric ion-pairing phase-transfer catalyst with phenoxide **3** could selectively facilitate the O−O bond cleavage, affording the enantioenriched spiroepoxydienone.

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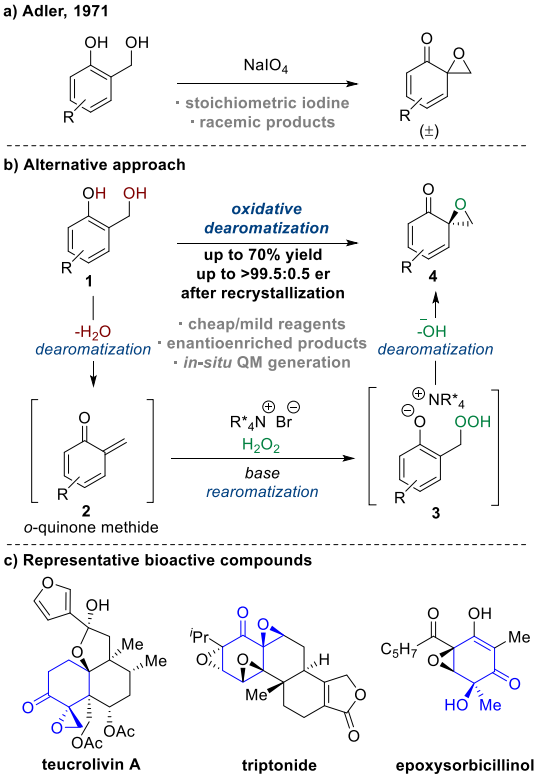
Scheme 1. Oxidative Dearomatization of 2-(Hydroxymethyl)phenols

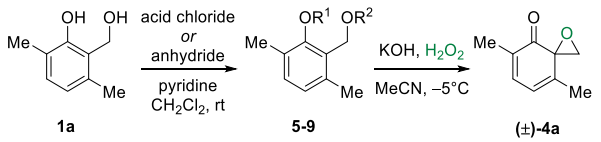


2. RESULTS AND DISCUSSION

Considering this hypothesis, we converted primary alcohol **1a**[16] to its unstable monoacetate **5** in low yield. When phenol **5** was subjected to KOH and H_2O_2 in MeCN at −5 °C, the desired spiroepoxydienone **4a** was observed (Table 1, entry 1). Diacetate **6** was prepared in 70% yield and exhibited better stability than **5**. Diacetate **6** in turn gave **4a** in somewhat higher yield relative to the preparation from the monoacetate **5** (entry 2). The efficiency of quinone methide formation could be affected by the rates of both the phenolic deacylation (loss of R^1) and expulsion of (−)OR^2; the electronic characteristics of both groups should be critical. To accelerate both steps, the more electron-deficient mono- and dichloroacetate analogues were prepared and exhibited drastically improved intermediate and product yields (entries 3 and 4). Bis(trifluoroacetate) **9** performed at a modest level (entry 5); consequently, bis(dichloroacetate) analogue **8** was selected for deployment with additional phenols.[17] Dichloroacetate merits some consideration of the molecular mass "sacrificed", but the attractiveness of this acid chloride as a dehydrating agent stems in no small part from its cheap access on scale, high yields (>90%), and wide applicability and the fact that bis-(dichloroacetates) **8** are stable and often exist as easily handled white solids.

Using the optimized racemic conditions identified in Table 1, alkyl-substituted 2-(hydroxymethyl)phenols afforded the highest yields of the desired spiroepoxide products (Table 2, **4a**−**c**, **i**−**k**). Alkyl groups promote the formation of QMs while reducing the rate of detrimental dimerization processes.[18] Electron-withdrawing substituents are reported to inhibit QM formation[18] and lead to oligomerization under basic conditions;[19] however, when using difluorophenol **8e**, the desired product **4e** was obtained (47%). In contrast, difluorophenol **1e** failed to provide any discernible product when $NaIO_4$ was used, highlighting the complementary nature of this method relative to the Adler−Becker oxidation. Mixed alkyl and halogen substitution afforded similar yields when 9

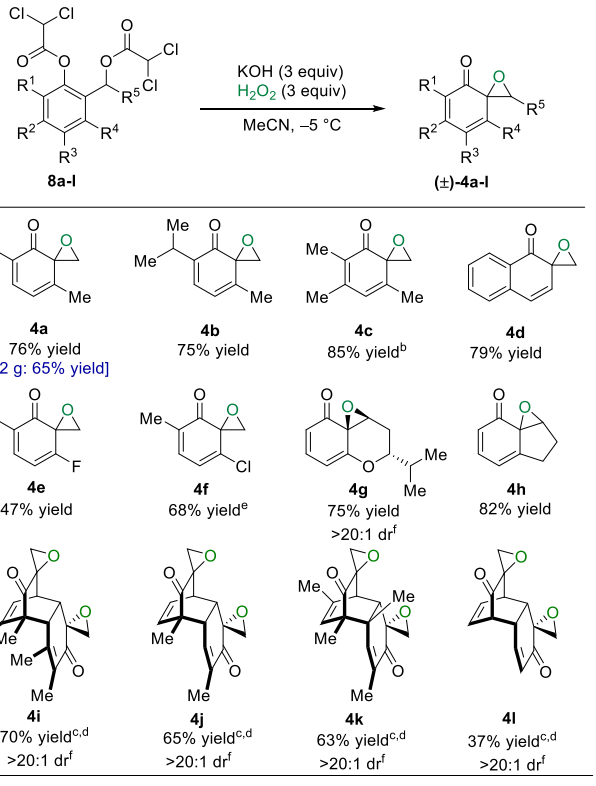
Table 1. Identification of an Optimal Activating Group for Quinine Methide Formation



entry	R^1	R^2	acetate product	yield **5-9** (%)[a]	yield **4a** (%)[b]	overall yield (%)
1	H		**5**	40	21	**8**
2			**6**	70	37	**26**
3			**7**	89	60	**54**
4			**8**	95	80	**76**
5			**9**	74	55	**41**

[a]Isolated yield. [b]^{1}H NMR yield versus internal standard

Table 2. Racemic Scope of Oxidative Dearomatization Using Bis(dichloroacetates) of 2-(Hydroxymethyl)phenols[a]



[a]Reactions performed with 1.0 equiv of **8** and 3.0 equiv of both H_2O_2 and KOH in MeCN ($[\mathbf{8}]_0$ = 0.05 M). Yields refer to isolated yields. [b]4 equiv of KOH was used. [c]Product isolated as dimer. [d]Slow addition of a solution of **8** and H_2O_2 over the course of 1 h. [e]9 equiv of H_2O_2 was used. [f]Determined by ^{1}H NMR spectroscopic analysis.

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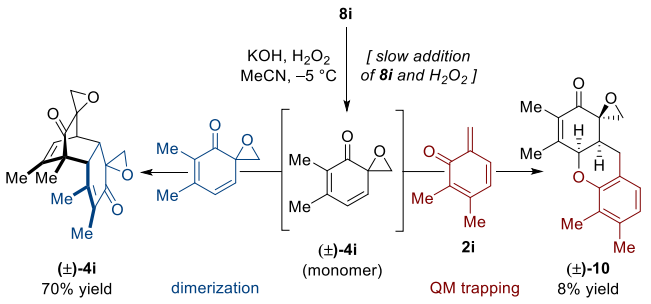
equiv of peroxide was used (**4f**). Because benzylic substitution (R^5) often promotes facile rearrangement of spiroepoxydienones to benzodioxoles,[5] we used bicyclic substrates **8g–h** to prevent rearrangement and observed good yields with excellent diastereoselectivity in **4g**.

The substitution pattern around the *o*-spiroepoxydienone was a critical determinant of whether the product was isolated in monomeric or dimeric form.[20] Compounds **4i–l** with no substitution at R^4 generally favored dimerization upon isolation. Unsubstituted salicyl alcohol **4l** afforded the lowest yield and resulted in a multitude of side products (i.e., oligomers, QM dimers). Substrates prone to dimerization required that bis(dichloroacetate) **8** and H_2O_2 were added over the course of 1 h to reduce excess QM accumulation in solution. Rapid addition (<1 min) of **8** and H_2O_2 to the KOH/MeCN mixture resulted in a 1:1 mixture of the dimer and chromane **10**, the product of trapping of the spiroepoxydienone with excess QM in solution (Scheme 2).

Scheme 2. Observed Competition between Product Dimerization and Quinone Methide Trapping

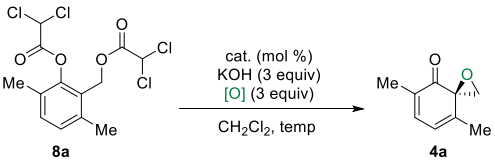


With a mechanistically distinct phenolic oxidation in hand, we became interested in developing an asymmetric variant of the title process. Enantioselective transformations utilizing *o*QMs lacking methide substitution under basic conditions are limited due to their high reactivity and propensity to dimerize rapidly in solution.[21] While asymmetric Weitz–Scheffer-type epoxidations are well established for chalcones and other *β*-substituted enones using cinchona alkaloid phase-transfer catalysts (PTCs), asymmetric epoxidations of enones lacking *β*-substitution are rare.[22] Employing *in situ*-generated *o*QMs that lack substitution at the methide position presents a formidable challenge in controlling the stereochemistry of the resultant spiroepoxide.

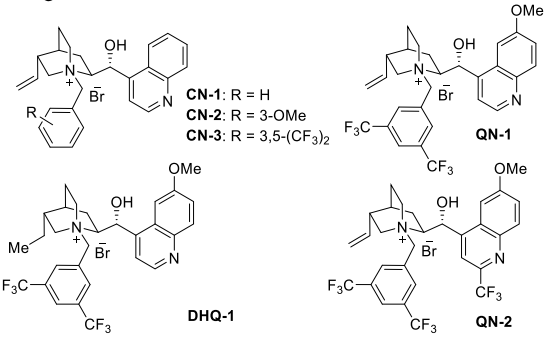
Toward this end, we envisioned employing an asymmetric ion-pairing PTC with phenoxide **3** as a method for controlling the facial selectivity of heterolytic O–O bond cleavage, a mechanism closely related to phase-transfer-catalyzed *α*-enolate substitution reactions.[23] Computational analyses of these enantioselective reactions have revealed tight catalyst control of the substrate and electrophile to direct the facial selectivity of the substitution.[24] While PTC *α*-enolate substitution reactions frequently involve the coordination of external electrophiles, more recent examples employ internal electrophiles using cinchona alkaloid PTCs bearing a free hydroxyl group.[25]

We therefore began our catalyst screening by employing various cinchona alkaloid PTCs with a free hydroxyl group.[26] Gratifyingly, phase-transfer catalyst **CN-1** with CH_2Cl_2 solvent using 30% aqueous H_2O_2 as the oxidant resulted in a 55:45 er (Table 3, entry 1). Further catalyst optimization revealed that

Table 3. Optimization of Enantioselective Oxidative Dearomatization[a]



entry	cat.	mol %	[O]	T (°C)	er[a]	yield (%)[b]
1	CN-1	20	H_2O_2 (aq)	0	55:45	<10
2	CN-2	20	H_2O_2 (aq)	0	50:50	<10
3	CN-3	20	H_2O_2 (aq)	0	63:37	<10
4	CN-3	20	UHP	0	69:31	33
5	QN-1	20	UHP	0	85:15	50
6	QN-1	20	UHP	−10	87:13	55
7	QN-1	20	UHP	−20	80:20	43
8	DHQ-1	20	UHP	−10	87:13	52
9	QN-2	20	UHP	−10	85:13	70
10	QN-2	20	UHP	−40	87:13	85
11	QN-2	10	UHP	−40	87:13	86



[a]Reactions were performed using **8a** (0.50 mmol), KOH (1.5 mmol), UHP (1.5 mmol), and $[\mathbf{8a}]_0$ = 0.05 M in CH_2Cl_2. **8a** was added over the course of 2.5 h. [b]er was determined by chiral HPLC. [c]Isolated yields.

more electron-deficient benzyl groups (i.e., **CN-3**) improved selectivity (entry 3). Employing urea·H_2O_2 (UHP) to limit water content gave appreciable increases in selectivities and yields. Switching to quinine as the cinchona alkaloid (**QN-1**) greatly improved the er while affording mediocre yields (entry 4). Cooling the reaction temperature to −20 °C resulted in lower yields and selectivities (entry 5). Dihydroquinine catalyst **DHQ-1** was investigated to minimize potential in situ derivatization of the catalyst's olefin via a Diels–Alder cycloaddition with a transient quinone methide (entry 6). Disappointingly, this catalyst resulted in the same yields and selectivities as **QN-1**. Upon further analysis, increased catalyst loading resulted in increased side product formation. Characterization revealed putative oxazonine **11** resulting from nucleophilic attack on a generated QM by the catalyst's quinoline nitrogen followed by cleavage of the quinuclidine core (Scheme 3). To minimize the nucleophilicity of the quinoline nitrogen while simultaneously providing steric hindrance,[27] catalyst **QN-2** with a trifluoromethyl group was developed (30% yield over 3 steps from quinine *N*-oxide), which considerably improved yields while maintaining selectivities (entry 7).

Using the optimized catalyst and reaction conditions, various bis(dichloroacetates) were evaluated for conversion to their derived enantioenriched epoxides (Table 4). Monomers **4a–d** were all found to afford modest selectivities with high yields;

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Scheme 3. Preventing Catalyst Decomposition

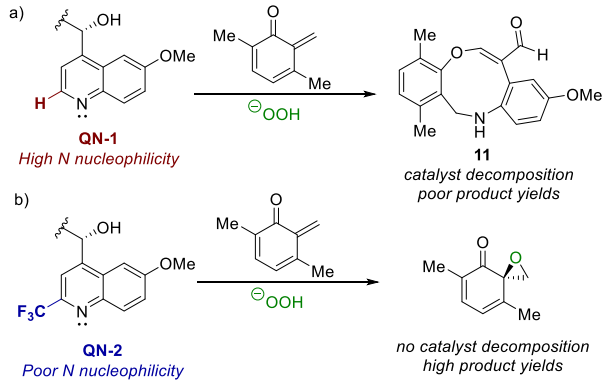
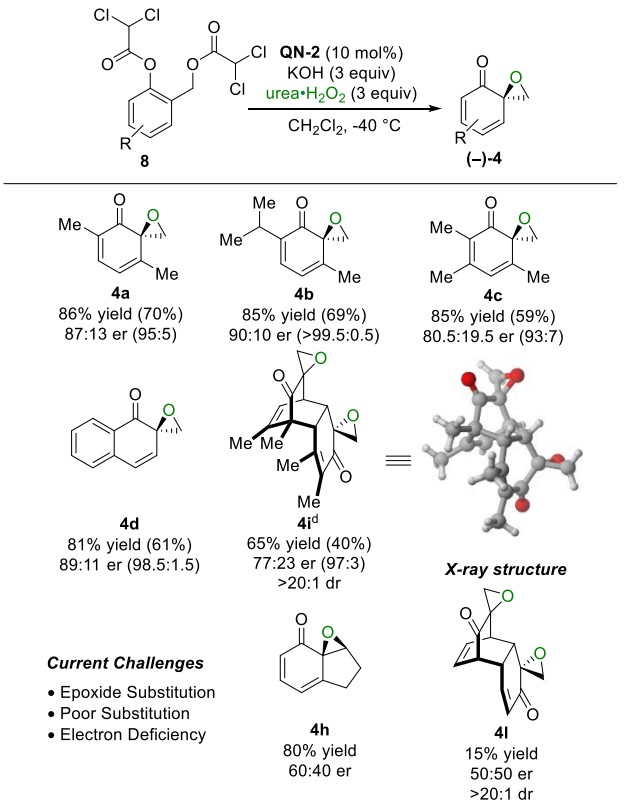


Table 4. Scope of Enantioselective Oxidative Dearomatization[a,b,c]

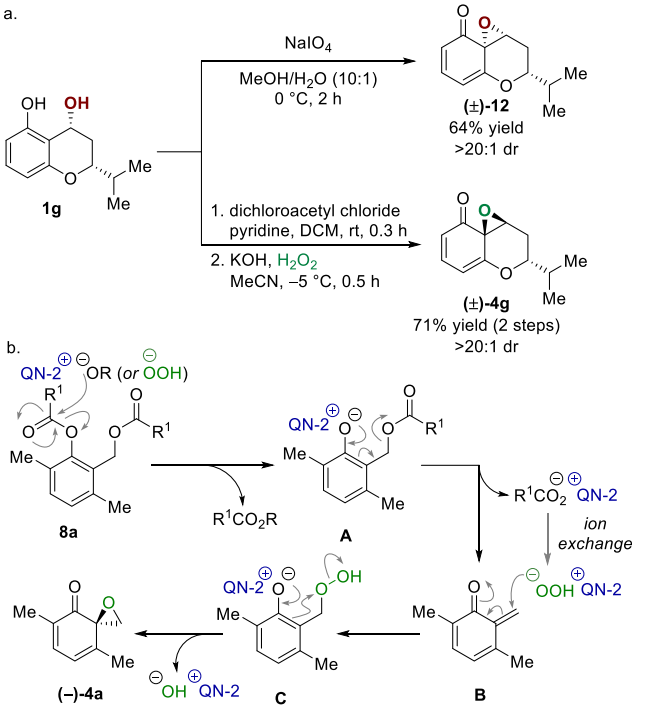


[a]Reactions were performed using **8** (0.50 mmol), **QN-2** (10 mol %), KOH (1.5 mmol), UHP (1.5 mmol), and [**8**] = 0.05 M in CH_2Cl_2, at −40 °C. [b]er was determined by chiral HPLC. [c]Values in parentheses represent recrystallized yields and enantiomeric ratios. [d]20 mol % QN-2.

however, good to excellent enantioselectivities with good mass recovery could be achieved via a single recrystallization. Similarly, dimer **4i** exhibited slightly diminished selectivities that could be upgraded by a single recrystallization, affording excellent selectivities and modest recovery. It was quickly apparent that the stability and substitution pattern of the generated QM were important factors in determining the yield and enantioselectivities of the reaction. Attempts to access the enantioenriched unsubstituted dimer **4l** resulted in low yields of the racemic dimer due to rapid QM oligomerization relative to epoxidation under the basic conditions. In contrast, bicyclic substrate **4h** gave excellent yields but afforded poor selectivity, although a change in the enantiodetermining step of the reaction should be noted with these β-substituted substrates.

An evaluation of the reaction mechanism was initiated by comparing the stereochemical outcome of the H_2O_2-mediated oxidative dearomatization of **1g** to that when $NaIO_4$ was employed (Scheme 4a). $NaIO_4$ oxidation proceeded with

Scheme 4. Mechanistic Insights and Proposed Mechanism



stereoretention (**12**), while Weitz−Scheffer epoxidation[9] of the planar QM intermediate proceeded with highly diastereoselective inversion at the benzylic position (**4g**). Based upon this observation, we propose the initial deacylation of the phenolic dichloroacetate **8a** to afford phenoxide **A** followed by formation of *o*QM **B** via elimination of the benzylic dichloroacetate. Conjugate addition by hydroperoxide affords the rearomatized phenoxide **C** that attacks the hydroperoxide to give the dearomatized epoxide **4a** (Scheme 4b).

The unique and critical role of PTC **QN-2** in both QM generation and stereoselective epoxide formation is evident in this mechanism. To further understand the catalyst's role in promoting the observed stereoselectivity, the transition state of the epoxidation step between **QN-2** and **3a** was studied computationally using density functional theory (DFT) calculations at the level of M062X[28a] approximate functional and a compound Pople basis set.[28b,c]

Upon analysis of the calculated major stereoisomer (Figure 1a), several important interactions emerge: (a) the hydroxide nucleofuge is stabilized by two significant hydrogen bonding interactions derived from the Ar−H on the electron-deficient $(CF_3)_2Ar$ ring (H···O distance 2.06 Å) and the benzylic C−H in close proximity to the ammonium cation (H···O distance 2.16 Å) as well as a weaker hydrogen bonding interaction from the C−H bond on the bridged quinuclidine (H···O distance 2.67 Å);[29] (b) the catalyst −OH group forms a strong hydrogen bond (H···O distance 1.83 Å) to the phenoxide of the substrate, orienting the hydroperoxide in close proximity to

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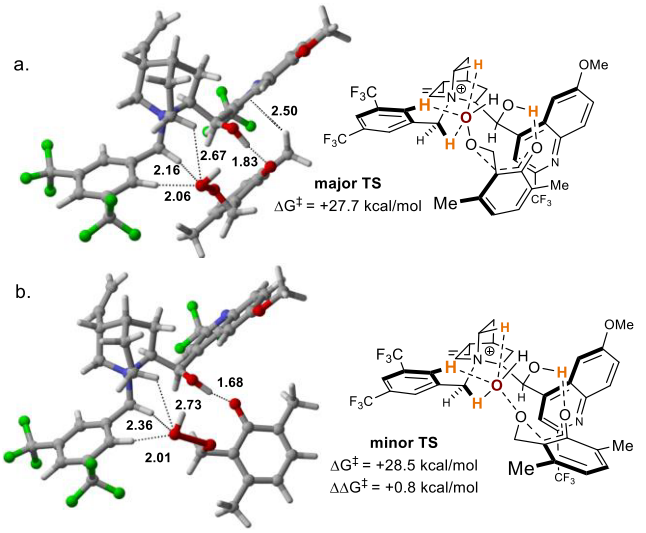


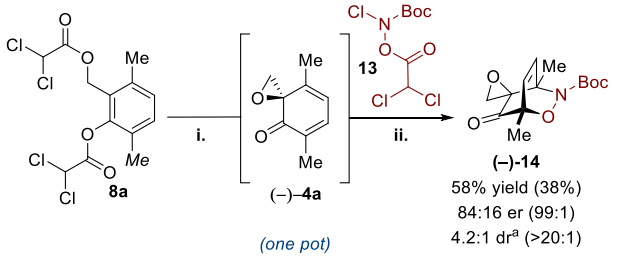
Figure 1. DFT-optimized stereodetermining transition states of **QN-2** and **3a**.

the three stabilizing hydrogen bond donors; and (c) the C-2 methyl group on **3a** experiences an attractive CH−π interaction with the quinoline ring (atom to plane distance of 2.50 Å).[30] The apparent synergistic role of the $R_3N^+CH_2$− cationic subunits and the $(F_3C)_2Ar$−H is to create an unconventional trifurcated oxyanion hole to stabilize and accommodate the nascent alkoxide during O−O scission (*vide infra*). Such interactions for nucleofuge stabilization have been previously identified via DFT calculations but arise principally or solely from the $R_3N^+CH_2$− cationic subunit.[24]

We were interested in comparing the stereodetermining catalyst−substrate interactions leading to the formation of the minor enantiomer to those leading to major isomer formation. These interactions were calculated to be similar to the major isomer (Figure 1b), with the distinction being a ∼90° rotation of the substrate's aromatic ring to afford the opposite epoxide facial selectivity. The transition state leading to minor enantiomer formation was calculated to be 0.84 kcal/mol greater in energy than the major enantiomer. This higher energy transition state can be explained by (a) the loss of the attractive CH−π interaction between the substrate C-2 methyl group and the quinoline ring and (b) the observed lengthening of the hydrogen bonding interaction between the hydroxide nucleofuge and the benzylic C−H (2.36 Å versus 2.16 Å), mitigating, in part, the stabilization of the leaving group. The increased transition state barrier due to the loss of the methyl CH−π interaction is in accord with experimental evidence demonstrating reduced enantiocontrol with lack of alkyl substitution.

1-Oxaspiro[2.5]octa-5,7-dien-4-ones (**4**) are highly reactive species which readily participate in Michael additions,[31] dihydroxylation,[31] epoxide openings,[32] and cycloadditions.[33] To further highlight the synthetic utility of this reaction in complexity building transformations, enantioenriched spiroepoxydienone generation was merged with subsequent base-promoted acyl-nitroso generation from **13**[34] to realize a one-pot oxidative dearomatization/acyl-nitroso Diels−Alder cycloaddition. The derived tricyclic oxazinanone **14** (Scheme 5) was obtained with excellent enantio- and diastereoselectivity after a single recrystallization. These tricyclic oxazinanones can be

Scheme 5. One-Pot Enantioselective Oxidative Dearomatization/Acyl-Nitroso Diels−Alder Cycloaddition



i. **QN-2** (10 mol %), KOH (3 equiv), UHP (3 equiv), CH_2Cl_2, −40 °C, 4.5 h; then *ii.* **13** (1.5 equiv), −40 to 0 °C, 1.5 h

[a]Isolated as an equilibrating mixture of diasteromers.[5] [b]Values in parentheses represent recrystallized yield, enantiomeric ratio, and diastereomeric ratio.

further elaborated to afford highly substituted cyclohexanone rings in a short number of synthetic steps.[5]

3. CONCLUSION

We have developed an enantioselective oxidative dearomatization of 2-(hydroxymethyl)phenols using H_2O_2 to afford stable, dearomatized 1-oxaspiro[2.5]octadienones employing a base-promoted in situQM activation technique. This reaction highlights the use of a mild and convenient oxidant to afford synthetically useful, dearomatized spiroepoxydienones. By using a new cinchona alkaloid-derived phase-transfer catalyst, the reaction allows for access to enantioenriched *o*-spiroepoxydienones which were previously inaccessible via the Adler−Becker oxidation. DFT calculations revealed a highly organized transition state involving a unique tripartite stabilization of the hydroxide leaving group leading to the observed facial selectivity. The synthetic utility of this method for rapid complexity generation has been demonstrated by preparing an enantioenriched tricyclic oxazinanone. This chemistry demonstrates the potential for complementary enantioselective dearomative processes involving quinone methides, and our laboratory is currently exploring these possibilities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b13006.

CIF file giving data for compound **4i** (CIF)
Experimental procedures, characterization, and spectral data for all new chemical compounds as well as crystal data and data collection parameters (PDF)

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Notes

The authors declare no competing financial interest.

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