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Michael Additions of Highly Basic Enolates to *ortho*-Quinone Methides

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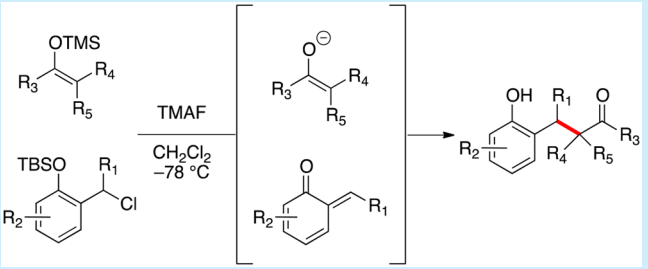
Supporting Information

ABSTRACT: A protocol by which ketone or ester enolates and *ortho*-quinone methides (*o*-QMs) are generated in situ in a single reaction flask from silylated precursors under the action of anhydrous fluoride is reported. The reaction partners are joined to give a variety of *β*-(2-hydroxyphenyl)-carbonyl compounds in 32−94% yield in a single laboratory operation. The intermediacy of *o*-QMs is supported by control experiments utilizing enolate precursors and conventional alkyl halides as competitive alkylating agents and the isolation of 1,5-dicarbonyl products resulting from conjugate additions that *do not* restore the aromatic system.



ortho-Quinone methides (*o*-QMs, **4**), or *o*-methylene cyclohexadienones, are highly reactive species that participate in a variety of organic reactions.[1] The *o*-QM has been known in chemical literature for over a century,[2] yet their great synthetic utility has not been fully harnessed; their high reactivity is often a liability that necessitates the generation and consumption of *o*-QMs in situ. The scope of enolates that are commonly joined with *o*-QMs has heretofore been limited owing to the tendency of the reagents employed or the byproducts produced in the course of generating enolates to unproductively engage the *o*-QM. For example, common alkoxide and amide bases and their conjugate acids are competent nucleophiles that readily attack *o*-QMs in a variety of contexts. Such behavior is the basis for the biological activity of a host of natural products.[3] Thus, there are few examples of the controlled addition of highly basic enolates to *o*-QMs, and to date, reactions have typically employed reversible formation of *o*-QMs,[4] malonic esters,[5,6b] and/or highly Lewis acidic conditions[6] or bench-stable electron-rich *o*-QM equivalents[7] (Scheme 1a, eqs 1−3). Asymmetric methods have also been described in these contexts,[7,8] but the utility of these important structural motifs is still limited.

We report herein a protocol by which ketone or ester enolates (**3**) and *o*-QMs (**4**) are generated in situ in a single reaction flask and joined to give a variety of *β*-(2-hydroxyphenyl)-carbonyl compounds (**5**) in one laboratory operation (Scheme 1b). Our work greatly expands the scope of conveniently available functionalized phenols, important building blocks, and structure types in the context of natural product synthesis.[9]

We were inspired by several reports from Rokita and co-workers wherein *O*-silylated phenolic benzyl halides and acetates can produce *ortho*-quinone methides upon treatment with anhydrous fluoride (Scheme 2).[10] This strategy has been elegantly exploited by Scheidt and co-workers in several studies exploring the union of *N*-heterocyclic carbene- and thiazolium-bound carbonyl anion equivalents and *o*-QMs under the action of anhydrous fluoride sources such as tetramethylammonium fluoride (TMAF) and cesium fluoride in the presence of crown ethers.[11] The same group has described chemistry utilizing a nitrogen equivalent that gives a putative aza-*ortho*-xylylene reaction partner.[12] Varvounis and co-workers showed that an *o*-QM could be released from a silylated nitrate ester under the action of fluoride and joined with nucleophiles including an exogenously generated malonic ester enolate.[5] We therefore reasoned that a highly basic enolate and an *o*-QM could be generated in a similar manner; treatment of a mixture of a silyl enol ether or silyl ketene acetal (**1**) and an *O*-silylated phenoxy benzyl halide (**2**) with anhydrous fluoride was expected to result in the generation and coupling of both the nucleophilic and electrophilic reaction partners in a single flask (Scheme 1b).[13] Moreover, we expected the highly reactive nature of the *o*-QMs to facilitate formation of congested carbon−carbon bonds that are difficult or impossible to realize using conventional enolate alkylation chemistry.

The preparation of substrates **2** from simple salicylaldehydes is straightforward (see Supporting Information). Protection of the phenol functions as the corresponding *tert*-butyldimethylsilyl ethers was achieved under standard conditions. Subsequent reduction of the aldehyde function with hydride or addition of an organolithium or Grignard reagent and conversion of the resultant alcohol to the corresponding chloride or bromide

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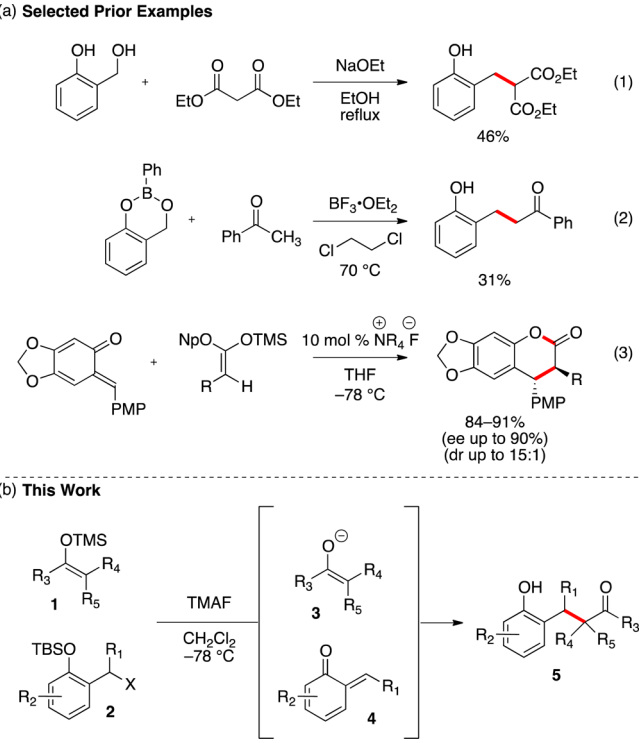
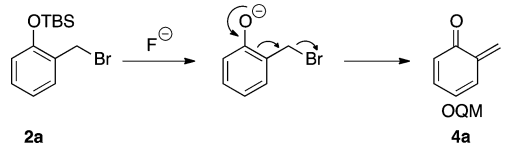
Scheme 1. (a) Selected Prior Examples of Reactions Involving *o*-QMs and Enolates; (b) Nucleophilic Alkylation of *o*-QMs by Discrete Enolates[a]



[a]TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl, TMAF = tetramethylammonium fluoride, Np = 2-naphthyl, PMP = *para*-methoxyphenyl, NR_4F = cinchona alkaloid salt.

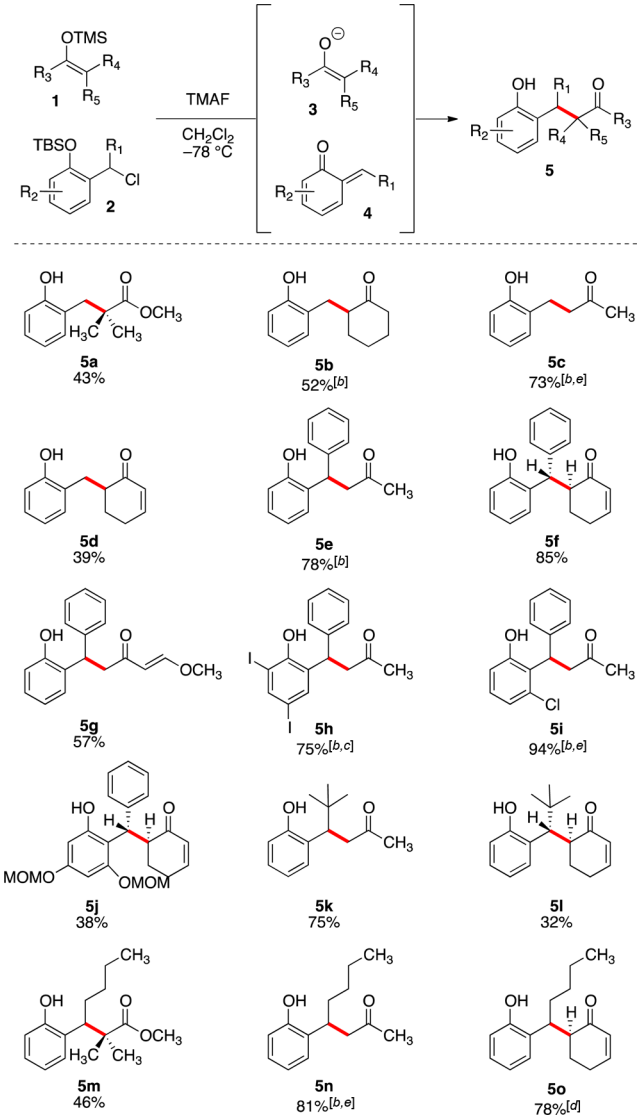
Scheme 2. Conversion of *O*-Silylated Phenolic Benzyl Halides to *ortho*-Quinone Methides as Described by Rokita and Co-workers



leaving group gave a variety of substrates **2** in good yields with little difficulty.

We screened a number of conditions under which we might join *o*-QM and enolate precursors, examining several fluoride sources and ultimately we found temperature and fluoride solubility to be critical. Reaction conditions employing TMAF in dichloromethane routinely delivered the desired adducts **5**, but often accompanied by several decomposition products that complicated rigorous purification. Our results and observations suggested that the release of the enolates **3** from the silyl precursors **1** was rapid at low temperature while the release of the *o*-QMs **4** from the precursors **2** was slower, particularly for large substituents at the R_1 position (e.g., *tert*-butyl or phenyl), but capture of the *o*-QM was rapid. Release of *o*-QMs can be accelerated by warming, but at the cost of decomposition. We addressed this issue by maintaining the temperature after the addition of fluoride; using our optimized procedures (addition of solutions of TMAF in dichloromethane to premixed solutions of components **1** and **2** in dichloromethane at −78 °C, incubation at that temperature for 1 h, followed by treatment with acetic acid prior to warming), we are able to routinely isolate the desired products **5** cleanly in 32−94% yield (Scheme 3).

Scheme 3. Michael Additions of Enolates to *o*-QMs[a]



[a]Yields of isolated products; reactions were performed on a 1.0 mmol scale (TMAF). [b]Product was isolated as a mixture of cyclic hemiacetal diastereomers. [c]Yield based on recovered starting material. [d]Product was isolated as a mixture of diastereomers (1.1:1 mixture with respect to the benzylic stereogenic center). [e]Product characterized as the corresponding methyl ether.

O-Silylated phenoxy benzyl bromides and chlorides are both effective *o*-QM precursors; however, the chlorides are more bench-stable and undergo the *o*-QM-enolate union much more cleanly. Our reaction conditions are amenable to the use of silyl enol ethers, silyl ketene acetals, and silyloxydienes, though some care must be taken when the corresponding enolates are not thermally stable (i.e., ketene acetals).

The characterization of products **5f**, **5j**, **5l**, and **5o** required special attention due to the formation of multiple stereogenic centers during the course of the *o*-QM-enolate reaction. Traditional NMR-based methods for the assignment of relative stereochemistry proved inadequate in this context; for example,

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methods based on derivatization, evaluation of coupling constants, or NOE analysis provided little insight. However, computational analysis methods proved quite useful in this context. Utilizing the methods described by Tantillo and co-workers,[14] we were able to assign the relative stereochemistry of **5f**, **5j**, **5l**, and **5o** with no ambiguity (see Supporting Information). These computational methods have been powerfully enabling in the stereochemical assignment of natural products,[14a,15] and moreover, we were able to perform these calculations with freely available open-source programs (see Supporting Information). As a testament to the maturity and power of these methods, we were able to later confirm our assignments by single crystal X-ray diffraction of **5f** and one diastereomer of **5o** (Figure 1). We found that these products

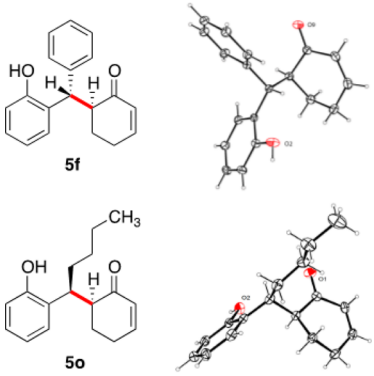


Figure 1. X-ray crystallographic structures for *o*-QM-enolate products.

form a homologous series and that the reaction is highly diastereoselective, with the exception of product **5o** (formed as a 1:1 mixture of diastereomers with respect to the benzylic stereogenic center). The diastereochemical outcome of these reactions is consistent with an open transition state model in which the dipoles associated with the C−O bonds oppose one another and there is no ion bridging between the reaction components (Figure 2).[16] The proposed model is also

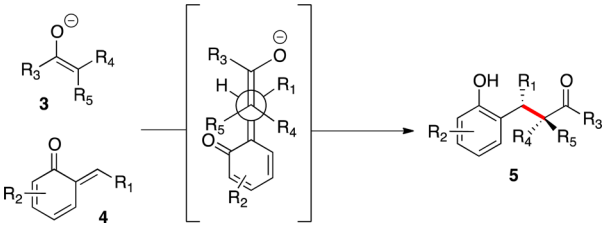


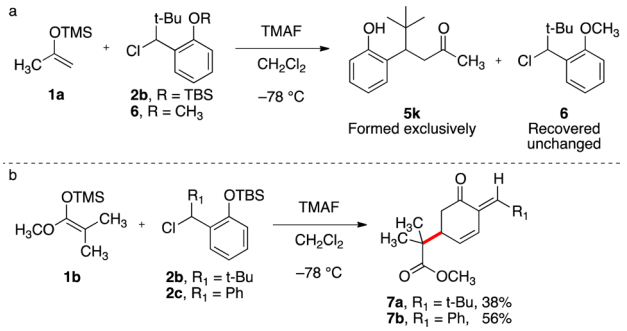
Figure 2. An open transition state model for the union of (*E*)-*o*-QMs and enolates with no ion bridging between reaction partners.

consistent with *tert*-butyl- and phenyl-bearing *o*-QM intermediates forming with (*E*)-olefin geometry (R_1 = *t*-Bu or Ph); we presume the diastereochemical outcome in product **5o** is a consequence of poor olefin geometry control when the *o*-QM contains a less sterically demanding group (R_1 = *n*-butyl).

Although we have not directly observed any *o*-QM intermediates thus far in our studies, we have gathered evidence that these reactions do indeed proceed via *o*-QMs and not via simple substitutive alkylation chemistry. The exceptional reactivity of the *o*-QM allows for the construction of highly congested carbon−carbon bonds that would normally not be possible via conventional enolate alkylation chemistry; for example, 2-(trimethylsilyloxy)-propene **1a** and 2-(trimethylsilyloxy)-cyclohexa-1,3-diene **1b** both join smoothly with the *tert*-butyl-substituted *o*-QM precursor **2b** under the action of fluoride to give the alkylated product (**5k**, **5l**); however, we were unable to productively engage **2b** with conventionally generated metal enolates derived from acetone or 2-cyclohexen-1-one.

As further evidence of the participation of *o*-QM intermediates in these reactions, we conducted control experiments in which mixtures otherwise identical to those described in Scheme 3 were doped with conventional alkyl chlorides prior to the addition of TMAF and observed that the *o*-QM precursors were consumed preferentially (Scheme 4a).

Scheme 4. Evidence for the Intermediacy of *o*-QMs: (a) Control Experiment with Conventional Alkyl Halide; (b) Unexpected Michael Addition Regiochemistry



For example, a mixture of 2-(trimethylsilyloxy)-propene **1a**, *o*-QM precursor **2b**, and 1-(1-chloro-2,2-dimethylpropyl)-2-methoxybenzene (**6**)[17] was treated with TMAF in dichloromethane as described in Scheme 3, and analysis of the crude reaction mixture by ^{1}H NMR showed two products: the ketophenol **5k** and 1-(1-chloro-2,2-dimethylpropyl)-2-methoxybenzene (**6**) unchanged.

Moreover, we were surprised to observe distinctly different products in some reactions that would not be possible without the intermediacy of the *o*-QM—those which result when both coupling partners are especially sterically hindered (e.g., electrophiles **2b** and **2c**, and methyl trimethylsilyl dimethylketene acetal **1b**). For example, we have found that when reaction mixtures containing **2b** and **2c** are treated with TMAF, the dominant product is *not* a *β*-(2-hydroxyphenyl)-carbonyl, but 1,5-dicarbonyls (**7a**, **7b**) instead. The 1,5-dicarbonyl products **7a** and **7b** were routinely isolated as the (*E*)-olefin geometrical isomer, which is consistent with the observed stereochemical outcome of the reactions described in Scheme 3.[18] Such products would only be possible if the enolate were to add to an *o*-QM via the latent aromatic ring rather than via the exocyclic enone function. These products were unexpected and unusual in that the alkylation event *does not* restore the aromatic system in its wake. These versatile and complex 1,5-dicarbonyl-containing products have become the subject of ongoing research in our laboratories and are the focus of upcoming communications, though they are prone to unproductive oligimerization reactions.

We have developed a protocol by which ketone or ester enolates and *o*-QMs are generated in situ in a single reaction flask from silylated precursors under the action of anhydrous fluoride. The reaction partners are joined to give a variety of *β*-(2-hydroxyphenyl)-carbonyl compounds that are not conven-

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iently available by conventional carbonyl-based akylation chemistry. Future efforts in our laboratories are directed toward expanding the utility of these reactions and toward the synthesis of natural products made possible by the *o*-QM-enolate coupling reactions.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and ^{1}H and ^{13}C spectra for all new compounds. Computational data and stereochemical analysis data for compounds **5f**, **5j**, **5l**, and **5o**. Crystallographic data for compounds **5f** and **5o**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) See Supporting Information for details.

(18) The enone geometrical configuration in **7a** and **7b** was established by ^{1}H NMR and NOE analysis. See Supporting Information for details.

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