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Applications of *ortho*-Quinone Methide Intermediates in Catalysis and Asymmetric Synthesis

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Abstract

Ortho -quinone methides are important synthetic intermediates and widely implicated in biological processes. In this Synopsis, recent advances concerning the synthesis and utility of these intermediates are discussed with a particular emphasis on metal-catalyzed formation of quinone methide intermediates. Additionally, applications of these intermediates as partners in asymmetric synthesis will be discussed including methods we have developed that involve the enantioselective Pd-catalyzed formation of *ortho*-quinone methides, and the trapping of aforementioned intermediates with diverse nucleophiles.

Quinone methides are versatile intermediates of wide utility in organic synthesis,[1–2] materials chemistry,[3] and biology.[3–7] The parent *ortho*-quinone methide, **1**, is composed of a cyclohexadiene core in conjugation with a carbonyl group and a methylene unit, attached to each other (Figure 1).[1–3,8–10] It is related to *ortho*-quinone, **2**, which has two carbonyl groups, and to *ortho*-quinone dimethide, **3**, which has two methylene units. Unlike intermediates **2** and **3**, which have two identical groups, *ortho*-quinone methides are highly polarized and, therefore, quite reactive.[11–12] This reactivity can be rationalized by considering the resonance hybridization of the two principal canonical forms: **4** is aromatic and exhibits charge separation while **1** is non-aromatic (Figure 1). From these forms, the predominant reactivity mode of *ortho*-quinone methide intermediates is understood, wherein nucleophiles react at the exocyclic carbon, and electrophiles at oxygen.

Ortho-quinone methide intermediates undergo 1,4-conjugate addition reactions with nucleophiles and [4+2] cycloaddition reactions with various dienophiles (Figure 2). Additionally, the biological activity of vitamins E and K and the anti-proliferative effects of drugs such as the anthracycline antibiotics are purportedly due to the reaction of *ortho*-quinone methide metabolites (Figure 3).[13–15] Because of their extensive utility, numerous methods have been established for their synthesis under thermal, photochemical, acidic, basic, and neutral conditions.[10,16] In this Synopsis, recent developments relating to the facile generation of *ortho*-quinone methide intermediates especially focusing on transition metal catalysis and their subsequent reaction with diverse nucleophiles will be discussed. Additionally, an emphasis on methods that generate products in enantiomerically enriched form from achiral quinone methide precursors will be presented. Since Van De Water and Pettus published an excellent review on the chemistry of *ortho*-quinone methides in 2002, we will largely focus on reports from the last decade.[10]

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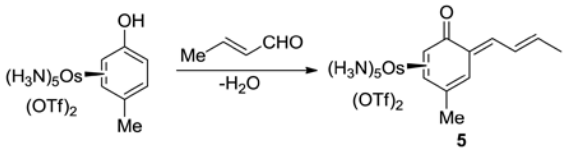
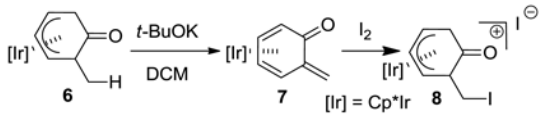
Os- and Ir-mediated ortho-quinone methide generation

In 1994, Hermann and coworkers reported the first metal complex of an *ortho*-quinone methide.[17] The Os-complex was generated via reaction of an Os-complex of *p*-cresol with an excess of crotonaldehyde (eq. 1). The complex **5** was characterized by NMR spectroscopy.



(1)

Later, in 1998, Amouri and coworkers reported the first example of an Ir-complex of the parent *ortho*-quinone methide.[1,18] Previously, the parent *ortho*-quinone methide was only observed via NMR spectroscopy at −100 °C.[19–22] The treatment of the oxo-η^5-dienyl iridium complex **6** with *t*-BuOK/CH_2Cl_2 at room temperature afforded a yellow microcrystalline η^4-*o*-quinone methide complex **7** (eq. 2). The structure was assigned by X-ray crystallography and provided the first direct evidence of the existence and structure of an *ortho*-quinone methide. Interestingly, *ortho*-quinone methide complex **7** showed umpulong reactivity, i.e. *ortho*-quinone methide complex **7** has nucleophilic character and reacts with electrophiles. For example, when complex **7** was treated with I_2, it afforded complex **8** as the major product.



(2)

Pd-Catalyzed ortho-quinone methide generation and reactivity

In 1971, Chapman and coworkers were the first to report the proposed formation of *ortho*-quinone methides from vinyl phenols using stoichiometric $Pd(OAc)_2$ (Figure 4).[23] They used this method for the oxidative coupling of vinyl phenol to form the natural product carpanone via the dimerization of the in-situ generated *ortho*-quinone methide. This method to generate quinone methide intermediates remained unexploited until 2006, when Sigman and coworkers reported the Pd-catalyzed difunctionalization reaction of vinyl phenols (Figure 5).[24] They observed the addition of two alcohol nucleophiles across the double bond, when vinyl phenol **9** was treated with MeOH and $Pd(MeCN)_2Cl_2$ as the catalyst. The scope of this reaction was limited to use of simple alcohols, furthermore the alcohol nucleophiles were used as the solvent. This reaction is proposed to proceed via a mechanism involving an *ortho*-quinone methide intermediate, similar to the proposal of Chapman, where the coordination of the alkene with Pd followed by an intermolecular nucleopalladation resulted in Pd-alkyl intermediate **A** (Scheme 1). The Pd-alkyl **A** is proposed to decompose to an *ortho*-quinone methide with concomitant reduction of Pd. The resultant proposed *ortho*-quinone methide intermediate **B** reacts with a second equivalent of the nucleophilic solvent to yield the observed product.

The proposed mechanism was supported by a variety of experiments. First, reaction of protected phenol substrate **10** did not yield the alkene difunctionalization product instead a mixture of regioisomeric Wacker products were obtained via hydrolysis of putative acetals upon workup, supporting the essential role of the phenol (Figure 6). Second, a deuterium labeling study was performed in which substrate **9** was submitted to the dialkoxylation reaction in CD_3OD. No deuterium incorporation into the alkyl chain of the product was observed. Finally, exposure of the deuterium labeled substrate **11** to the reaction conditions resulted in no deuterium transfer within the product (Figure 6). These experiments suggest that no β-hydride elimination of substrate or nucleophile is occurring during the reaction. It should be noted that Le Bras, Muzart, and coworkers reported a similar Pd-catalyzed dioxygenation reaction of an *ortho*-vinyl phenol in 2005 where they suggest a Pd-catalyzed alkene epoxidation with hydrogen peroxide followed by epoxide opening with an exogenous oxygen nucleophile as the essential mechanistic steps.[25–26]

Interestingly, when EtOH rather than MeOH was used as the solvent and (–)-sparteine was used as the ligand, the authors observed the alkene hydroalkoxylation product **12** as the major product (Figure 7).[27] Under optimized conditions, various alcohols can be used as both the nucleophile and a hydride source as supported by isotopic labeling experiments (vide infra). The major limitation of this reaction is its sourcing of the nucleophilic alcohol from solvent, which discourages the use of precious alcohols, or alcohols in the solid state. To overcome this issue, the authors expanded the scope of this transformation to include *sec*-phenyl ethyl alcohol as a sacrificial alcohol, which allowed for the use of other solvents and more precious alcohols as nucleophiles (Figure 8).[28]

A Pd-catalyzed alcohol oxidation is proposed to be the source of Pd-hydride **A**, which reacts with alkene to give Pd-alkyl intermediate **B** (Scheme 2). Pd-alkyl **B** undergoes electron transfer to give an *ortho*-quinone methide intermediate and Pd(0), which reacts with an equivalent of the solvent to give the alkene hydroalkoxylation product. The proposed mechanism was supported by the following observations: 1) the use of $PhCD(OH)CH_3$ as the sacrificial alcohol results in two isotopomers **13** and **14** in a 2.5:1 ratio, consistent with proton incorporation into the product from the oxidation of *sec*-phenethyl alcohol (Figure 9); 2) the reaction of **15** with ethyl vinyl ether gave chromane **16** in 19% yield, which provides strong evidence for the intermediacy of an *ortho*-quinone methide under these reaction conditions (Figure 9).

In 2011, Sigman and Pathak reported the hydrofunctionalization of vinyl phenols with heteroaromatics using an alkyl chloride as the sacrificial hydride source.[29] The scope of this transformation is found to be broad in both reaction partners (Figure 10). Here, oxidative addition of the alkyl chloride to Pd^0 results in Pd-alkyl intermediate **A**. β-Hydride elimination from intermediate **A** leads to formation of a Pd-hydride **B**, which reacts with vinyl phenol to give intermediate **C**. Intermediate **C** decomposes to an *ortho*-quinone methide intermediate, which reacts with an exogenous nucleophile to give the desired product (Scheme 3). The proposed mechanism was supported by isotopic labeling experiments.

Asymmetric reactions of ortho-quinone methide intermediates

Pettus and coworkers were the first to demonstrate substrate-controlled asymmetric reactions of *ortho*-quinone methide intermediates.[30] Using their reported three component coupling protocol[31–33] with chiral (non-racemic) enol ethers, the desired chromanes were produced in excellent diastereoselectivity (Figure 11). The major limitations of this method are 1) the limited availability of chiral enol ethers and 2) the use of chiral enol ethers as a source of chirality dictates that only chiral (non-racemic) chromanes can be easily obtained

using this method. In a similar vein, Freccero and coworkers reported reactions of binol derived *ortho*-quinone methide intermediates generated photochemically and subsequent highly diasteroselective addition of L-proline.[34]

In 2009, Lectka and coworkers reported a catalytic asymmetric cycloaddition of an *ortho*-quinone methide with a ketene enolate.[35] Chiral cinchona alkaloid-derived tetraalkylammonium fluoride **18** was used as a precatalyst to generate the ketene enolate in situ (Figure 12 and Scheme 4). The scope of this reaction was limited to the use of **17** as the *ortho*-quinone methide. The proposed mechanism, shown in Scheme 4, is initiated by fluoride ion-promoted desilylation of the ketene acetal **19**, forming the chiral ion-paired ketene enolate **A**. The resultant ketene enolate regioselectively alkylates the *ortho*-quinone methide to produce intermediate **B**. Subsequently, **B** undergoes lactonization to form the desired cycloadduct **20**, releasing 2-naphthoxide.

In 2007, Sigman and coworkers reported an enantioselective Pd-catalyzed reaction of in-situ generated *ortho*-quinone methides with a modest range of nucleophilic alcoholic solvents (Figure 13).[36] The use of (*S*)-*i*Pr-Quinox as a chiral ligand delivered the alkene dialkoxylation product in excellent enantioselectivity and good diastereoselectivity. The major limitations of this process were the addition of identical nucleophiles across the alkene and the use of the nucleophile as the solvent.

Sigman and coworkers were able to overcome some of these limitations by careful substrate design, wherein one of the nucleophiles was incorporated into the substrate (Figure 14).[37] Using this strategy, the authors reported the highly enantioselective sequential intra/intermolecular difunctionalization of substituted vinyl phenols. This method tolerates various simple alcohols as exogenous nucleophiles to give products in good yield with excellent enantioselectivity. However, excessive nucleophile loading (50 equiv) was required for satisfactory yields. Notably, water may be used as the exogenous nucleophile to yield the benzylic alcohol product in good yield and excellent enantioselectivity. Furthermore, NaN_3 was also found to be an effective nucleophile, demonstrating that an exogenous nitrogen-centered nucleophile is viable. Finally, enol ether **22** gave the corresponding chromane derivative in good yield with good diastereo- and enantioselectivity (Figure 15).

The proposed mechanism for the sequential difunctionalization reaction is shown in Scheme 5.[38] Coordination of Pd to the alkene and phenol provides intermediate **A**, which undergoes intramolecular nucleopalladation to give Pd-alkyl intermediate **B**. It is proposed that coordination of the phenol and rapid decomposition of **B** to the *ortho*-quinone methide intermediate **C** inhibits undesired β-hydride elimination to give the Wacker cyclization product. Intermediate **C** further reacts with another equivalent of nucleophile to provide the alkene difunctionalization product. Interestingly, kinetic analysis provided evidence for attack of the proposed quinone methide intermediate with the exogenous nucleophile being the turnover-limiting step.[38] Additionally, it also suggested that copper is involved in product formation and not just in catalyst turnover.[38]

Sigman and coworkers later expanded the scope of this process to include nucleophilic heterocycles, including indoles and pyrroles as exogenous nucleophiles (Figure 16).[39] This reaction exhibits broad substrate scope in both reaction partners and provides biologically-relevant bisarylmethines in good yields and with excellent diastereoselectivity and enantioselectivity. Interestingly, the authors observed anti-proliferative activity against breast cancer cell lines (MCF-7) for various newly-synthesized bisarylmethines.[39]

Conclusion

Since their initial discovery, the chemistry of *ortho*-quinone methide intermediates has significantly impacted synthesis. Major advances have been achieved in the characterization and synthesis of *ortho*-quinone methide intermediates under mild conditions. This has allowed for the rapid and efficient synthesis of phenol-containing natural products and chroman derivatives mainly through efforts of the Pettus group. More recent advances have concentrated on the use of these generally reactive intermediates as participants in asymmetric synthesis although only a modest number has been reported. Using oxidative Pd-catalysis, our group has made progress in this area but a more general manifold to access a broad range of scaffolds with high enantioselectivity remains desirable.

Acknowledgments

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Biography

Pathak recently completed his Ph.D. in Prof. Matt Sigman’s laboratory at university of Utah and is currently a postdoctoral researcher in Prof. Scott Miller’s laboratory at Yale University. Sigman joined the faculty of the University of Utah in 1999, where his research group has focused on the development and mechanistic studies of new synthetic methodology.

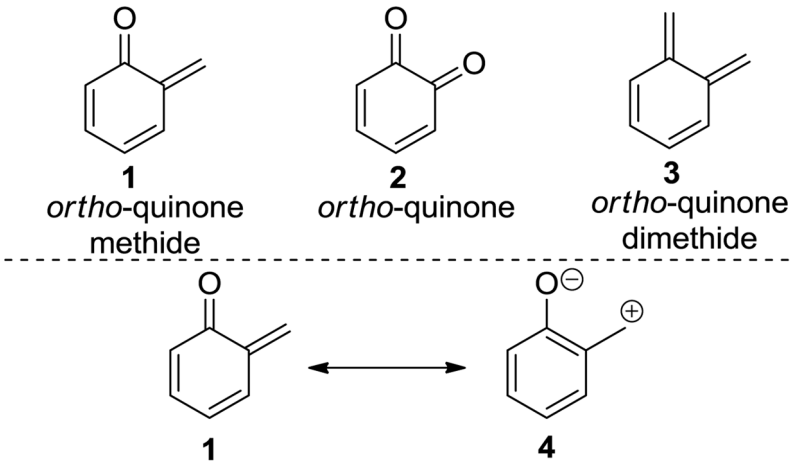


Figure 1.
Structural differences between *ortho*-quinone methide, *ortho*-quinone and *ortho*-quinone dimethide.

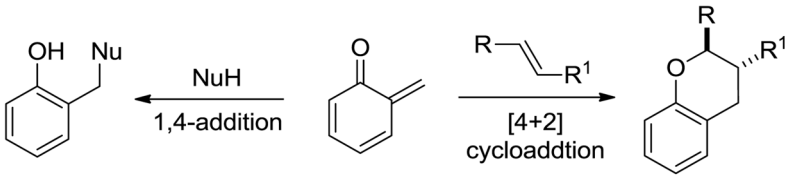


Figure 2.
General modes of reactivity of *ortho*-quinone methides.

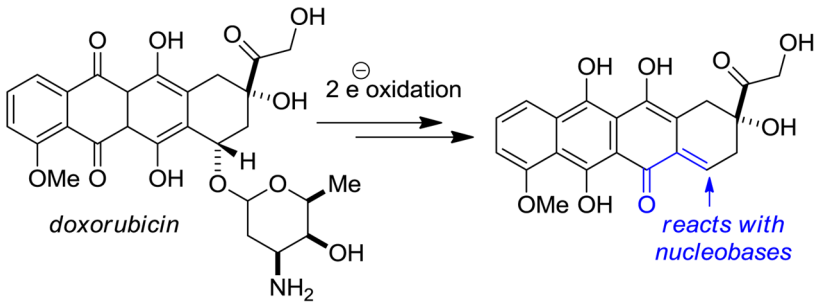


Figure 3.
Proposed mechanism of action of anthracyclin antibiotics.

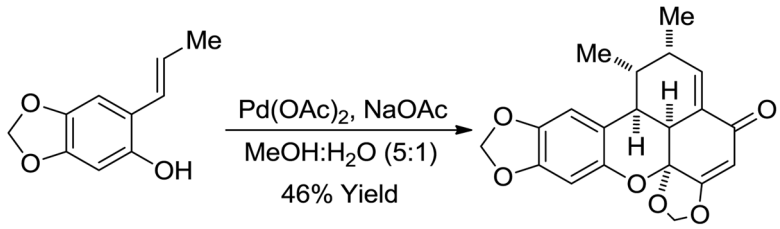


Figure 4.
Pd-catalyzed total synthesis of carpanone, Chapman and coworkers, 1974.

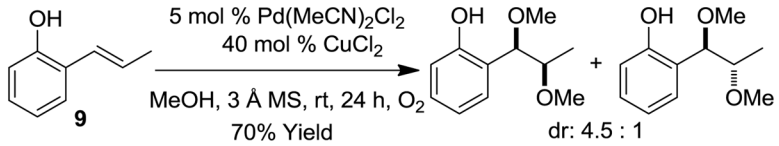


Figure 5.
Pd-catalyzed dialkoxylation of vinyl phenols, Sigman and coworkers, 2006.

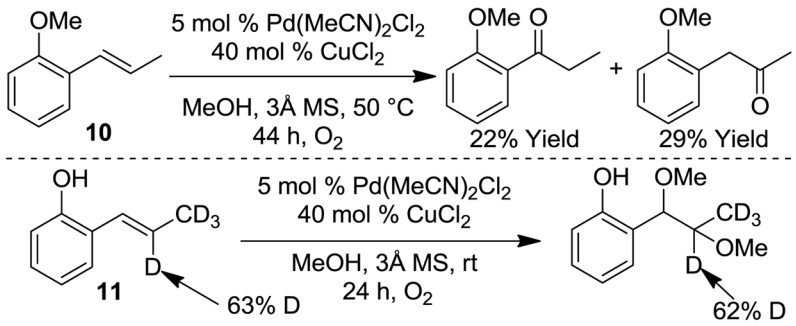


Figure 6.
Preliminary mechanistic experiments, Sigman and coworkers, 2006.

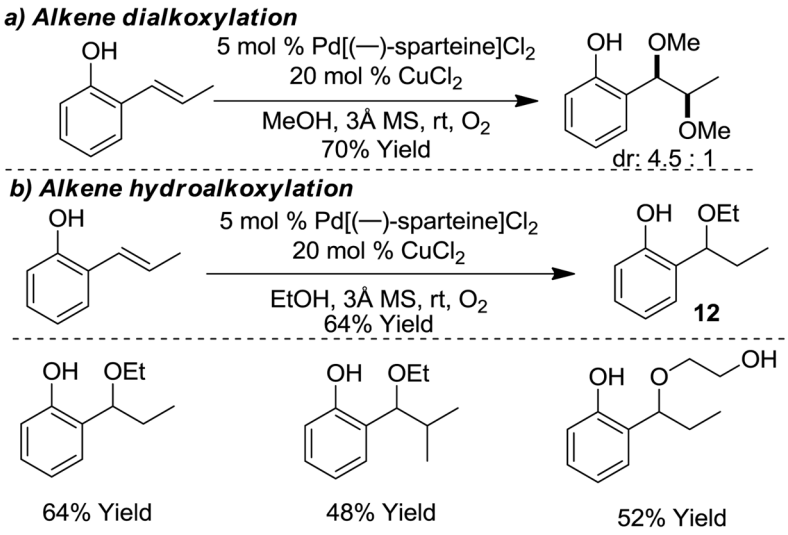


Figure 7.
Effect of solvent in the Pd-catalyzed alkene functionalization of vinyl phenols, Sigman and coworkers, 2006.

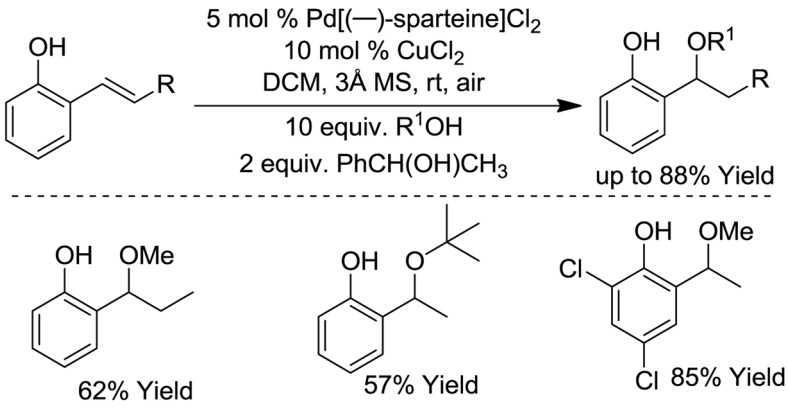


Figure 8.
Scope of Pd-catalyzed hydrofunctionalization of vinyl phenols using a sacrificial alcohol as the hydride source, Sigman and coworkers, 2007.

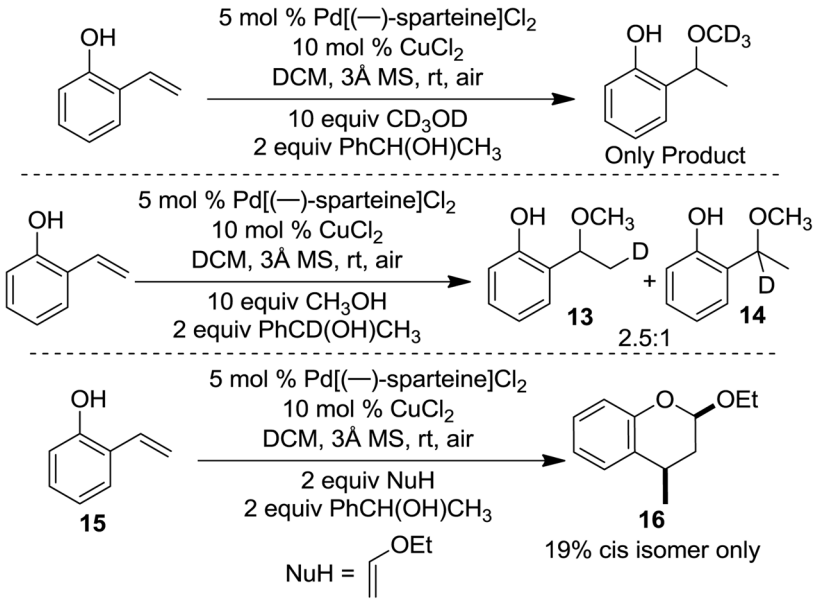


Figure 9.
Evidence to support the proposed mechanism, Sigman and coworkers, 2007.

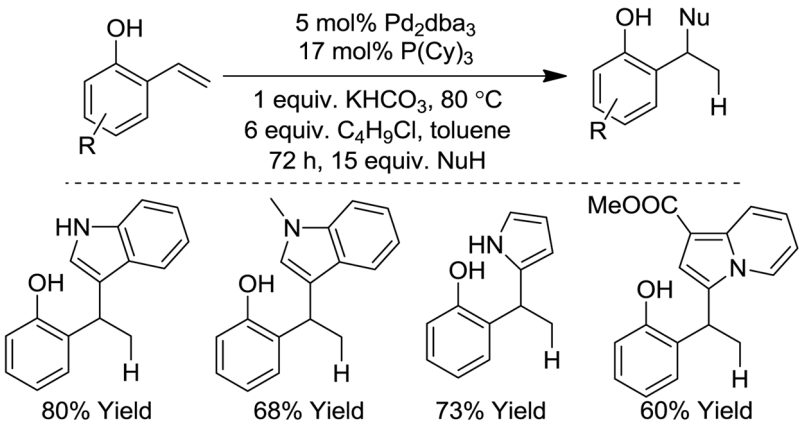


Figure 10.
Hydrofunctionalization of styrene using *n*-butyl chloride as a sacrificial hydride source, Sigman and coworkers, 2011.

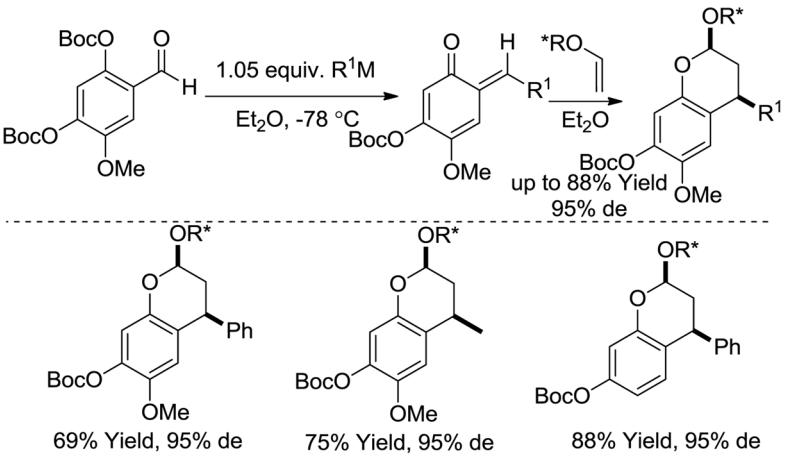


Figure 11.
Diastereoselective reaction of chiral enol ethers with *ortho*-quinone methides, Pettus and coworkers, 2004.

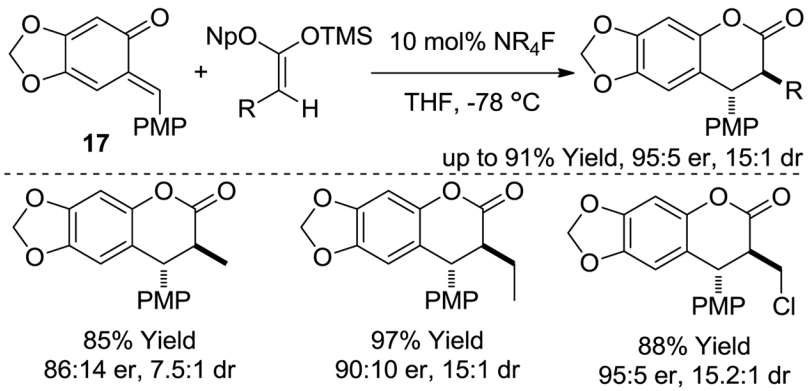


Figure 12.
Enantioselective reaction of *ortho*-quinone methides with ketene enolate using chiral ammonium fluoride pre-catalyst, Lectka and coworkers, 2009.

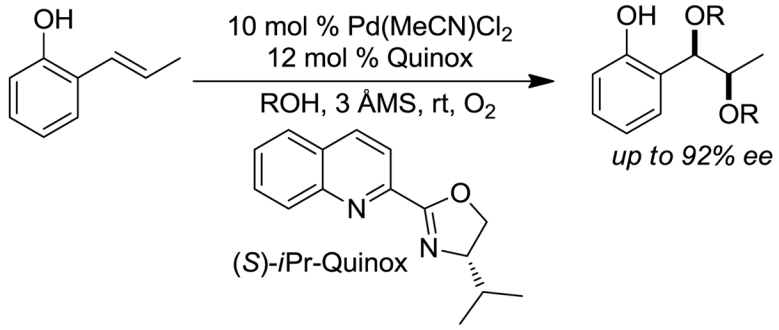


Figure 13.
Enantioselective Pd-catalyzed dialkoxylation of vinyl phenols, Sigman and coworkers, 2007.

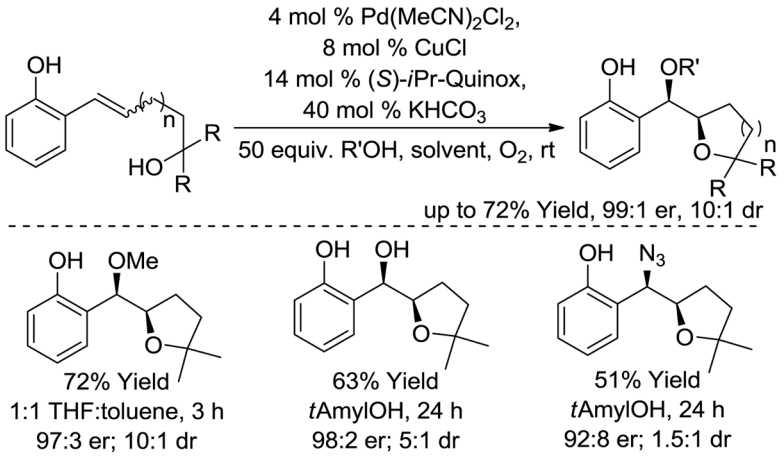


Figure 14.
Scope of enantioselective Pd-catalyzed alkene difunctionalization reactions of vinyl phenols, Sigman and coworkers, 2009

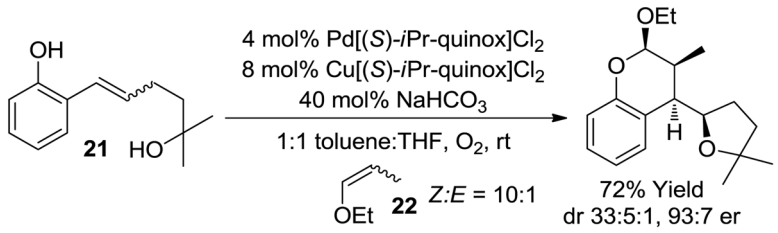


Figure 15.
Inverse electron demand Diels-Alder reaction with enol ether **22**, Sigman and coworkers, 2009.

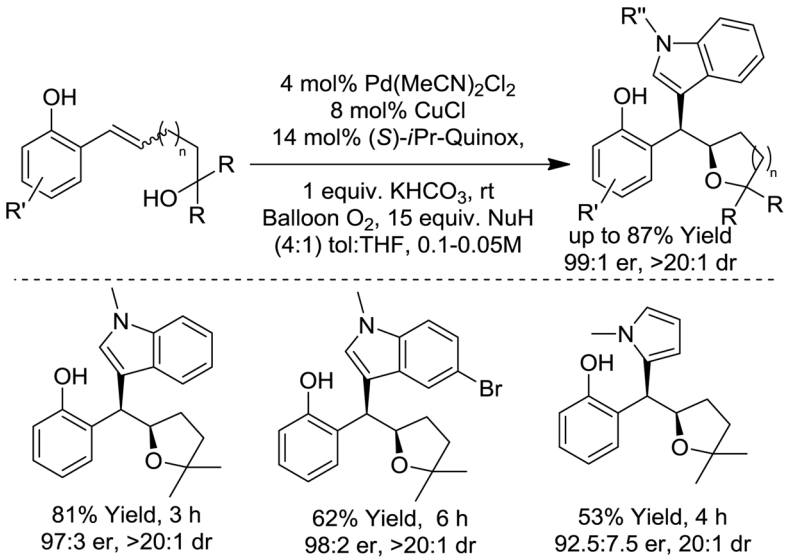
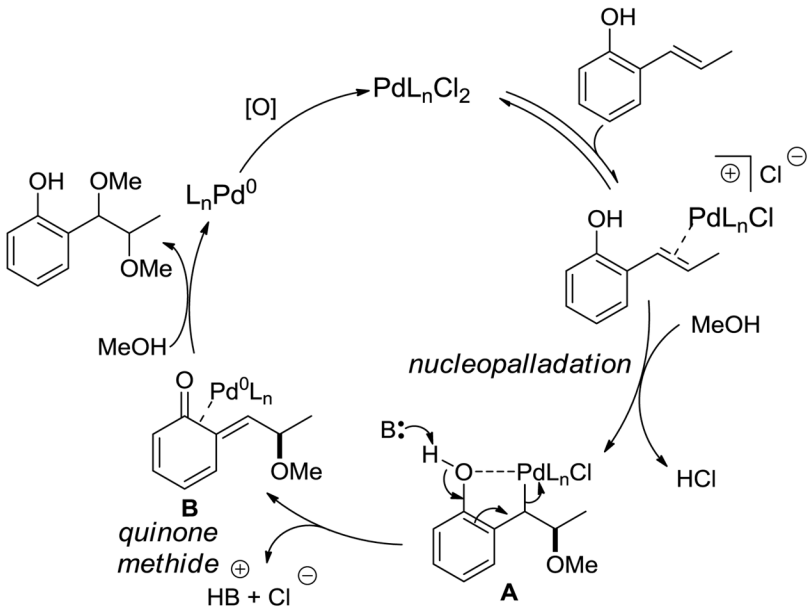
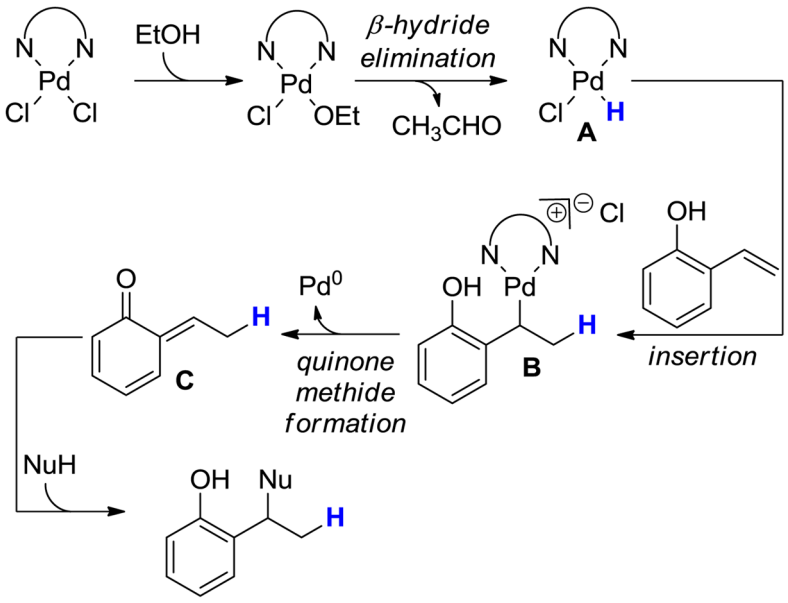


Figure 16.
Scope of the enantioselective Pd-catalyzed alkene difunctionalization reaction of vinyl phenols with electron rich heteroaromatics, Sigman and coworkers, 2009.

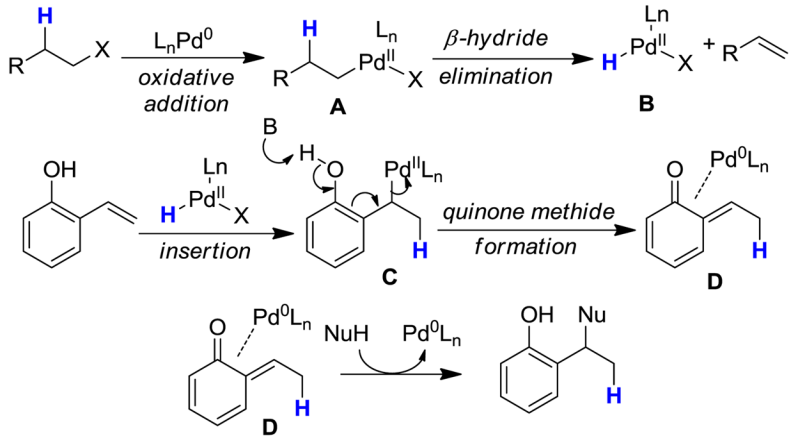


Scheme 1.

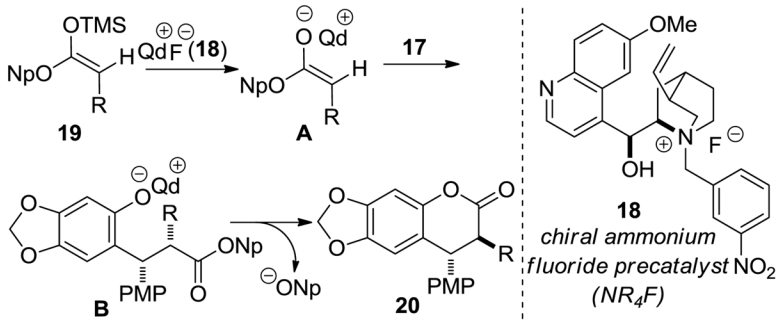
Proposed mechanism for Pd-catalyzed vinyl phenol dialkoxylation reaction, Sigman and coworkers, 2006.



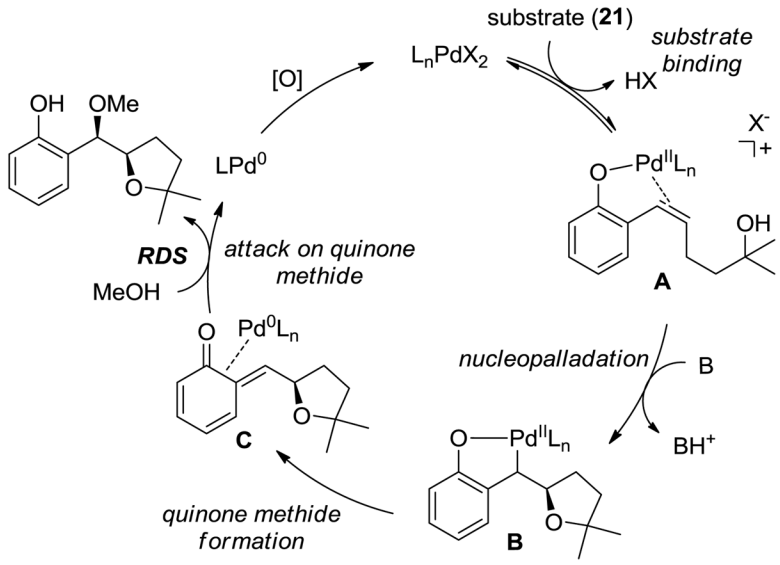
Scheme 2.
Proposed mechanism, Sigman and coworkers, 2007.



Scheme 3.
Proposed mechanism, Sigman and coworkers, 2011.



Scheme 4.
Proposed mechanism, Lectka and coworkers, 2009.



Scheme 5.
Proposed mechanism of alkene difunctionalization, Sigman and coworkers, 2009