Benzoquinone Cocatalyst Contributions to DAF/Pd(OAc)$_2$-Catalyzed Aerobic Allylic Acetoxylation in the Absence and Presence of a Co(salophen) Cocatalyst

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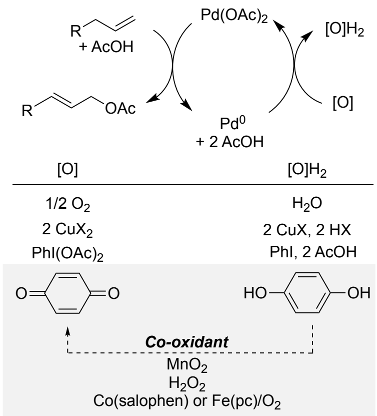
Abstract: Palladium(II)-catalyzed allylic acetoxylation has been the focus of extensive development and investigation. Methods that use molecular oxygen (O_2) as the terminal oxidant typically benefit from the use of benzoquinone (BQ) and a transition-metal (TM) cocatalyst, such as Co(salophen), to support oxidation of Pd^0 during catalytic turnover. We previously showed that Pd(OAc)$_2$ and 4,5-diazafluoren-9-one (DAF) as an ancillary ligand catalyze allylic oxidation with O_2 in the absence of cocatalysts. Herein, we show that BQ enhances DAF/Pd(OAc)$_2$ catalytic activity, nearly matching the performance of reactions that include both BQ and Co(salophen). These observations are complemented by mechanistic studies of DAF/Pd(OAc)$_2$ catalyst systems under three different oxidation conditions: (1) O_2 alone, (2) O_2 with cocatalytic BQ, and (3) O_2 with cocatalytic BQ and Co(salophen). The beneficial effect of BQ in the absence of Co(salophen) is traced to synergistic roles of O_2 and BQ, both of which are capable of oxidizing Pd^0 to Pd^{II}. The

reaction of O_2 generates H_2O_2 as a byproduct, which can oxidize hydroquinone to quinone in the presence of Pd^{II}. NMR spectroscopic studies, however, show that hydroquinone is the predominant redox state of the quinone cocatalyst in the absence of Co(salophen), while inclusion of Co(salophen) maintains oxidized quinone throughout the reaction, resulting in better reaction performance.

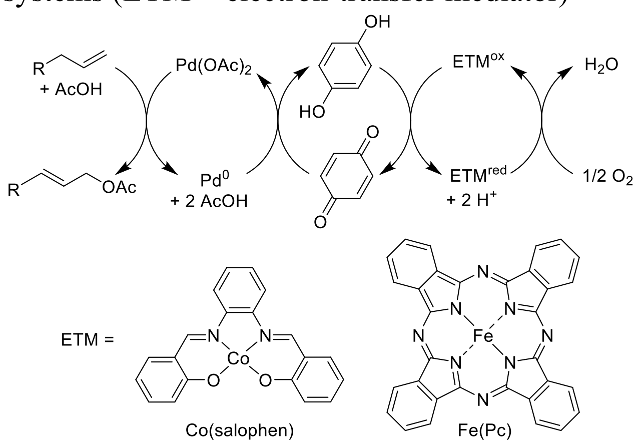
Introduction

Palladium(II)-mediated allylic C–H acetoxylation was first reported nearly 60 years ago.[1] Since then, many other catalytic applications of this method have been reported that employ various stoichiometric oxidants, including benzoquinone derivatives,[1,2-10] peroxides,[11–14] copper salts,[15,16] and hypervalent iodine reagents[17,18] (Scheme 1). Benzoquinone (BQ) is commonly used in cocatalytic quantities with a stoichiometric oxidant, such as MnO_2[19-21] or a peroxide.[11,14,22] Molecular oxygen (O_2) has been used effectively, typically in combination with BQ and a transition-metal (TM) complex, such as iron phthalocyanine or Co(salophen), as a cocatalyst to support catalytic turnover (Scheme 2).[20,21,23-30] In rare cases, O_2 is an effective oxidant for Pd-catalyzed allylic acetoxylation without any cocatalysts.[31,32]

Scheme 1. Pd-catalyzed allylic acetoxylation with various oxidants

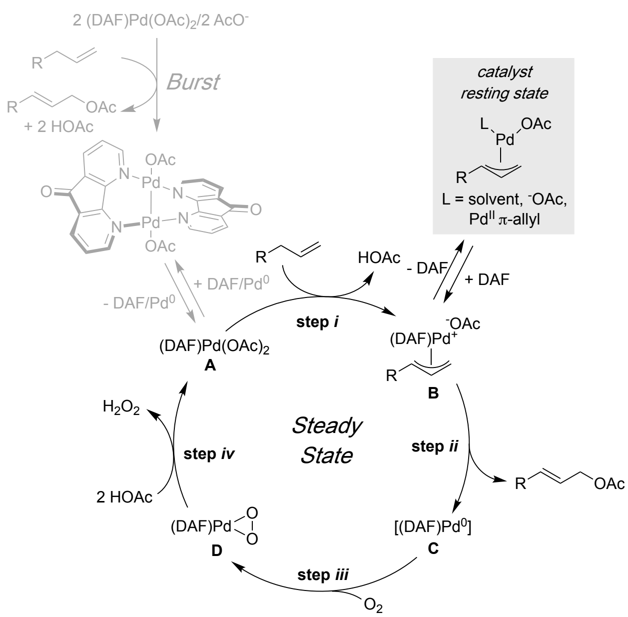


Scheme 2. Proposed mechanism for aerobic allylic acetoxylation with multicomponent catalyst systems (ETM = electron-transfer mediator)



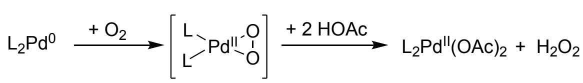
Our initial studies of Pd-catalyzed allylic acetoxylation were motivated by an interest in developing a ligand-based strategy to support the use of O_2 as an oxidant and led to the discovery of 4,5-diazafluoren-9-one (DAF) as an effective ancillary ligand for these reactions.[30,32-35] Subsequent mechanistic studies revealed that these reactions exhibit a kinetic "burst" of product formation at the start of the reaction, coinciding with the formation of a Pd^{I} dimer,[36] followed by steady-state catalytic turnover in which the catalyst resting state consists of an allyl-Pd^{II} species (Scheme 3).[37] The catalytic rate exhibits a dependence on pO_2 during steady-state turnover, implicating catalyst reoxidation by O_2 as the turnover-limiting step. Recognizing that BQ is capable of promoting both C–O bond-formation (formally, reductive elimination) from allyl-Pd^{II} species and reoxidation of Pd^0,[38] we evaluated BQ derivatives as additives in a recent study of allylic acyloxylation with diverse carboxylic acids.[30] In the course of this work, we found that use of 5 mol% 2,6-dimethylbenzoquinone (Me_2BQ) in the absence of a TM cocatalyst more than doubled the yield relative to a reaction with O_2 in the absence of quinone. This result is not readily understood from prior studies, which suggest that the cocatalyst is needed to reoxidize hydroquinone (H_2Q).[23-30,39]

Scheme 3. Mechanistic steps in DAF/$Pd(OAc)_2$-catalyzed aerobic allylic acetoxylation



The mechanistic model commonly invoked for multicomponent catalyst systems of this type features a redox cascade in which O_2 oxidizes the TM cocatalyst, the TM cocatalyst oxidizes H_2Q, BQ oxidizes Pd^0, and Pd^{II} oxidizes the organic substrate (Scheme 2).[23,24,40] This cascade sequence is widely invoked, but few studies have interrogated mechanistic features of the cocatalyst system[40,41] and prior studies do not provide a rationale for the beneficial role of BQ in the absence of a TM cocatalyst. Two recent studies seemed to offer possible insights. DAF/$Pd(OAc)_2$ was found to undergo redox equilibration with H_2Q, generating BQ and reduced Pd species;[39] however, this reactivity doesn't provide a clear basis for improved catalyst performance. A separate study showed that Pd^{II} salts catalyze oxidation of H_2Q to BQ derivatives using *t*BuOOH as the oxidant.[42] This reactivity contributes to the Pd/BQ-cocatalyzed 1,4-diacyloxylation of cyclohexadiene with *t*BuOOH, complementing other Pd/BQ cocatalyst systems that use peroxides as the stoichiometric oxidant,[11] including one case using DAF/$Pd(OAc)_2$ as the Pd catalyst.[14] The relevance of these insights is apparent upon recognizing that oxidation of Pd^0 by O_2 in the presence of AcOH generates H_2O_2 (Scheme 4),[35,43-45] and we postulated that this in situ-generated H_2O_2 could promote oxidation of H_2Q to BQ, thereby accounting for the beneficial effect of BQ on Pd-catalyzed aerobic allylic oxidation, even in the absence of a TM cocatalyst.

Scheme 4. Reaction of Pd^0 with O_2 resulting in the formation of H_2O_2



The present study surveys the influence of various quinones on Pd-catalyzed aerobic allylic acetoxylation in the absence and presence of Co(salophen) as a cocatalyst. We then investigate the relative rates of H_2Q oxidation by O_2 in the presence of different components of the catalyst system and employ NMR spectroscopy to probe the quinone speciation in the absence and presence of cocatalytic Co(salophen). Collectively, the results provide unique mechanistic insights into commonly used multicomponent catalyst systems in Pd-catalyzed oxidation reactions.

Results and Discussion

Influence of quinones on Pd-catalyzed allylic oxidation. We initiated our study by investigating Pd-catalyzed acetoxylation of allylbenzene (**1**) with 5 mol% loading of quinones **3a-3m**, which have different steric properties and redox potentials (Figure 1A). Reactions carried out in the absence and presence of 0.5 mol% Co(salophen) show a "volcano"-like dependence of the cinnamyl acetate (**2**) yield on the quinone $2e^-/2H^+$ redox potential (Figure 1B).[46] Reaction times were shortened from 14 to 7 h when using Co(salophen) in order to enhance the contrast among different quinones. The variations in yields among the best quinones probably reflect the superposition of steric and electronic contributions to the outcome. But, optimal yields of **2** were generally obtained with BQs with redox potentials ranging from ~ 550-635 mV (**3d**–**3h**) in the absence of Co(salophen). The range of optimal quinone redox potentials expands for reactions conducted in the presence of Co(salophen), accommodating quinones with potentials of ~ 550-700 mV (**3d**–**3k**).

The poor performance of low and high potential quinones in both cases is rationalized by offsetting electronic effects on the redox processes involving quinones: (a) BQ promotion of Pd-catalyzed substrate oxidation, including C–O bond formation from allyl-Pd^{II} species and reoxidation of Pd^0, is expected to benefit from high-potential quinones, while (b) reoxidation of H_2Q will be more facile for low-potential quinones. The positive shift in quinone redox potentials for reactions with Co(salophen) is consistent with the ability of this cocatalyst to promote H_2Q oxidation (see below).

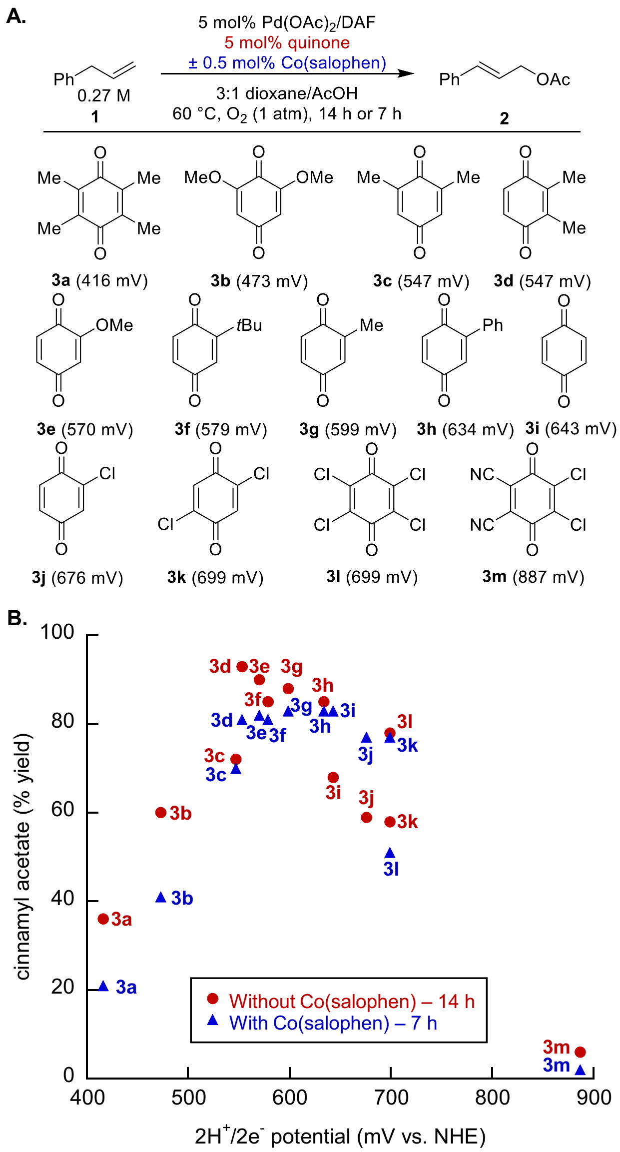


Figure 1. Allylic acetoxylation of allylbenzene with different benzoquinone derivatives. (A) Benzoquinone additives and their redox potentials. (B) Observed yields relative to the $2H^+/2e^-$ redox potential of the quinone for conditions without Co(salophen) (14 h) and with Co(salophen) (7h).

The effect of quinone on DAF/$Pd(OAc)_2$-catalyzed acetoxylation of **1** was evaluated further by monitoring the reaction time course under three different aerobic oxidation conditions: (1) with 1 atm O_2 in the absence of cocatalysts, (2) with 1 atm O_2 and 5 mol% 2-*tert*-butyl-1,4-benzoquinone (*t*BuBQ) as a cocatalyst, and (3) with 1 atm O_2, 5 mol% *t*BuBQ, and 0.5 mol%

Co(salophen) as cocatalysts (Figure 2). The reaction conducted under O_2 in the absence of cocatalysts exhibits a rapid burst of product formation during the first ~10 min followed by slower steady state turnover, consistent with previous reports.[36,37] Both reactions with *t*BuBQ exhibit higher rates and lead to high yields of **2** after 15 h, at which time the O_2-alone reaction has reached only ~40% yield. The presence of both *t*BuBQ and Co(salophen) leads to the best performance, as expected,[23] but the good results observed with *t*BuBQ in the absence of Co(salophen) is noteworthy. Similar results were obtained with a series of other substrates, including electronically differentiated allylbenzene derivatives (**1a**-**1c**) and aliphatic substrates (**1d**, **1e**). In each case, addition of *t*BuBQ to the reaction substantially improves the yield, and further improvements are evident when both *t*BuBQ and Co(salophen) are included as cocatalysts in the reaction mixture (Figure 3).

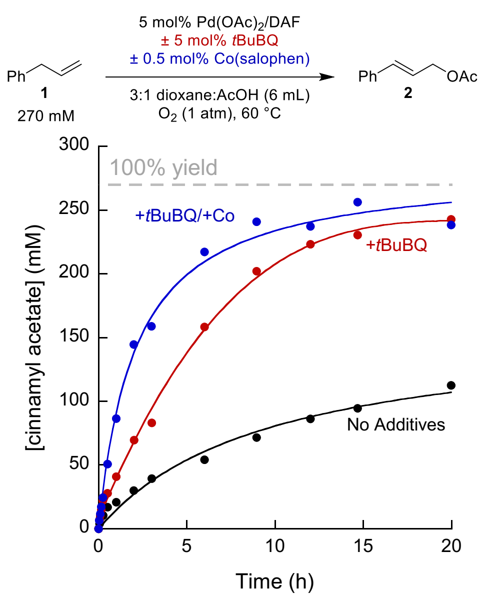


Figure 2. Time course of cinnamyl acetate formation during the aerobic allylic acetoxylation of allylbenzene without additives, with 5 mol% *t*BuBQ, and with 5 mol% *t*BuBQ and 0.5 mol% Co(salophen). Trendlines reflect empirical fits to guide the eye (see Supporting Information for details).

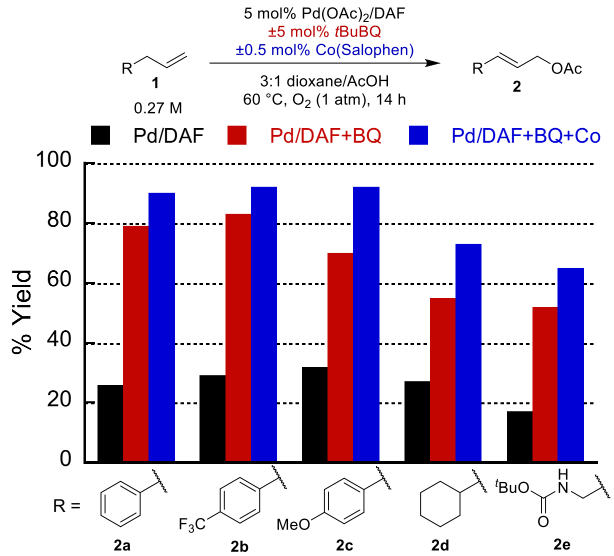


Figure 3. [1]H NMR yields of allylic acetates **2a-2e** obtained from substrates **1a-1e** under three different aerobic reaction conditions: without cocatalysts (black), with 5 mol% *t*BuBQ (red), and with 5 mol% *t*BuBQ and 0.5 mol% Co(salophen) (blue).

Analysis of H_2Q oxidation and quinone speciation under catalytic conditions. BQ cocatalysts can play at least two roles in these reactions: (a) promote C–O bond formation/reductive elimination from allyl-Pd^{II} species[5,38,47-49] and (b) promote reoxidation of Pd^0 to Pd^{II}.[50] The first role does not alter the redox state of the BQ,[51] while the second will generate H_2Q, which must be reoxidized to BQ in order to continue serving as a cocatalyst. The latter process is typically thought to require Co(salophen) or a related cocatalyst,[23,24] raising questions about the beneficial effect of BQ in the absence of a TM cocatalyst.

Experiments were undertaken to probe methods for oxidation of *t*BuH_2Q to *t*BuBQ that could be operative under the Pd-catalyzed oxidation conditions (Figure 4). The reaction temperature for these studies was lowered to 40 °C to facilitate data collection at early time points for some of the rapid reactions. O_2 alone does not promote oxidation of *t*BuH_2Q to *t*BuBQ (Figure 4a) and only minor oxidation was observed with H_2O_2 in the absence of metal (co)catalysts (4% yield after 6 h, Figures 4b). Similar moderate rates of *t*BuH_2Q oxidation were observed with Co(salophen) under

O_2 and DAF/Pd(OAc)$_2$ under O_2 (52% and 55% yields after 6 h, Figure 4c and 4d, respectively). The DAF/Pd(OAc)$_2$/O_2 outcome is somewhat unexpected considering BQ derivatives are typically used to oxidize Pd^0; however, it aligns with the recent observation of redox equilibria between DAF/Pd(OAc)$_2$ and H_2Q derivatives[39] and indicates that net O_2 reduction to H_2O drives *t*BuH$_2$Q oxidation under these conditions. In this context, DAF/Pd(OAc)$_2$ mediates rapid oxidation of *t*BuH$_2$Q by H_2O_2 under anaerobic conditions (75% yield after 6 h, Figure 4e). Oxidation of *t*BuH$_2$Q is most rapid when both DAF/Pd(OAc)$_2$ and Co(salophen) are used as cocatalysts under an O_2 atmosphere (Figure 4f).

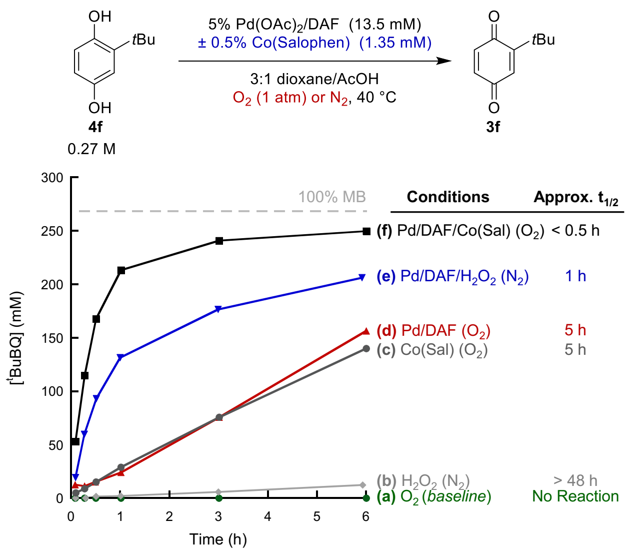


Figure 4. Time course plots obtained from the oxidation of *t*BuH$_2$Q to *t*BuBQ under a series of different conditions.

The redox state of the quinone cocatalyst during the catalytic acetoxylation reaction was then interrogated for reactions conducted in the absence and presence of the Co(salophen) cocatalyst. The quinone speciation was determined by analyzing aliquots of the reaction mixture throughout the reaction time course by ^{1}H NMR spectroscopy (samples were quenched with pyridine and diluted in $CDCl_3$ for analysis; see Supporting Information for details). In the absence of Co(salophen), *t*BuBQ is completely consumed during the first 30 min with concomitant formation of tBuH$_2$Q. Then, tBuH$_2$Q is slowly oxidized to tBuBQ as the allylic oxidation reaction proceeds to completion over the next 15-20 h (Figure 5A). The reaction conducted in the presence of Co(salophen) also shows an initial reduction of tBuBQ to tBuH$_2$Q; however, this progression is reversed after 25-30% conversion to tBuH$_2$Q, and tBuBQ is present in a high steady-state concentration throughout most of the reaction (Figure 5B).

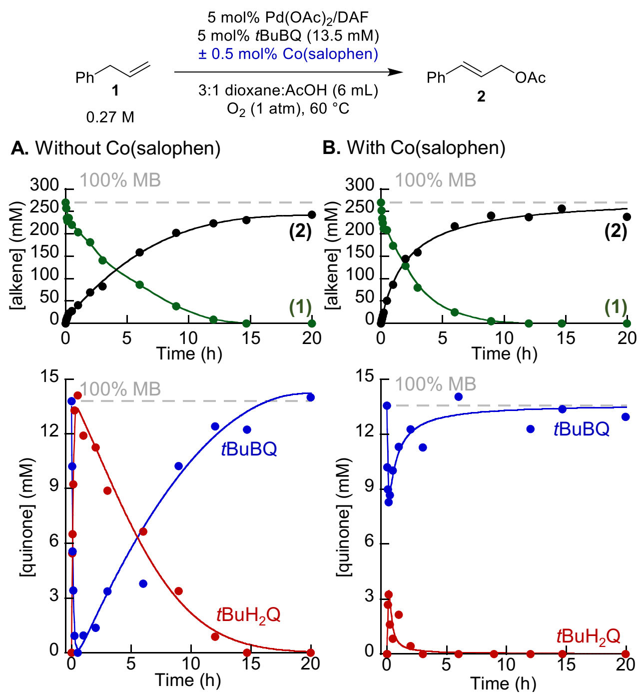


Figure 5. Time courses of product formation and starting material depletion (top plot) and tBuBQ speciation (bottom plot) during the aerobic allylic acetoxylation of allylbenzene (A) without Co(salophen) and (B) with 0.5% Co(salophen). Trendlines reflect empirical fits to guide the eye based on functions described in the Supporting Information.

We then used the Wisconsin High-Pressure NMR Reactor (WiHP-NMRR)[52] to conduct operando analysis of the reactions. This apparatus enables reactions to be run under a continuous supply of a gaseous reagent while recording NMR spectra,[37,53-55] and it enabled us to probe the Pd catalyst under three different reaction conditions: (1) O_2 alone, (2) O_2 + 5 mol% tBuBQ, and (3) O_2 + 5 mol% tBuBQ + 0.5 mol% Co(salophen) (Figure 6). These experiments exhibit relatively low signal-to-noise, but still provide valuable insights into the Pd speciation.

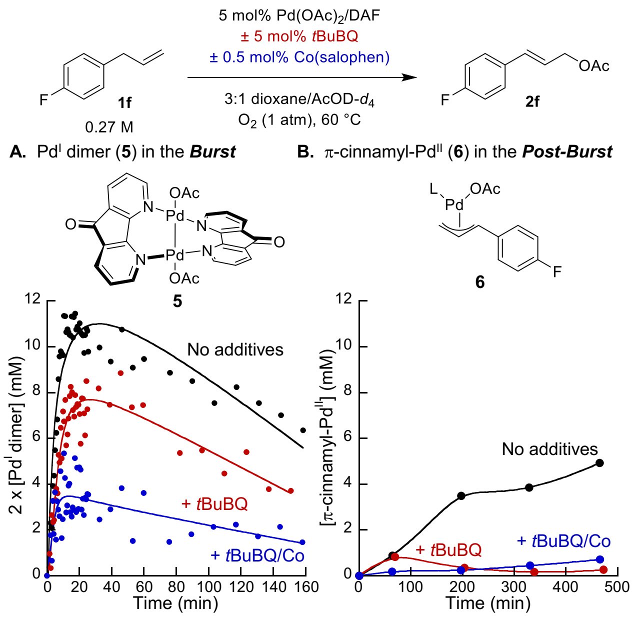


Figure 6. Palladium speciation monitored by operando WiHP-NMRR during the acetoxylation of 4-fluoroallylbenzene **1f** to the allyl acetate **2f**. (A) Formation/decay of [Pd^{I} dimer **5**] analyzed by ^{1}H NMR spectroscopy, and (B) appearance of [π-cinnamyl-Pd^{II} **6**] (or lack thereof) determined by ^{19}F NMR analysis. Trendlines reflect empirical fits to guide the eye (see Supporting Information for details).

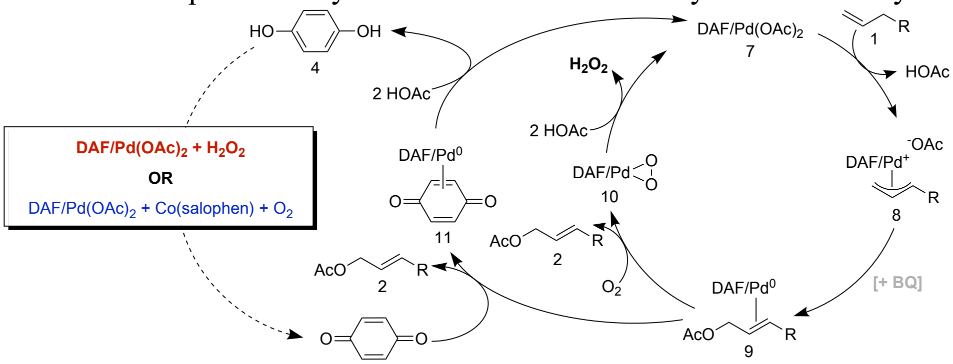
Previous investigation of DAF/Pd(OAc)$_2$-catalyzed allylic oxidation under aerobic conditions (i.e., in the absence of cocatalysts) revealed formation of the dimeric Pd^{I} species **5** at early stages of the reaction, arising from comproportionation of Pd^{0} and Pd^{II} species present in the reaction mixture (cf. Scheme 3).[37] These observations were reproduced under the O_2-alone conditions (black data, Figure 6A). Inclusion of *t*BuBQ leads to reduced build-up of the Pd^{I} dimer intermediate early in the reaction (red data, Figure 6A) and even less formation of Pd^{I} when both *t*BuBQ and Co(salophen) are included in the reaction (blue data, Figure 6A). As the reaction progresses, π-cinnamyl-Pd^{II} species (**6**) become evident in the reaction mixture lacking cocatalysts (Figure 6B, black data), implicating an allyl-Pd^{II} resting state during steady-state turnover. This species is not evident, however, in both reaction mixtures containing cocatalysts (Figure 6B, red and blue data, respectively).

The reduced formation of the Pd^{I} dimer in the presence of *t*BuBQ (Figure 6A) is rationalized by the ability of *t*BuBQ to coordinate to Pd^0 and reoxidize it to Pd^{II},[50] thereby minimizing Pd^0/Pd^{II} comproportionation to form the Pd^{I} dimer. The lack of allyl-Pd^{II} species when cocatalysts are present (Figure 6B) is consistent with the ability of BQ cocatalysts to promote C–O bond formation from allyl-Pd^{II}.[5,38,47-49] These data provide direct operando evidence for the two commonly invoked roles of quinones in Pd-catalyzed allylic oxidation reactions.

Summary and catalytic mechanism. The data presented herein illuminate a number of features that have not been characterized previously for multicomponent Pd/cocatalyst systems for aerobic oxidation. The results show a synergistic role of O_2 and BQ, in which the H_2O_2 byproduct of Pd^0 aerobic oxidation supports oxidation of the H_2Q species. This feature allows BQ to be an effective cocatalyst, even in the absence of a Co(salophen) cocatalyst (cf. Figure 2). Nonetheless, the catalytic reaction is more effective when both quinone and Co(salophen) are included in the reaction. This mutual benefit reflects improved rates of H_2Q oxidation when Co(salophen) is present (cf. Figure 4), resulting in oxidized BQ species being available throughout the catalytic reaction (cf. Figure 5) to support C–O bond formation and reoxidation of the Pd catalyst.

The catalytic mechanism in Scheme 5 accounts for many of the observations described herein. In the absence of cocatalysts, DAF/$Pd(OAc)_2$ activates the allylic C–H bond of the olefin substrate, leading to the formation of an allyl-Pd^{II} intermediate that can undergo (reversible[32]) C–O bond formation to afford a DAF/Pd^0 species that can be reoxidized by O_2 via a peroxo-Pd^{II} intermediate (right catalytic cycle, Figure 5). The presence of BQ promotes C–O bond formation from the allyl-Pd^{II} species and provides an alternative pathway for reoxidation of Pd^0 via a DAF/Pd^0-BQ adduct. The latter step will generate H_2Q, which can undergo reoxidation to BQ, using H_2O_2 from the aerobic pathway or a cocatalytic process involving DAF/Pd/Co(salophen)/O_2 (cf. Figure 4).

Scheme 5. Proposed catalytic mechanism for Pd-catalyzed aerobic allylic acetoxylation.



Conclusion.

This study provides new insights into the cooperative contributions of O_2, BQ, and Co(salophen) in promoting Pd catalyst reoxidation in allylic acetoxylation reactions. O_2 can reoxidize the Pd catalyst directly when a suitable ancillary ligand, such as DAF, is present to ensure catalyst stability and promote the reaction with O_2. The beneficial effect of BQ reflects its ability to promote both C–O bond formation in the substrate oxidation half-reaction and its ability to oxidize Pd^0 under acidic reaction conditions. But, a method is needed to ensure reoxidation of H_2Q after each catalytic cycle. Hydroquinone does not react readily with O_2, but we show that O_2/BQ are effective together in the Pd-catalyzed conditions. Under these conditions, O_2 reduction generates H_2O_2, which then supports efficient oxidation of H_2Q in the presence of the Pd catalyst. The best conditions feature a combination of quinone and Co(salophen) cocatalysts, reflecting the ability of the Co(salophen) to promote rapid oxidation of the H_2Q species, maximizing the steady-state quantity of quinone available to support substrate and catalyst oxidation steps. The results described herein provide new insights and direct evidence for previous mechanistic proposals.

ASSOCIATED CONTENT

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Notes
The authors declare no competing financial interests.

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website. Experimental details and NMR data.

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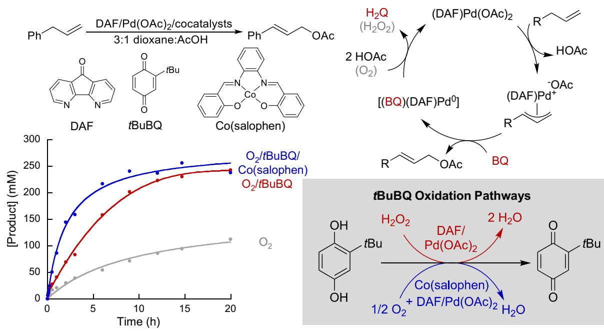
TOC Graphic



DAF/Pd(OAc)2/cocatalysts
3:1 dioxane:AcOH
Ph
OAc
DAF
tBuBQ
Co(salophen)
(DAF)Pd(OAc)2
HOAc
2 HOAc
(O2)
H2Q
(H2O2)
[(BQ)(DAF)Pd0]
BQ
O2/tBuBQ/
Co(salophen)
O2/tBuBQ
O2
[Product] (mM)
Time (h)
tBuBQ Oxidation Pathways
H2O2
DAF/
Pd(OAc)2
2 H2O
Co(salophen)
+ DAF/Pd(OAc)2
1/2 O2
H2O