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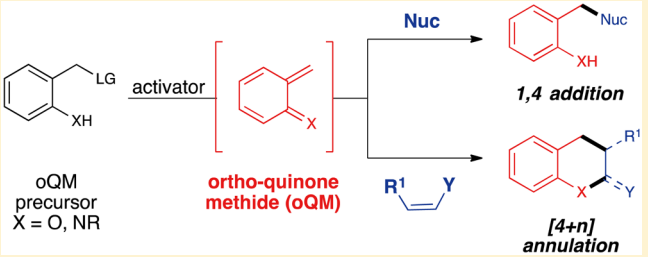
Emerging Roles of in Situ Generated Quinone Methides in Metal-Free Catalysis

Ashley A. Jaworski and Karl A. Scheidt*

Department of Chemistry, Center for Molecular Innovation and Drug Discovery, Northwestern University, 2145 Sheridan Road, Evanston, Illinois 60208, United States

ABSTRACT: *ortho*-Quinone methides have emerged recently as useful electrophiles in metal-free catalysis. New strategies to access these species in situ that are compatible with simultaneous nucleophile generation have provided a suite of innovative and selective transformations accessing heterocycles for use in organic synthesis.



1. INTRODUCTION

ortho-Quinone methides (oQMs) are reactive intermediates that have been utilized for decades in organic chemistry.[1,2] Many early studies on oQMs employed high temperatures, irradiation, or harsh reagents to overcome the thermodynamic penalty associated with breaking aromaticity in the oQM precursor. These high-energy oQM intermediates have been observed to dimerize and/or react unselectively, presumably in order to restore aromaticity. The perception that oQMs formed under these traditional approaches are highly unstable reactive intermediates may have contributed to the dearth of oQMs as substrates for metal free catalytic transformations until recently.[3−5]

In the face of this conventional wisdom, several strategies have emerged to generate oQMs in situ, allowing for controlled rates of addition and predictable concentrations of reactive intermediate in a single flask (Figure 1). These new, mild methods for generating oQMs have enabled different laboratories to tap into the potential of these interesting substrates for modern catalytic transformations. In these processes, a reactant and catalyst/activator typically combine to form a transiently generated nucleophile (Nuc). In a simultaneous event in the same flask, the oQM precursor undergoes a thermodynamically unfavorable bond cleavage to unmask the oQM, which then combines with the nucleophile to provide either 1,4-addition products or a [4 + *n*] annulation via stepwise and/or concerted pathways. In this carefully orchestrated general process, *there are multiple mechanistic considerations/challenges:* (a) the "activation"/generation of the oQM and the associated ΔH_f, (b) the compatibility of this process with concomitant nucleophile production, (c) the matching of rates and concentrations of different reactive intermediates to produce a viable reaction, and (d) the potential for catalyst regeneration/turnover. In this Synopsis, representative developments in the chemistry of oQMs that meet these criteria are presented, highlighting the shifting overall perception of the utility of oQMs in organocatalysis. Additional important contributions to the chemistry of oQMs mediated by organometallic and transition-metal reactions have been summarized recently by Sigman[6] and Pettus[7] and are not included in this Synopsis. Taken collectively, these previous contributions and the information herein form a comprehensive ensemble capturing the exciting and modern transformations of oQMs over the past decade and set the stage for further creative applications of these unique electrophiles in catalysis and synthesis.

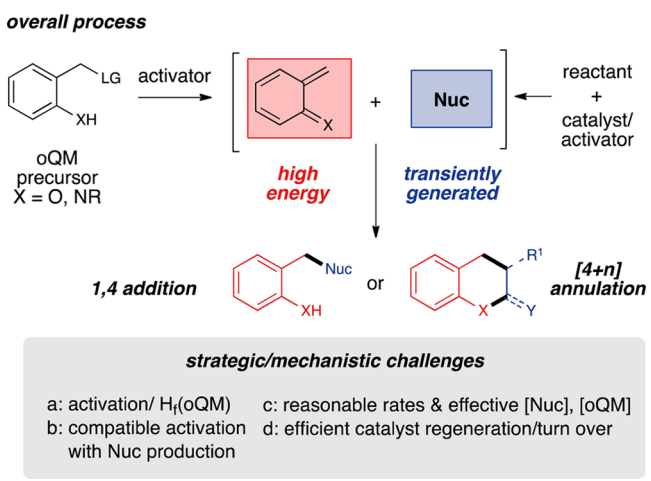


Figure 1. General oQM activation with strategic considerations.

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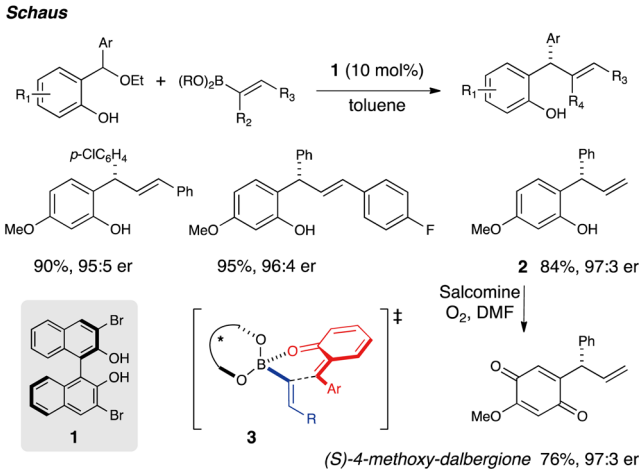
2. ACID-MEDIATED GENERATION OF OQMS

In 2012, the Schaus group developed an enantioselective addition reaction between vinyl boronates and stabilized oQMs. In an effort to expand the scope of the reaction beyond the limited number of isolable oQMs, they also investigated the possibility of generating the requisite oQM substrates in situ by effecting ionization of a benzhydryl alcohol or ether under their Lewis acidic reaction protocol.[8] Different benzhydryl ethyl ethers were found to be effective substrates when treated with BINOL-derived chiral phosphoric acid (CPA) catalyst **1** and vinyl boronates. Product styryl phenols were obtained in good yields and with high enantioselectivities (Scheme 1). While the

Scheme 1. Addition of Vinyl Boronates to oQMs

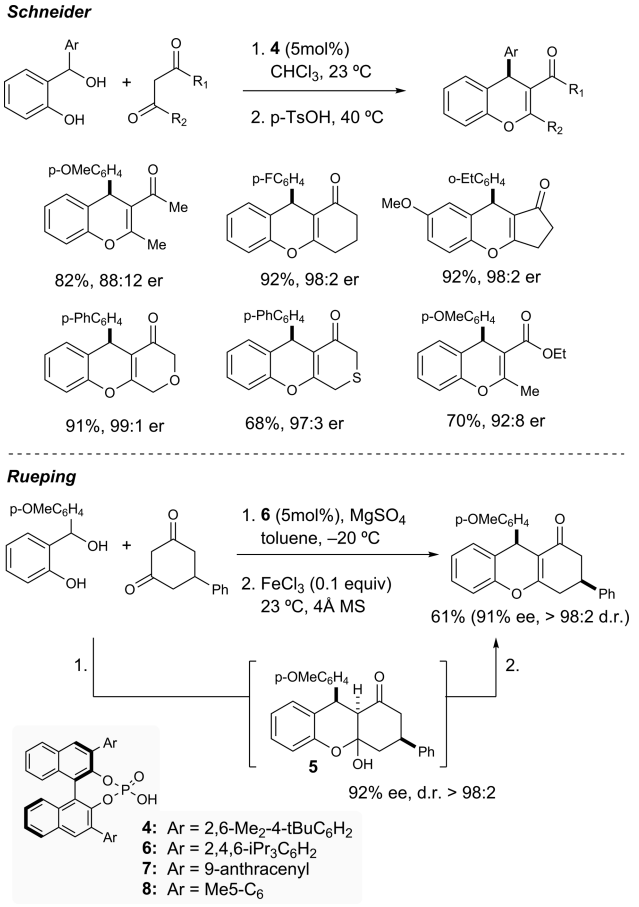


oQM precursors were limited to benzhydryl alcohol derivatives that possessed a para-electron-donating group on at least one of the aromatic rings, the new in situ method offered a significant advance beyond the limited pool of stabilized oQM substrates. The product **2** arising from the addition of a simple vinyl boronate to an oQM was converted in a single oxidation step to the *para*-quinone natural product 4-methoxydalbergione, demonstrating the potential that in situ oQMs could provide to synthetic chemists as strategic intermediates (Scheme 1, bottom right). A follow-up DFT study on asymmetric boronate-mediated alkylations was performed by the Goodman laboratory, who proposed that the reaction likely proceeds via a six-center transition state (i.e., **3**, Scheme 1). Their model indicates that the boronate reagent acts as a Lewis acidic activator for the oQM via coordination at its carbonyl group, facilitating delivery of the pendant vinyl nucleophile.[9]

A computational DFT study by Freccero in 2003 investigated bonding and solvent effects in the alkylation of pyrimidine bases by an oQM electrophile. This work suggested that hydrogen bonds between oQMs and acids and/or aqueous media could greatly activate a model oQM toward nucleophilic attack.[10] However, reported attempts to activate potential oQM precursors with chiral Brønsted acids indicated that cationic intermediates with chiral counterions, rather than oQMs, were likely responsible for the formation of enantioenriched products.[11,12]

In 2014, the groups of Schneider[13] and Rueping[14] successfully achieved an enantioselective alkylation of oQMs generated in situ under Brønsted acidic conditions using the bifunctional capability of chiral phosphoric acid catalysts (Scheme 2). When oQM generation was merged with the

Scheme 2. Addition of 1,3-Dicarbonyl Compounds to oQMs



directing effect of the CPA by choosing nucleophiles bearing highly coordinating hydrogen-bond donors (1,3-dicarbonyl compounds), good yields and enantioselectivities of the resulting addition products were observed (Scheme 2, top). The reaction requires substituted benzhydryl alcohol substrates akin to those employed by Schaus to generate oQMs in situ under Lewis acidic conditions. Symmetrical 1,3-dicarbonyl compounds could be desymmetrized using this protocol to give products as single diastereomers with good levels of enantioinduction (Scheme 2, bottom). The intermediate hemiketal **5** was isolable, and the conserved ee and dr observed indicates that the absolute and relative stereochemical configuration of the product is established by the catalyst in the initial attack of the acid-bound enol on the oQM (Figure 2).

The requirement that the reacting nucleophile possesses a hydrogen-bond donating group suggests a typical bifunctional role for the chiral phosphoric acid, in which it activates the oQM via its carbonyl group while simultaneously coordinating the substrate and directing the enantioselective attack of the nucleophile within the CPA's chiral sphere (Figure 2).[15] Based on this principle, the chemistry of oQMs with CPA catalysis has since been extended to other acid-compatible nucleophiles with hydrogen-bond donor groups such as indoles,[16,17] napthols,[17] enamides,[18,19] and Hantzch esters.[20]

Fewer examples of oQM precursors that are *not* derived from benzhydryl alcohols (substrates above in the Schneider and Rueping reports) have been reported as effective reacting partners in acid-mediated reactions. One exception was noted

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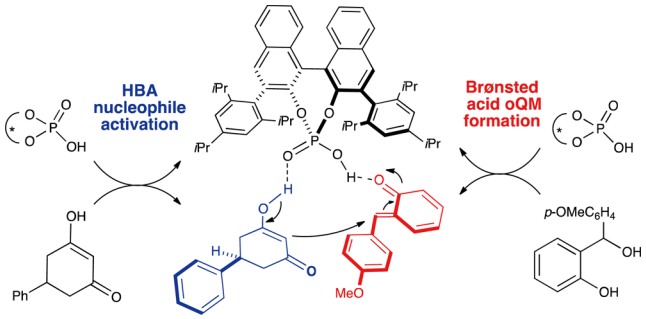
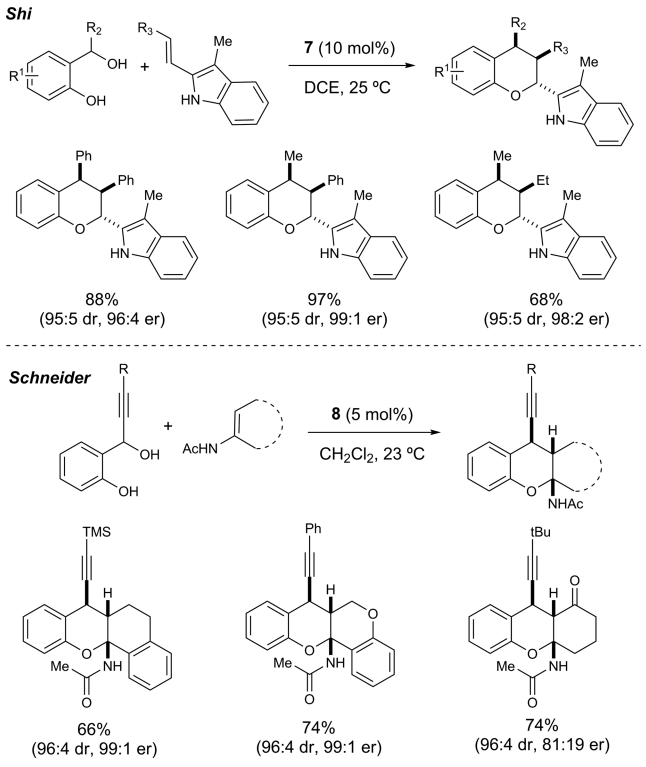


Figure 2. Possible TS for dual/bifunctional activity of CPAs with oQMs. HBA = hydrogen bond acceptor.

in 2015 by the Shi group, who found that alkyl benzyl alcohols were competent oQM precursors in a CPA-mediated inverse-electron-demand hetero-Diels–Alder reaction of 3-methyl-2-vinylindoles with oQMs.[21] High yields and enantiomeric excesses of tetrahydropyran products were observed even when oQM precursors bearing simple alkyl substituents on the benzyl alcohol (R_2, Scheme 3, top). The dual role played by the

Scheme 3. Additional oQM Precursors Compatible with Brønsted Acid Activation

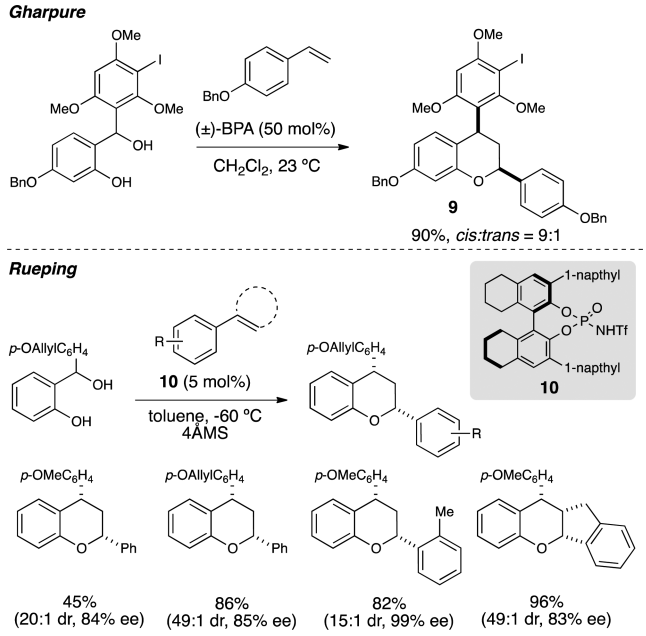


CPA in activating the oQM precursor while simultaneously engaging the 2-vinylindole was corroborated by the observation that a corresponding *N*-methylated 2-vinylindole substrate failed to react under their protocol.

Efforts by the Schneider group to expand the scope of available oQM precursors compatible with in situ acid-activation reaction strategies led to the development of a novel class of oQM precursors derived from propargylic benzyl alcohols in 2015 (Scheme 3, bottom). These new oQM precursors were suitable substrates for annulations with enamides, giving rise to highly functionalized substructures bearing multiple synthetic handles in good yields and enantioselectivities.[19]

One exception to the apparent requirement of a strong hydrogen-bond donor group on the nucleophilic partner in acid-mediated oQM reactions was reported in 2013 by the Gharpure laboratory, who discovered that treatment of benzhydryl alcohols with an enantiopure BINOL-phosphoric acid (BPA) in the presence of styrenes gave rise to racemic diarylbenzopyran products.[22] Racemic BPA was employed to explore the scope of the reaction, and they found that despite the propensity for styrenes to polymerize under Brønsted acidic conditions, only 1.1 equiv of styrene to benzhydryl alcohol was required to observe good yields of racemic annulation products. Compound **9** was synthesized as an intermediate in a concise formal synthesis of the natural product myristinin B/C (Scheme 4, top).[23]

Scheme 4. Addition of Non-coordinating Styrenes to oQMs under Brønsted Acid Catalysis[a]



[a]BPA = BINOL-phosphoric acid.

Rueping rendered this transformation enantioselective in 2015 by employing a more acidic *N*-triflylphosphoramide (NTPA) catalyst (Scheme 4, bottom). The enantiocontrol in this reaction was proposed to result from activation of the electrophilic oQM by the catalyst, which undergoes addition by styrene without precoordination in a monofunctional mode of activation.[24]

A significant advance in CPA-mediated oQM chemistry was achieved by the Schneider group in 2016, who successfully merged catalytic rhodium carbene catalysis with oQMs generated in situ.[25] In this system, diazoester substrates must undergo two sequential activation steps in order to generate the activated nucleophilic species: first, rhodium(II) displaces nitrogen from the subtrate, forming a reactive rhodium-bound carbene (Figure 3). Next, it is postulated that a molecule of water adds to the rhodium-bound carbene to give the active nucleophilic oxonium ylide species **12**. The hydrogen-bond donating capability of **12** is thought to facilitate coordination and attack on the CPA-associated oQM (Figure

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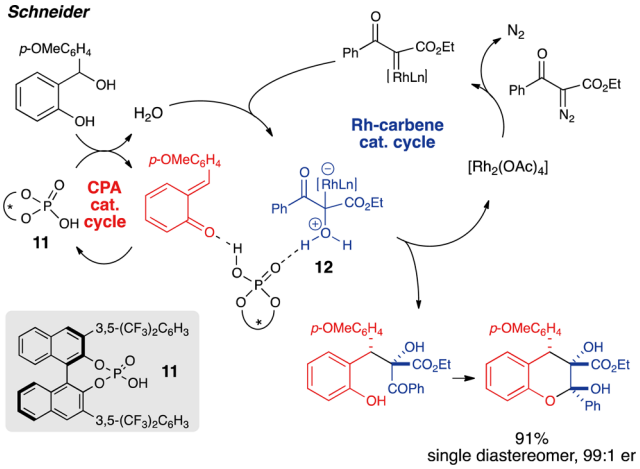


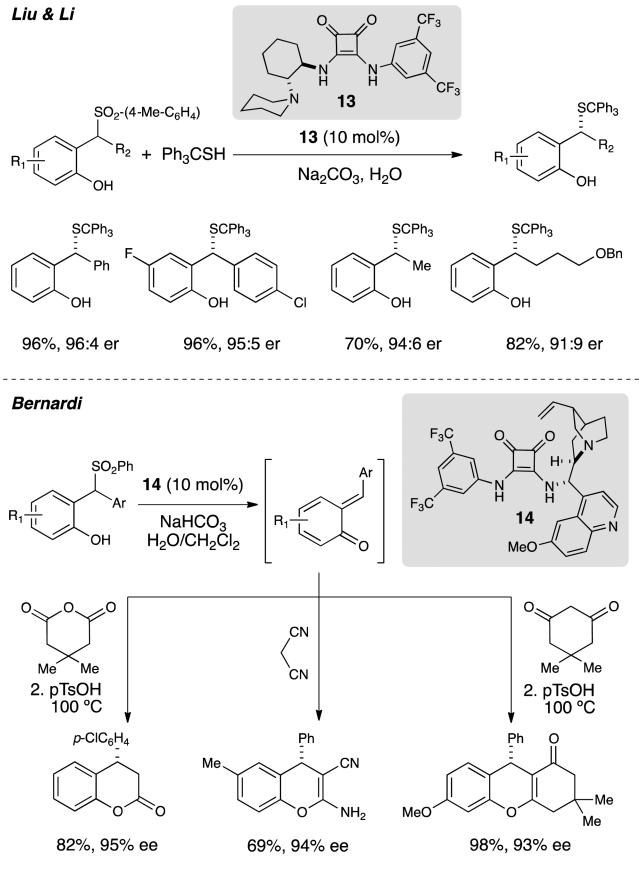
Figure 3. Dual CPA and rhodium catalysis to give chroman derivatives.

3). Control experiments established an essential role of water in the transformation, supporting the postulated origins of stereocontrol in this unique dual Brønsted acid and transition-metal catalytic process, leading to highly enantiopure substitued chroman derivatives.

3. BASE-MEDIATED GENERATION OF OQMS

Bifunctional Brønsted base catalysts based on the squaramide scaffold such as **13** and **14** (Scheme 5) have been shown to promote certain enantioselective reactions via oQMs. Under basic conditions, appropriately substituted benzylsulfones can undergo elimination to form transient oQMs.[26] Subsequent enantioselective addition of a nucleophile to the oQM is then controlled by the dual activating nature of the bifunctonal catalyst, which activates the oQM by hydrogen bonding and also serves to deprotonate the nucleophile through its appended base. In 2015, Liu and Li's laboratory reported a successful asymmetric synthesis of triphenylmethyl sulfides by treating benzylsulfone substrates with triphenylmethanethiol, catalytic bifunctional base **13**, and a stoichiometric inorganic base under biphasic conditions (Scheme 5, top).[27] The benzylsulfone starting materials tolerated can be either 2-aryl- or 2-alkylbenzyl sulfones, with both classes of substrates leading to highly enantiopure products. With the aid of several control experiments, the authors proposed that bifunctional catalyst **13** was likely deprotonating the substrates in the organic phase via a reaction at the amine portion of the catalyst (see the mechanism in Figure 4). Using stoichiometric chiral base and omitting sodium carbonate still resulted in a productive reaction, indicating that the role of the stoichiometric sodium carbonate was to regenerate the catalyst after oQM formation, sequestering the displaced sulfinate as its sodium salt in the aqueous phase.

Scheme 5. Brønsted Base Catalyzed Generation of oQMs Using Chiral Bifunctional Catalysis



Contemporaneous studies by the Bernardi group extended the catalytic asymmetric chemistry of benzylsulfone oQM precursors to engage with 1,3-dicarbonyl-derived enolates upon oQM formation.[28] Chiral bifunctional base catalyst **14** facilitated the enantioselective addition of a range of base-compatible substrates to the intermediate oQM, including Meldrum's acid, malonitrile, 1,3-diketones, and β-ketoesters (Scheme 5, bottom).

An alternative method for the generation of oQMs is to treat an *o*-siloxybenzyl halide with a fluoride source, as initially reported by Rokita.[29] Our group successfully merged a fluoride-mediated oQM generation protocol with a Lewis base facilitated activation of acyl anion precursors in 2007.[30] When silyl-protected thiazolium carbinols were employed as acyl anion precursors alongside *o*-siloxybenzyl halide oQM precursors, an intermolecular reaction between the two transiently generated reactive intermediates was observed (Scheme 6).

An initial attack by a triazole-bound acyl anion equivalent on a transient oQM, followed by a collapse of the addition adduct with expulsion of a thiazolium carbene, gives rise to α-aryl ketone products in good yields. Notably, the acylation proceeded without the need for bifunctional additives to facilitate a reaction between the nucleophile and the transient oQM. This preferential reactivity between oQM and acyl anion equivalent, despite of the presence of multiple other nucleophilic sources in the reaction flask (e.g., fluoride, thiazolium carbene) highlights the remarkable selectivity of N-heterocyclic carbene (NHC)−nucleophilic equivalents for polar π-electrophiles.

The Chain group applied an elegant dual Lewis base activation strategy to realize an alkylation of oQMs by enolates that are generated in situ from their corresponding silyl enol ethers in the presence of silylated oQM precursors in 2015.[31] The intermediates generated in situ reacted productively to give β-aryl carbonyl compounds in good yields and exhibited high diastereoselectivities when oQM precursors bearing a bulky substituent at the benzylic position (R_2, Scheme 7) were employed. Predictive computational methods were successful in aiding the assignment of the relative stereochemistry of

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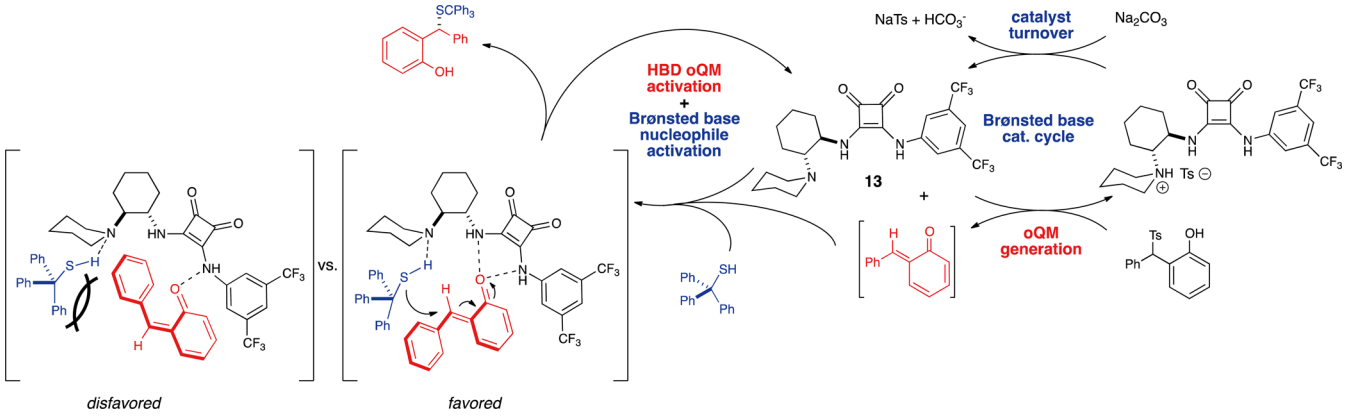
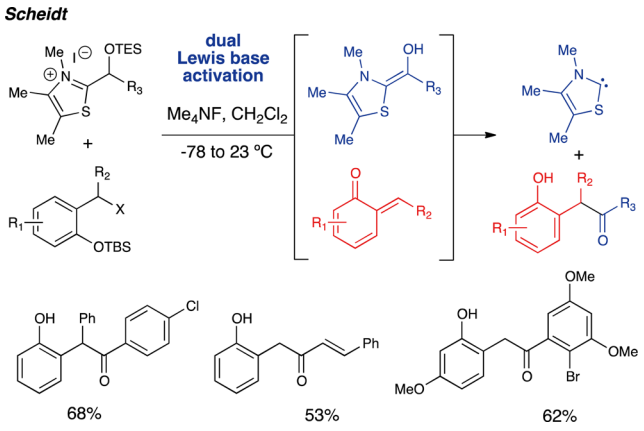
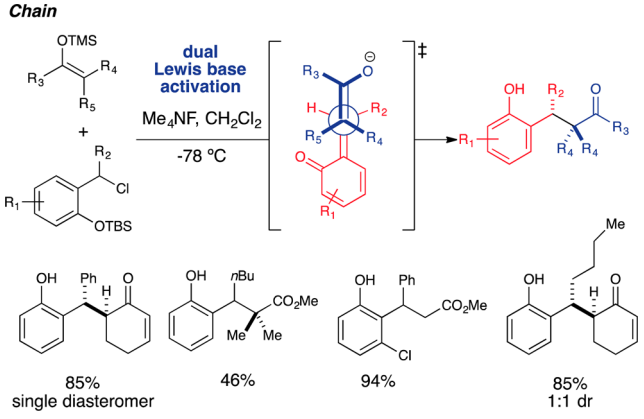


Figure 4. Transition-state model and catalytic cycle proposed by Liu and Li for chiral bifunctional Brønsted base-mediated reactions of oQMs. HBD = hydrogen bond donor.

Scheme 6. Fluoride-Mediated Additions of Acyl Anion Equivalents to oQMs



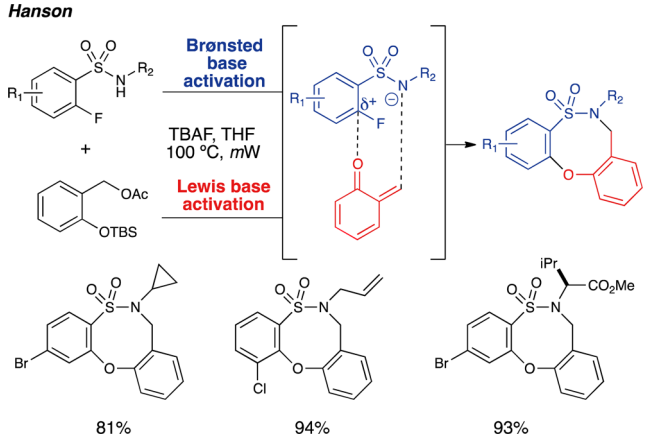
Scheme 7. Fluoride-Mediated Additions of Enolates to oQMs



diastereomeric products,[32] which were eventually unambiguously assigned by crystal structure analysis of the products. The diastereomeric outcome of the alkylation can be attributed to the dipole-minimized transition structure as depicted in Scheme 7. oQMs with a high preference for *Z*-geometry at the methide olefin (e.g., R_2 = Ph, bottom left) led to highly diastereomerically pure products, whereas a less sterically demanding substituent on the oQM precursor (e.g., R_2 = *n*-Bu, bottom right) is thought to form both *E* and *Z* oQM olefins, resulting in a 1:1 mixture of diastereomeric products.

A novel formal [4 + 4] annulation was reported by the Hanson group in 2010, wherein fluoride-mediated oQM generation was accomplished alongside Brønsted base mediated activation of 1,4-ambiphilic reaction partners derived from *o*-fluorobenzenesulfonamides (Scheme 8).[33] In their protocol,

Scheme 8. Fluoride-Mediated Generation of Ambiphilic Reacting Partners in the Presence of oQMs



fluoride deprotonates the sulfonamide of their ambiphilic precursor, which adds to a simultaneously generated oQM under microwave conditions. The resulting phenolate can displace the electrophilic aryl fluoride, forming new 8-membered sultam products that have never been reported in the literature before.

Homoenolate formal [4 + 3] annulations with oQMs have been reported to occur by treating oQMs with homoenolate equivalents generated from *α,β*-unsaturated aldehydes and N-heterocyclic carbene catalysts. The Ye group reported in 2013 that NHC−homoenolate equivalents could participate in a formal [4 + 3] annulation with preformed, stabilized oQMs.[34] Contemporaneous work by us uncovered the same novel annulation in their studies toward merging the reactivity of catalytically generated NHC−nucleophiles with orthogonally activated electrophiles in situ.[35] Chiral NHC−homoenolate equivalents could be generated in the presence of an *o*-siloxybenzyl halide, and upon treatment with fluoride the homoenolate was observed to selectively alkylate the transient oQM (Scheme 9). The resulting phenol is acylated intramolecularly, liberating free NHC catalyst and giving rise to

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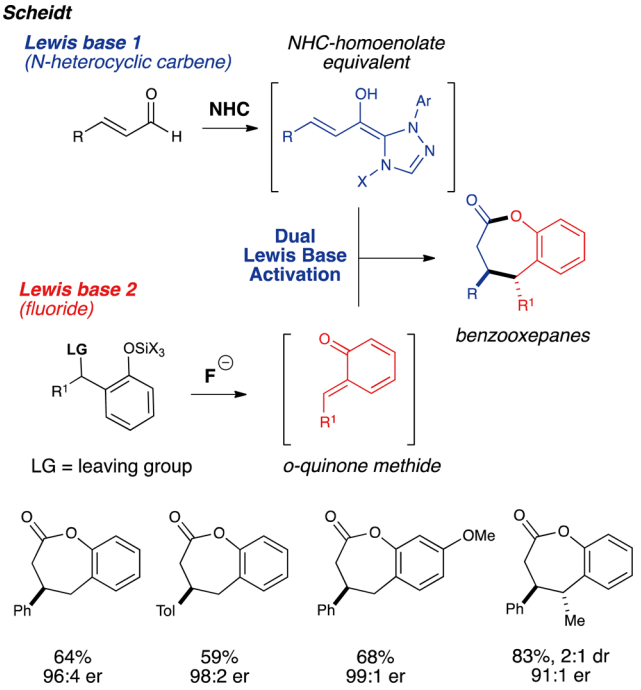
Scheme 9. Dual Lewis Base [4 + 3] Annulation of NHC–Homoenolates and oQMs

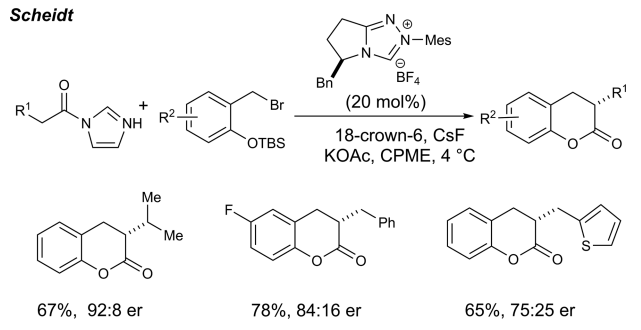


benzooxepane products with good yields and high enantiomeric excess. This report advanced the potential for dual reaction paradigms employing fluoride-generated oQMS, demonstrating that an oQM reactive partner can be generated catalytically, the oQM is compatible with multiple nucleophilic species in solution, and the scope of these processes are not limited to only other fluoride-activated substrate classes.

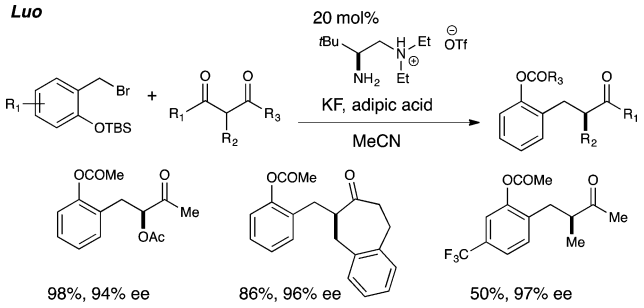
In the course of investigations on the aforementioned [4 + 3] annulation, it was observed that α,β-unsaturated aldehydes partners that tend to favor protonation of the homoenolate equivalent (Scheme 9, top) lead to formal [4 + 2] annulation products via an NHC–enolate intermediate. In an interesting development, this [4 + 2] pathway can be favored exclusively by using acylimidazole starting materials in order to generate the requisite NHC–enolate intermediates, leading to dihydrocoumarin products (Scheme 10).[36]

An exciting contribution from the Luo laboratory reported the successful merging of fluoride-generated oQMs with chiral iminium/enamine catalysis. The addition of chiral enamines to transiently generated oQMs based on the Rokita/Scheidt approach leads to retro-Claisen products as depicted in Scheme 11.[37]

Scheme 10. Addition of NHC–Enolate Equivalents to oQMs



Scheme 11. Luo's Merged oQM Generation with Chiral Amine Catalysis



1,3-Diketones participated in the reaction, and the selectivity of the amine catalysts for the least hindered carbonyl on the substrates gives rise to retro-Claisen products in which the more hindered carbonyl moiety is transferred to the phenolic oxygen (see Figure 5 for the proposed mechanism). oQM

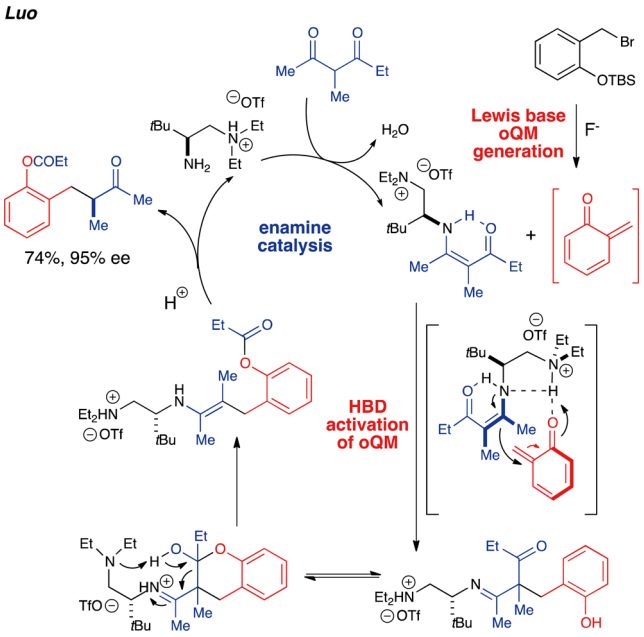


Figure 5. Luo's dual oQM reaction with catalytically generated enamines.

precursors bearing different varied alkyl and halogen substitution on the aromatic ring were all competent electrophiles for the chiral enamines employed in this transformation.

4. AZA-*ORTHO*-QUINONE METHIDES

While oQM generation under mild conditions and subsequent utilization in catalytic reactions has undergone significant development (vide supra), reports of in situ generation of related aza-*ortho*-quinone methides (aoQMs) as reactive intermediates under ambient conditions are much less common. There are examples of aoQMs being formed as a result of pyrolysis, photolysis, with nonremovable stabilizing groups or from even more reactive precursors, but the difficulty of its generation under mild conditions have limited aoQMs as general electrophiles in catalysis and synthesis.

aoQMs can be generated under basic conditions, although the conditions required to effect aoQM formation are usually more forcing due to the relative instability of the nitrogen

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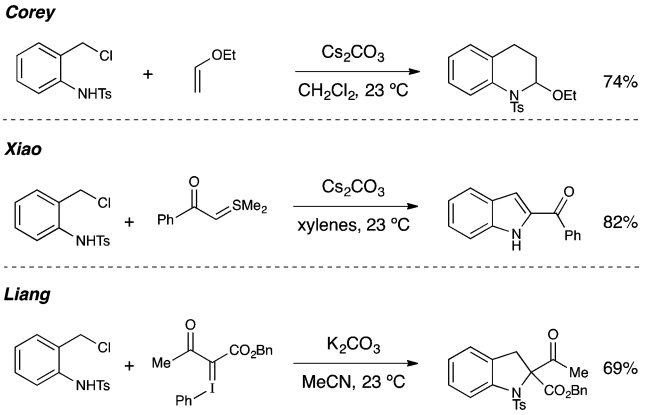
analogue of oQM. In 1995, two reports by Corey disclosed that *o*-aminobenzyl halides protected with electron-withdrawing groups were privileged precursors to aoQMs using relatively mild conditions (Scheme 12, top).[38,39] *o*-Aminobenzyl

Scheme 12. Mild Brønsted Base-Promoted Generation of aoQMs



chlorides bearing electron-withdrawing protecting groups enabled the generation of aoQMs, which underwent [4 + 2] annulations in the presence of a 2π component to give hydroquinoline products. These conditions have been extended to annulations with sulfur ylides to give indoles in a 2012 report from the Xiao group (Scheme 12, center),[40] as well as iodonium ylides to give spiroindolines as reported in 2013 by Liang (Scheme 12, bottom).[41]

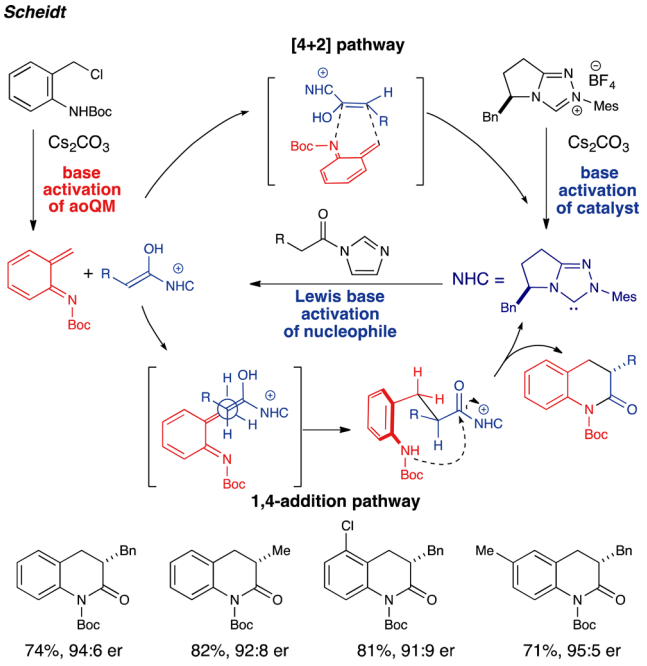
In 2014, we discovered that aoQMs generated in situ using the protocol originally described by Corey were compatible with NHC catalysis.[42] Brønsted base facilitated generation of aoQMs in the presence of NHC−enolate equivalents led to a formal [4 + 2] annulation, generating dihydroquinolones efficiently and with high enantioselectivity. The overall reaction could proceed by either 1,4-addition of the NHC−enolate to a transient aoQM, followed by amide bond formation and catalyst turnover (Scheme 13, bottom), or a more concerted [4 + 2] trajectory (Scheme 13, top).

An additional report from our group developed in parallel with the aforementioned aoQM/enolate reaction demonstrated that acyl anion equivalents were also competent nucleophiles for aoQMs generated under base-mediated activation conditions (Scheme 14).[43] Acyl anion equivalents add to aoQMs to give benzyl ketone products, which can be further converted to indoles in a single flask procedure. The overall transformation provides a metal-free approach to 2-aryl indoles which is complementary to established transition-metal-catalyzed strategies.

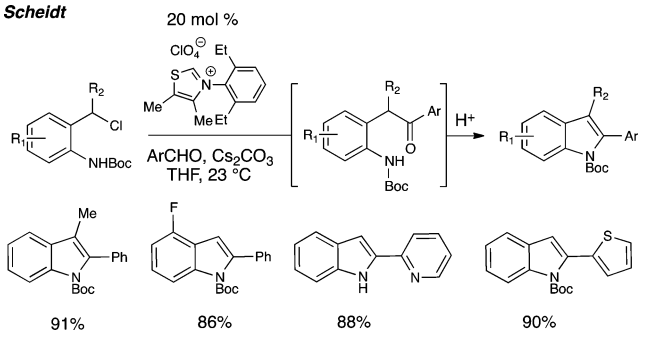
Analogous to oQM generation by chiral Brønsted acids, the Rueping group reported in 2015 that chiral phosphoramidate catalysts **15** and **16** facilitated the generation of aoQMs from ortho-amino benzhydryl alochols.[44] The intermediate aoQMs could be alkylated by substituted indole nucleophiles to synthesize triarylmethane derivatives in high yields and enantioselectivities (Scheme 15). They found the reaction to be substrate controlled, with 2-substituted indole substrates yielding 3-arylated indole products, while 3-substituted indoles conversely yielded 2-arylated indole products.

The use of *ortho*-quinone methides and related nitrogen analogues in organocatalytic reactions recently has greatly

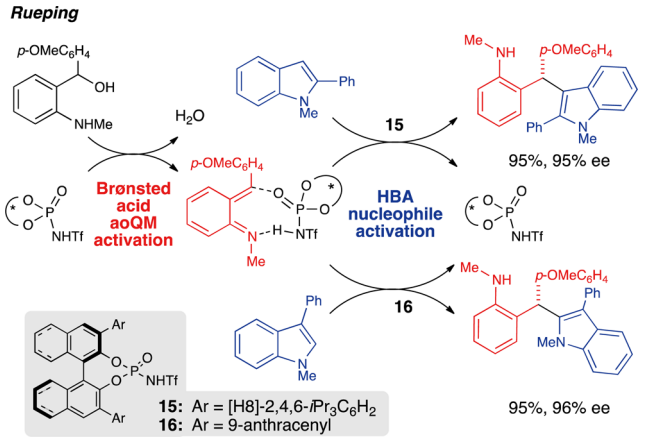
Scheme 13. Annulation of NHC−Enolate Equivalents with aoQMs



Scheme 14. NHC-Mediated Additions of Acyl Anions to aoQMS



Scheme 15. Chiral *N*-Triflyl Phosphoramidate Mediated Generation of aoQMs



expanded access to privileged molecules in unique and selective means. The various activation tactics employed to generate these seemingly unstable intermediates (such as base, acid, and

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fluoride) have provided creative new processes when appropriately combined with different modes of catalysis, including chiral Brønsted acids, Lewis bases, and hydrogen bond donors. A surprising aspect of these reports is that oQMs and related aoQMs can be engendered while in the presence of many different nucleophilic species with productive bond-forming results. Additionally, the challenges of oQM dimerization and nonproductive pathways based on previous conventional wisdom have been surmounted. With this growing assembly of successful new reactions, it is anticipated that additional new tactics to produce and control *ortho*-quinone methides in catalytic processes will continue as will new transformations that tame this reactivity and leverage their inherent utility.

AUTHOR INFORMATION

Corresponding Author

*E-mail: scheidt@northwestern.edu.

Notes

The authors declare no competing financial interest.

Biographies

Ashley Jaworski is a Visiting Scholar in the Scheidt group at Northwestern University. Her research is focused on mechanistic and theoretical studies of high energy reactive intermediates for use in organocatalytic reaction development.

Karl Scheidt is Professor of Chemistry and the director of Northwestern University's Center for Molecular Innovation and Drug Discovery. His research focuses on the development of new organic methods, particularly the discovery of new catalytic reactions, and their application to the synthesis of bioactive molecules with translational potential.

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