

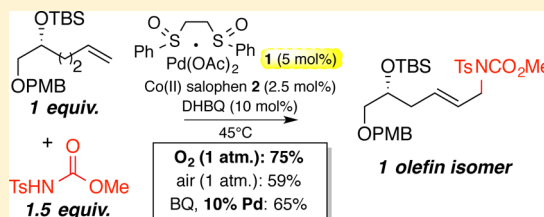
Aerobic Linear Allylic C–H Amination: Overcoming Benzoquinone Inhibition

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S Supporting Information

ABSTRACT: An efficient aerobic linear allylic C–H amination reaction is reported under palladium(II)/bis-sulfoxide/Brønsted base catalysis. The reaction operates under preparative, operationally simple conditions (1 equiv of olefin, 1 atm O₂ or air) with reduced Pd(II)/bis-sulfoxide catalyst loadings while providing higher turnovers and product yields than systems employing stoichiometric benzoquinone (BQ) as the terminal oxidant. Pd(II)/BQ π -acidic interactions have been invoked in various catalytic processes and are often considered beneficial in promoting reductive functionalizations. When such electrophilic activation for functionalization is not needed, however, BQ at high concentrations may compete with crucial ligand (bis-sulfoxide) binding and inhibit catalysis. Kinetic studies reveal an inverse relationship between the reaction rate and the concentration of BQ, suggesting that BQ is acting as a ligand for Pd(II) which results in an inhibitory effect on catalysis.



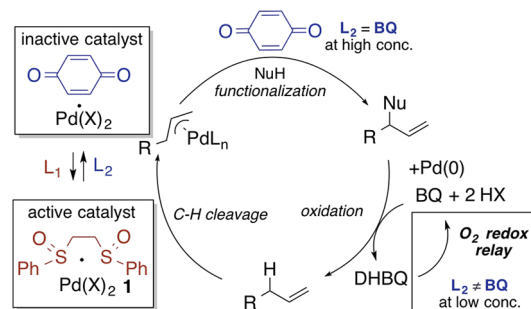
INTRODUCTION

Nature routinely uses molecular oxygen (O₂) as a stoichiometric oxidant for metalloenzyme catalyzed C–H bond oxidations.¹ In the context of chemical synthesis, the economic and environmental advantages of using O₂ for these purposes are clear: O₂ is an abundant, highly atom-efficient oxidant per weight that generates no toxic byproducts.² Less evident, however, is the potential for employing this oxidant in a manner that would increase the catalytic efficiency of oxidation reactions.

Since an early report that benzoquinone (BQ) is capable of acting as an effective stoichiometric oxidant for Pd-catalyzed olefin oxidations, BQ has become the most common terminal oxidant for palladium-catalyzed oxidations proceeding via Pd(II)/Pd(0) redox cycles.^{3,4} We and others have demonstrated that at BQ may fill a dual role in Pd-catalyzed C–H oxidation reactions by acting as both an oxidant and a π -acidic ligand to promote reductive eliminations at the metal.⁵ Allylic C–H oxidations that benefit from this effect operate under the principle of *serial ligand catalysis*, wherein distinct ligands promote specific steps along a catalytic cycle (Scheme 1A).^{5c} Under these conditions, the reversibly coordinating bis-sulfoxide ligand coordinates to Pd(II) to promote a C–H cleavage step and generate a reactive π -allylPd(II) intermediate. BQ may then coordinate to this electrophilic intermediate via an η^2 - π complex and act as a π -acidic ligand to promote reductive eliminations at the metal center.⁵ We hypothesized that when activation of the electrophilic metal center is not required for functionalization, these BQ–Pd(II)L_n interactions may prove detrimental in systems using weakly coordinating ligands. By competing with the essential bis-sulfoxide binding

Scheme 1. Benzoquinone (BQ) Ligand Effects

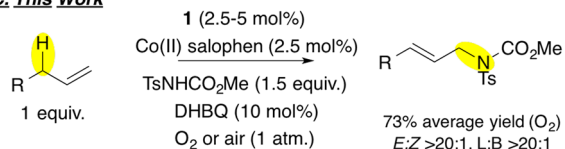
A. Serial Ligand Catalysis Disrupted



B. Previous Work



C. This Work



event at the metal, BQ binding at high concentrations may lead to an inhibitory effect on catalysis.

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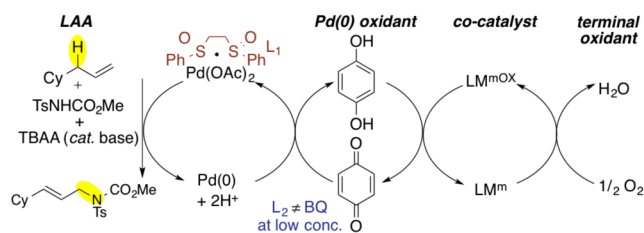
Herein, we describe the development of an efficient intermolecular linear allylic C–H amination (LAA) reaction employing a cobalt-mediated redox-relay catalytic cycle that uses molecular oxygen as the terminal oxidant under mild (1 atm, 45 °C) and preparatively useful conditions (1 equiv of olefin, 1.5 equiv of nitrogen nucleophile). This improved system enables the reaction to proceed with catalytic quantities of BQ, thus reducing the potential for inhibitory binding of BQ to the Pd(II) catalyst. As a result, this system affords higher or comparable yields while operating at lower catalyst loadings than those previously developed using superstoichiometric BQ as the terminal oxidant. The aerobic LAA reaction even remains operational at reduced oxygen concentrations found in air. Kinetic experiments substantiate the hypothesis of an inhibitory BQ effect at high concentrations and indicate that the improved efficiency of the aerobic system results from the low concentration of BQ present in the reaction mixture.

DESIGN PRINCIPLES

Palladium(II)/bis-sulfoxide catalysis has emerged as a general platform for allylic C–H oxidations, aminations, dehydrogenations, halogenations, and alkylations of α -olefins.^{6,7} Common to all of these C–H functionalization reactions is the use of 10 mol% Pd/bis-sulfoxide catalyst and stoichiometric quinone oxidants such as BQ. Additionally, the majority of these reactions exploit BQ as a π -acidic ligand, often in combination with Lewis or Brønsted acid cocatalysts, to activate the electrophilic π -allylpd intermediate toward functionalization.^{5,6h,7a}

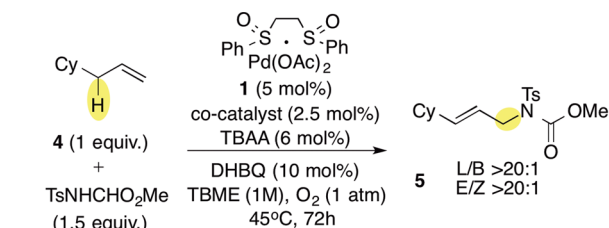
Given the ubiquity of nitrogen functionality in bioactive compounds, its selective and general introduction represents a particularly powerful synthetic strategy.⁸ We disclosed a catalytic Brønsted base activation mode for the intermolecular LAA reaction that proceeds via activation of the nitrogen nucleophile.^{7b} Importantly, this reaction is no longer dependent on the π -acidic effect of BQ for functionalization. Under these conditions, we noted a slight increase in reaction yield when a bulky quinone—having diminished ability to coordinate to Pd—was employed as a terminal oxidant.^{7b} With these considerations in mind, we chose the LAA reaction as a platform to evaluate the hypothesis that replacing BQ with O₂ as a stoichiometric oxidant can improve the catalytic efficiency of Pd(II)-catalyzed oxidations with catalysts employing weakly coordinating ligands.

Scheme 2. Proposed Mechanism for Aerobic Linear Allylic Amination (LAA) with Redox-Relay Catalysis



While a variety of important Pd-catalyzed oxidations of alcohols and olefins have been developed using O₂ as a stoichiometric oxidant, analogous C–H oxidation processes are scarce.^{4,9–14} Pd(II)-catalyzed C–H oxidation reactions often proceed with no formal ligands [e.g., Pd(OAc)₂] or weakly coordinating, oxidatively stable ligands such as bis-sulfoxide.¹⁰

Table 1. Reaction Optimization



Entry ^a	catalyst/co-catalyst	Oxidant	Yield of 5 ^b
1 ^c	10 mol% 1/--	BQ (2 equiv.)	84%
2 ^c	5 mol% 1/--	BQ (2 equiv.)	20%
3 ^d	1/Co(II)(salophen) 2	O ₂ (1atm)	68%
4	1/Co(II)(salophen) 2	O ₂ (1atm)	79%(78%) ^e
5	1/Co(II)(TPP)	O ₂ (1atm)	60%
6	1/Co(II)(salen)	O ₂ (1atm)	74%
7	1/Mn(III)(salen)	O ₂ (1atm)	8%
8	1/Fe(II)Pc	O ₂ (1atm)	39%
9	1/VO(acac) ₂ 3	O ₂ (1atm)	48%
10 ^f	1/VO(acac) ₂ 3	O ₂ (1atm)	75% (80%) ^g
11 ^f	1/VO(TPP)	O ₂ (1atm)	53%
12 ^f	1/VO(Salophen)	O ₂ (1atm)	54%
13 ^{f,h}	1/VOSO ₄	O ₂ (1atm)	65%
14	1/--	O ₂ (1atm)	17%
15 ⁱ	Pd(OAc) ₂ /DAF	O ₂ (1 atm)	trace
16 ^c	1/--	2,5-DMBQ (1 equiv.)	72%

^a Conditions are as listed above unless noted. Co(II)(salophen) = N,N'-bis(salicylidene)-1,2-phenylenediaminocobalt(II); Co(II)(TPP) = cobalt(II) meso-tetraphenylporphine; Co(II)(salen) = (1R,2R)-(-)-1,2-cyclohexanediamino-N,N'-bis(3,5-di-*t*-butylsalicylidene)cobalt(II); Mn(III)(salen) = (1R,2R)-(-)-1,2-cyclohexanediamino-N,N'-bis(3,5-di-*t*-butylsalicylidene)manganese(III) chloride; Fe(II)Pc = iron(II) phthalocyanine; VO(acac)₂ = vanadyl acetylacetonate; VO(TPP) = vanadyl meso-tetraphenylporphine; VO(salophen) = N,N'-bis(salicylidene)-1,2-phenylenediaminovanadium(IV) oxide. ^b Isolated yield; average of at least 2 runs at 0.4 mmol scale. ^c Conditions from ref. 7b. ^d 1M TBME, 2 equiv. TsNHCO₂Me. ^e Number in parenthesis is yield at 24h. ^f 2 equiv. TsNHCO₂Me, 1M THF. ^g Number in parentheses is yield with 1 mol% co-catalyst on a 0.8 mmol scale for accurate co-catalyst weight. ^h 1 mmol scale used for accurate co-catalyst weights. ⁱ 5 mol% Pd(OAc)₂, 5 mol% 4,5-diazfluoren-9-one (DAF), with identical conditions to entries 4-9.

For allylic C–H acetoxylation and aminations under such conditions, the slow electron transfer directly between Pd(0) and O₂ relative to the rapid formation of palladium black via precipitation of palladium metal is thought to result in deleterious olefin isomerization processes and contribute to the requirement for high catalyst loadings.^{11–14} While aerobic Pd(II)-catalyzed LAA reactions have been reported, their utility is limited by requirements such as excess alkene (e.g., 3–7 equiv relative to nucleophile), high Pd catalyst loadings (e.g., 10–20 mol%), and elevated pressures (e.g., 6–10 atm O₂ or air).^{12,13} Significant amounts of double bond isomerization in both the starting materials and products (up to 50%) necessitate the use of large excesses of olefin and limit applications in fine chemical synthesis.^{12–14}

We considered two possible strategies for engaging molecular oxygen as the terminal oxidant for the LAA reaction under preparatively useful conditions. While oxidatively stable ligands which promote direct oxidation of Pd(0) with molecular oxygen have been developed, these ligands have not yet demonstrated the same generality in C–H oxidation processes as compared to the bis-sulfoxide ligand class.^{2a,4,15} A more general approach, compatible with the continued use of bis-sulfoxides, would be through the use of redox-active cocatalysts that act as electron transfer reagents to relay electrons from

Pd(0) to O₂ at rates that compete with Pd(0) precipitation (Scheme 2). An early example of this is seen in the Pd(II)-catalyzed Wacker oxidation of ethylene to acetaldehyde that uses catalytic Cu(II)Cl₂ to shuttle electrons from Pd(0) to O₂.¹⁶ Unfortunately, unligated metal salts generally have a deleterious effect on Pd(II)/bis-sulfoxide catalysis, possibly by sequestering the bis-sulfoxide ligand that binds weakly and reversibly to Pd(II). Alternatively, a variety of base metal complexes with covalent, nonexchangeable ligands are known to catalyze the oxidation of dihydroquinones to the corresponding quinones with O₂.^{17,18} In a notable series of seminal publications, Bäckvall and co-workers demonstrated that this form of redox-relay catalysis enabled catalytic quantities of BQ to be effective at regenerating Pd(II)(OAc)₂ catalysts for the 1,4-diacetoxylation of dienes, acetoxylation of cyclohexene, and oxidation of terminal olefins to methyl ketones.¹⁹ Mechanistic studies of processes proceeding via serial ligand catalysis have demonstrated that high concentrations of BQ are required to effectively interact with the Pd(II) species to promote π -allyl Pd(II) functionalizations.^{5c,fg} Collectively, this led us to hypothesize that in the context of an aerobic redox-relay catalytic cycle, the low concentration of BQ present would diminish its ability to effectively compete with the bis-sulfoxide ligand for Pd(II) but would remain an efficient electron carrier for Pd(0)/Pd(II) reoxidation.

REACTION DEVELOPMENT

An efficient aerobic LAA process (1 equiv of olefin, reduced Pd catalyst loadings, 1 atm O₂) was first evaluated with a series of established redox-active cocatalysts. At reduced catalyst loading (5 mol%), a substantial diminishment in yield is observed under standard LAA conditions using stoichiometric BQ as the oxidant (Table 1, entry 1 versus 2). In contrast, the combination of Co(salophen) (2.5 mol%)/dihydroquinone (10 mol%) under a balloon of O₂ (1 atm) allowed for the Pd/bis-sulfoxide catalyst 1 loading to be cut in half (10 mol% to 5 mol%) and the nitrogen nucleophile loadings reduced (2 equiv to 1.5 equiv) with no diminishment in selectivity while maintaining a good yield (entries 3 and 4 versus 1). We were also encouraged by the observation that, under these optimized conditions, no significant decrease in yield was observed after reducing the reaction time to 24 h (79% versus 78% yield, entry 4). A series of other base metal cocatalysts were evaluated; however, none was found to be more efficient than Co(salophen) 2 (entries 5–8). Interestingly, VO(acac)₂ 3/DHBQ in THF solvent appeared to be equally effective as a redox cocatalyst system to Co(salophen) 2/DHBQ, albeit at higher loadings of nitrogen nucleophile (1.5 equiv versus 2 equiv, entries 9 and 10). Although never explored in aerobic Pd(II)-catalyzed reactions, VO(acac)₂ 3 had been reported to catalyze the aerobic oxidation of hydroquinones to quinones at ambient temperatures and pressures of O₂.¹⁸ We were initially encouraged by the observation that the vanadium cocatalyst loading could be reduced to 1 mol% with no diminishment in yield, suggesting it is an efficient electron-transfer agent (entry 10). Additional vanadium catalysts were also evaluated (entries 11–13), and under these conditions only VOSO₄ was comparable to VO(acac)₂ 3, affording a 65% yield of the desired product (entry 13). Omission of the redox cocatalyst under these aerobic conditions resulted in significantly diminished yields, confirming its central role in Pd(II)/bis-sulfoxide 1 catalyst regeneration (entry 14). The Pd(OAc)₂/4,5-diazafluoren-9-one (DAF) system known to enable linear

allylic acetoxylation using O₂ as the terminal oxidant provided only trace quantities of aminated product under these conditions (entry 15).¹⁵ Notably, when using stoichiometric amounts of bulky 2,5-dimethylbenzoquinone (2,5-DMBQ) as a terminal oxidant, where methyl groups shield both olefin faces from binding to Pd, we observed comparable yields to the aerobic conditions (Table 1, entry 4 vs 16).

REACTION SCOPE

We began our investigations into the scope and reproducibility of the aerobic LAA reaction with a variety of unactivated α -olefins, the most challenging substrates for amination (Table 2). Both the Co(salophen) 2 and VO(acac)₂ 3 redox cocatalyst systems were evaluated under fragment-coupling stoichiometries of olefin (1 equiv of terminal olefin and 1.5 or 2 equiv of nitrogen nucleophile). It is significant to note that these preparative conditions contrast those of previously reported aerobic allylic C–H amination methods (*vide supra*).^{12,13}

Table 2. Aliphatic Substrates

Entry	Product	This Work		Previously	
		Co ^{a,b}	V ^{a,c}	BQ or O ₂	
1	TBDPSO-CH ₂ -CH=CH-CH ₂ -N(Ts)CO ₂ Me	6	77% ^d	46%	-
2	BnO-CH ₂ -CH=CH-CH ₂ -N(Ts)CO ₂ Me	7	54% ^e (30%) ^f [±2%]	44% [±14%]	-
3	BzO-CH ₂ -CH=CH-CH ₂ -N(Ts)CO ₂ Me	8	75% ^g (70%) ^f	81%	78% ^h 92% ⁱ
4	(Cyclohexane ring)-CH ₂ -CH=CH-CH ₂ -N(Ts)CO ₂ Me	9	67%	58%	53% ^j
5	(Methyl)-CH ₂ -CH=CH-CH ₂ -N(Ts)CO ₂ Me	(-)-10	55%	23% ^k	54% ^l
6	(NHCbz)-CH ₂ -CH=CH-CH ₂ -N(Ts)CO ₂ Me	(+)-11	86%	15% ^k	55% ^l
7	(PMBO, OTBS)-CH ₂ -CH=CH-CH ₂ -N(Ts)CO ₂ Me	(+)-12	75% (64%) ^f	69%	65% ^l
8	TBDPSO-CH ₂ -CH=CH-CH ₂ -N(Ts)CO ₂ Me	(+)-13	77%	67%	57% ^l

^a Isolated yield, average of at least 2 runs at 0.4 mmol scale. ^b 5 mol% 1, 2.5 mol% 2, 6 mol% TBAA, 10 mol% DHBQ, 1.5 equiv. TsNHCO₂Me, 1M TBME, O₂ balloon. ^c 5 mol% 1, 2.5 mol% 3, 6 mol% TBAA, 10 mol% DHBQ, 2 equiv. TsNHCO₂Me, 1M THF, O₂ balloon. ^d 20:1 L:B. ^e 11:1 E:Z. ^f 14:1 L:B. ^g Number in parenthesis is yield after 24 hours. ^h 15:1 L:B. ⁱ Yield reported in ref. 12; conditions employing 3 equiv. of olefin substrate, 10 mol% Pd, and 6 atm. O₂. ^j Ratio of allylic to non-allylic isomers (see ref. 12). ^k Yield reported in ref. 12; conditions employing 1 equiv. of olefin substrate, 20 mol% Pd, and 6 atm. O₂. ^l Reported yield of one run. ^m Yield reported in ref. 7a.

When comparing the Co(salophen) **2** and VO(acac)₂ **3** redox cocatalysts over a range of substrates at reduced Pd/bis-sulfoxide **1** catalyst loadings (5 mol%), we found both furnished products generally in excellent regio- and stereoselectivities (>20:1 linear:branched and >20:1 *E:Z*). The system employing Co uniformly furnished allylic amination products with higher turnover numbers (TON) and product yields comparable to or exceeding those using BQ.⁷ For example, substrates with branching oxygen, carbon, or nitrogen functionality in the homoallylic or bis-homoallylic positions (Table 2, entries 5–8) proceed on average with 16% higher isolated yields and average TON of 14.6 versus average TON of 5.7 when compared to the Pd/bis-sulfoxide **1**/Cr(salen) catalyzed system using BQ as a stoichiometric oxidant.^{7a} Additionally, for substrates where a direct comparison can be made with previously reported aerobic LAA reactions, the same trend in yields and TONs is observed (entries 3 and 4).¹² We also note that higher yielding substrates can be run for 24 h without a significant decrease in yield (entries 3 and 7). The mass balance for these reactions is generally high, with unbranched substrates (e.g., entries 1–3) furnishing predominantly linear *E*-allylic amine (L:B = 20:1, 14:1, and 15:1, respectively) and small quantities of isomerized recovered starting material (entries 1 and 3, 11% and 4%, respectively). Branched substrates (e.g., entry 7) give isomerically pure products and small amounts of recovered starting material as a mixture of isomerized (ca. 10%) and terminal olefin (ca. 9%) (see Supporting Information; Table 2, entry 7).

Unfortunately, the VO(acac)₂ **3** system proved to be less robust, generally providing linear allylic amine products in diminished yields and with significantly lower reproducibility between experiments than the Co system (see Table 2 entry 2 standard deviation, and Supporting Information). Although in several cases yields for the vanadium system were comparable (entries 4, 7, and 8; see also Scheme 4, below) or even exceeded (entry 3) those of the Co system, no clear trend emerged for predicting these observed differences in reaction efficiency (see Supporting Information).

We next investigated the reactivity of the new aerobic LAA system for a variety of activated allylarene substrates (Table 3). Under these conditions, both electron poor and electron rich aromatic rings are well tolerated, furnishing products as one olefin isomer in good to excellent yields (entries 1–3). Additionally, efficient reactivity is observed for highly functionalized, electron rich aromatic systems (entries 4 and 5). Tolerance for medically relevant heterocyclic aromatic functionality is demonstrated in the aerobic LAA of an indole heterocycle (entry 6). In some cases, reactions may be run for 24 h without a significant decrease in yield (entries 4 and 5). We were also pleased to find that often the Pd catalyst loading could be further reduced to 2.5 mol% while still maintaining useful yields of aminated product (entries 1–5). In general, under these aerobic conditions, the yields and TONs are significantly higher than those of the BQ system (entries 4 and 5). When comparing these results with a previous aerobic system, we again observe higher catalyst TONs and product yields (entry 1).¹²

It was previously demonstrated that substrates containing sensitive terminal epoxides and unprotected alcohols may be aminated with the base-promoted LAA reaction in useful yields.^{7b} A potential limitation of this aerobic LAA system, which employs a Lewis-acidic redox cocatalyst, is poor tolerance of highly Lewis basic functionality. Under our optimized aerobic LAA conditions employing the Co-

Table 3. Aromatic Substrates

Entry	Product	Co ^a	BQ or O ₂
1	R = <i>o</i> -OMe	14 96% (69%) ^b	75% ^c
2	R = <i>o</i> -OTBS	15 91% (47%) ^b	-
3	R = <i>p</i> -CF ₃	16 79% (60%) ^b	-
4		17 94% ^d (63%) ^{b,e}	81% ^f
5		18 91% (70%) ^b [69%] ^g	72% ^h
6		19 56%	-
7		(+)-20 68% ⁱ	54% ^f

^a Isolated yield, average of at least 2 runs at 0.4 mmol scale. ^b 2.5 mol% **1** was used. ^c Yield reported in ref. 12; conditions employing 3 equiv. of olefin substrate, 10 mol% Pd, and 6 atm. O₂. ^d Reaction complete at ca. 12 h. ^e Reaction complete after 24 hours. ^f Yield reported in ref. 7b; conditions employing 10 mol% **1**, 2 equiv BQ. ^g Number in brackets is yield after 24 hours with 2.5 mol% of catalyst **1**. ^h Yield reported in ref. 7a; conditions employing 10 mol% **1**, 2 equiv BQ. ⁱ 5 mol% **1**, 6 mol% DIPEA, 1 equiv. 2,5-DMBQ, 0.66M TBME, 2 equiv. TsNHCO₂Me, 45°C, 24h.

(salophen) **2** cocatalyst, we obtained a lower (ca. 30%) yield for a terminal epoxide substrate (Table 3, entry 7). We attribute this diminished reactivity to deleterious side reactions of the terminal epoxide in the presence of the Lewis acidic Co cocatalyst. Analogous Co(salen) complexes are known to catalyze ring opening reactions of terminal epoxides with water.²⁰ Additional attempts to use the VO(acac)₂ system with a similar terminal epoxide substrate led to no significant improvement in yield. We next looked to conditions employing the sterically hindered quinone oxidant 2,5-DMBQ, which had shown equal efficiency to the aerobic conditions at reduced Pd loadings (Table 1, entry 16), and found that C–H amination proceeded in 68% yield after 24 h (Table 3, entry 7). This constitutes a nearly 15% increase in yield relative to stoichiometric BQ conditions run with twice the Pd loading and longer reaction times (72h).^{7b} This result illustrates the complementarity of a bulky, readily available quinone to our aerobic conditions, allowing for efficient amination of substrates containing Lewis-acid-sensitive functionality.

Reactivity with Reduced O₂ Concentrations. We next sought to assess the efficiency of the aerobic LAA conditions under reduced concentrations of O₂ considered beneficial for application of such aerobic chemistry in the synthesis of fine chemicals (Table 4).²¹ The aerobic LAA reaction was evaluated under identical conditions of temperature, pressure and catalyst loadings (45 °C, 1 atm, 5–2.5 mol%), now at the significantly reduced O₂ concentrations found in air.

The aerobic LAA reaction run with air furnished aliphatic and aromatic aminated products with the same isomeric purities while maintaining synthetically useful yields at 1 equiv of substrate and low catalyst loadings. Yields of aminated products were generally diminished relative to those of the analogous system using O₂. Decreasing the catalyst loadings from 5 mol% to 2.5 mol% with aromatic substrates in some cases still allowed for a useful reaction to proceed (Table 4, entries 5–7). These findings demonstrate that the DHBQ/Co(salophen)/O₂ redox-relay is able to remain operative even under reduced concentrations of molecular oxygen. Whereas focused reaction optimization to develop an aerobic LAA reaction using air is an important future goal, it is significant to note that for the majority of substrates run under air, aminated products were generated in comparable yields with higher TONs relative to the LAA reaction using stoichiometric BQ oxidant.⁷

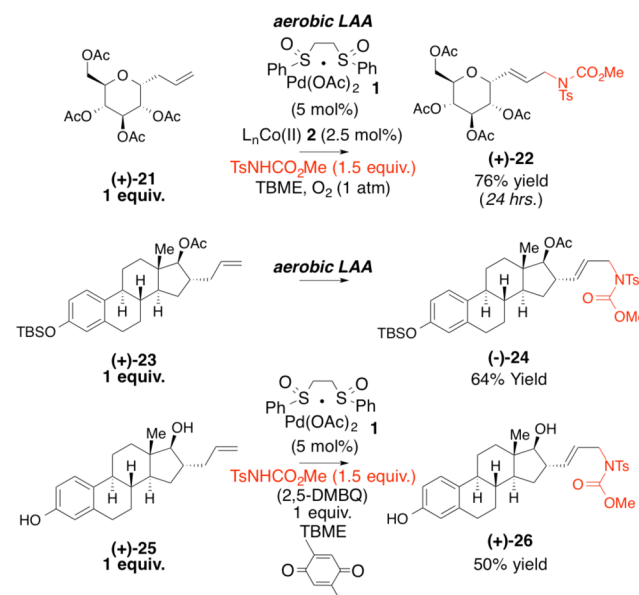
Table 4. Allylic C–H Amination Using Air

Entry	Product	Yield ^a
1		66%
2		52% ^b
3		57%
4		59%
5		62% ^c
6		71% (45%) ^c
7		90% (75%) ^c

^a Isolated yield, average of at least 2 runs at 0.4 mmol scale. ^b 11:1 E/Z
^c 2.5 mol% **1** was used.

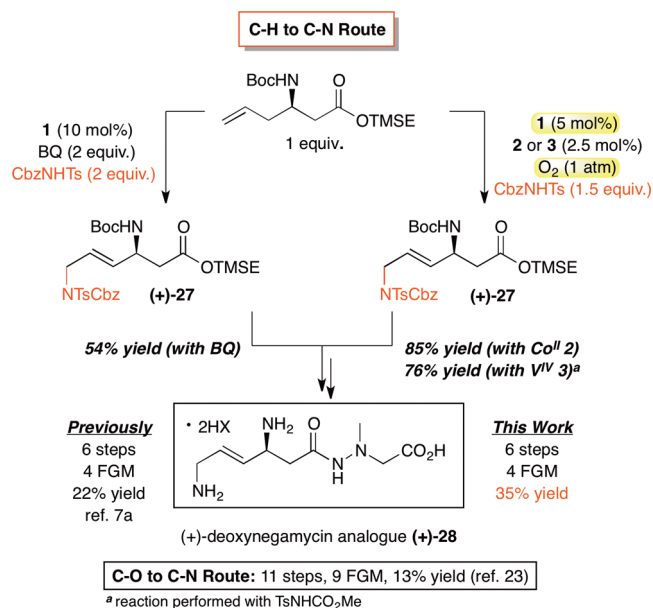
Late-Stage C–H Amination and Streamlining. Late-stage C–H oxidation is a powerful approach for the streamlining and diversification of complex natural products and compounds of medicinal interest.²² With optimal conditions in hand, we sought to evaluate the performance of functionally and topologically complex substrates under our aerobic LAA reaction (Scheme 3). A glucose-derived substrate **21**, bearing an abundance of oxygenated functionality, furnished the corresponding allylic amine **22** in 76% yield as a single diastereomer, after only 24 h.

Scheme 3. Reactivity of Functionally Diverse Substrates



Estrone derivatives were evaluated in both their protected **23** and unprotected forms **25**. When the aerobic LAA reaction was applied to protected estrone derivative **23**, the LAA product **24** was furnished in good yield (64%).^{7b} Based on previous results demonstrating the limited compatibility of Lewis basic functionality under our aerobic LAA conditions, we evaluated **25** under conditions employing 2,5-DMBQ (1 equiv.) as the stoichiometric oxidant. Gratifyingly, these conditions afforded the allylic amine product **26** in 50% yield using only 5 mol% of Pd catalyst.^{7b} These results demonstrate the applicability of these aerobic LAA conditions to afford useful yields of functionalized complex molecules, as well as the increase in reaction efficiency possible under conditions that limit detrimental Pd–quinone interactions.

Scheme 4. Streamlined Synthesis of a Deoxyngamycin Analogue



Given the improved synthetic efficiency of the aerobic LAA reaction with respect to both catalyst loadings and product yields, we sought to re-evaluate the LAA reaction in the context of synthetic streamlining. The LAA reaction has been previously used in the context of a streamlined synthesis of **28**, a rigidified analogue of the antibiotic deoxyneqamycin (Scheme 4).^{7a} This C–H to C–N bond-forming route eliminated five steps, all of which were functional group manipulations, and proceeded with higher overall yield as compared to the previous route based on allylic C–O substitution.^{7a,23} When applying the new aerobic amination conditions to the key C–H amination step of the previous synthesis, we were delighted to find that these optimized conditions afforded a nearly 30% increase in yield of aminated intermediate under Co **2** cocatalysis with 5 mol% of Pd/bis-sulfoxide catalyst **1** (Scheme 4). The increased efficiency of this key C–N bond-forming step now affords a 35% overall yield of deoxyneqamycin analogue **28**, a nearly 3-fold increase in yield as compared to the C–O to C–N route.²³

THE BENZOQUINONE EFFECT

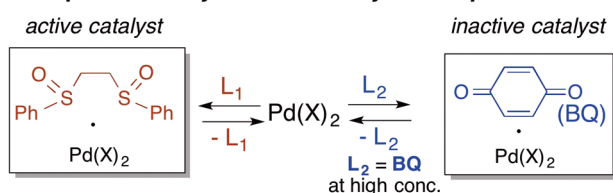
We have demonstrated that the linear allylic amination (LAA) reaction run under aerobic conditions and conditions using bulky quinone terminal oxidants (2,5-DMBQ) lead to both improved product yields and catalyst turnover relative to the previous system relying on stoichiometric BQ as the terminal oxidant. We hypothesized that the mechanistic basis for these differences is that at high concentrations, BQ acts as an inhibitory ligand for this Pd(II)/bis-sulfoxide catalysis (Table SA). As a preliminary evaluation of this, we increased the concentration of BQ under the aerobic reaction conditions and

measured the effect on overall yields. Strikingly, under both Co(salophen) **2** and VO(acac)₂ **3** cocatalysis, a significant diminishment in yield was observed (Table SB, entries 1–3 and 4–6, respectively).

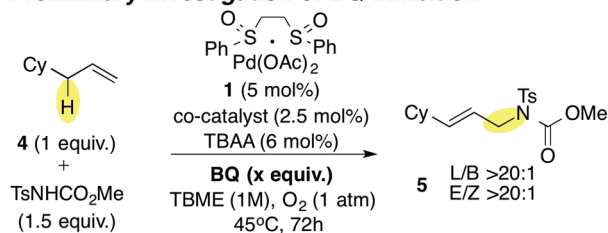
Although stable Pd(0)/BQ complexes are known, Pd(II)/BQ complexes are fleeting and have been proposed as intermediates within catalytic cycles largely based on kinetic studies.²⁴ In the Pd(OAc)₂-catalyzed diacetoxylation of 1,3-dienes using MnO₂ as the stoichiometric oxidant, a linear dependence of reaction rate on BQ concentration supported the hypothesis that BQ acts as a π -acidic ligand for Pd(II) to promote functionalization.^{5a} In order to more definitively demonstrate the inhibitory effect of BQ, we measured the rate of reaction under the aerobic LAA conditions—a scenario where an appreciable accumulation of dihydroquinone is unlikely—in the presence of increasing amounts of BQ. Reaction rates were measured at 5 mol% Pd(II)/bis-sulfoxide **1** while varying the BQ concentration between 0.066 and 0.66 M (10–100 mol% relative to substrate). These experiments were performed in triplicate between 1 and 150 min after initiating the reaction (Figures S3–S8, Supporting Information). A plot of the inverse of the reaction rate at various concentrations of BQ is shown in Figure 1. The LAA reaction rate shows a clear inverse dependence on BQ: a 10-fold increase in [BQ] results in a nearly 9-fold decrease in reaction rate.

Table 5. Effect of Elevated BQ on Reaction Yields

A. Proposed Catalyst Inhibition by Benzoquinone



B. Preliminary Investigation of BQ Inhibition



Entry ^a	co-catalyst	BQ equivalents	Yield of 5 ^b
1	Co(II)(salophen) 2	0.1 equiv.	81%
2	Co(II)(salophen) 2	0.5 equiv.	56%
3	Co(II)(salophen) 2	1 equiv.	50%
4	VO(acac) ₂ 3	0.1 equiv.	70%
5	VO(acac) ₂ 3	0.5 equiv.	40%
6	VO(acac) ₂ 3	1 equiv.	25%

^a Conditions are as listed above unless otherwise noted.

^b Isolated yield; average of two runs at a 0.4 mmol scale.

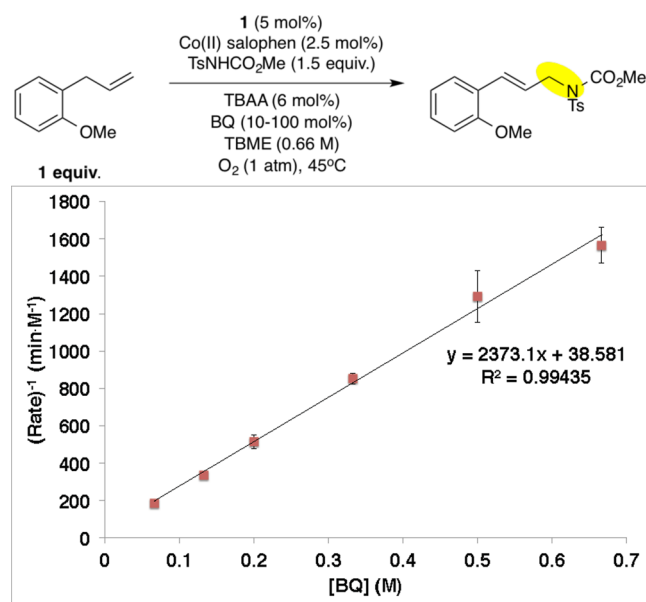


Figure 1. Inverse relationship between rate and BQ concentration.

Collectively, these data indicate that BQ has an inhibitory effect on the LAA reaction at high concentrations. While this is consistent with the hypothesis that interactions of BQ with the Pd(II)/bis-sulfoxide catalyst are detrimental to reaction efficiency, future mechanistic studies will be directed at elucidating the precise mechanism for BQ inhibition.

CONCLUSIONS

We have demonstrated that using an O₂/Co/catalytic dihydroquinone redox relay in combination with our Pd/bis-sulfoxide catalysis enables aerobic linear allylic amination reactions of terminal olefins to proceed at reduced Pd catalyst

loadings and higher reaction efficiency than the previous system relying on stoichiometric BQ. Kinetic experiments show for the first time an inhibitory effect of BQ on Pd(II) oxidative catalysis. Collectively this data implies that for reactions relying on Pd(II) catalysts with weakly coordinating ligands (e.g., bis-sulfoxide) to promote key steps in the catalytic cycle (e.g., C–H cleavage), interactions of BQ when present in high concentrations with the Pd(II) catalyst may be detrimental to reaction efficiency. For such systems, adopting a system which uses molecular oxygen as a stoichiometric oxidant offers not only practical environmental benefits but may also lead to enhanced catalytic efficiency.

EXPERIMENTAL PROCEDURE

General Procedure for the Linear Allylic Amination (LAA) Reaction. To an oven-dried 10 mL round-bottom flask containing a PTFE-covered stir bar was added tetra-*n*-butylammonium acetate in the glovebox, followed by carbamate nucleophile, dihydroquinone, metal cocatalyst, and catalyst **1** on the benchtop. Due to the hygroscopic nature of TBAA, the reaction flask was not opened until all solids were ready to be transferred into the flask. The terminal olefin (preweighed in a 0.5 dram vial) was transferred to the reaction flask using the corresponding solvent (1 M). The flask was then attached to a cold-water condenser, previously purged briefly with oxygen, and equipped with an O₂ balloon. The flask was secured with a Teflon adaptor, sealed with Teflon tape, and the reaction was allowed to stir at 400 rpm in a 45 °C oil bath for 24–72 h or until completed by TLC. Upon completion, a workup with an aqueous solution of 5% K₂CO₃ may be used to remove remaining nucleophile and water-soluble impurities. (*Generally this workup leads to higher purity of isolated products.*) Alternatively, the reaction may be diluted with dichloromethane and flushed through a 3–5 cm silica gel plug with an 80% ethyl acetate/20% hexanes mixture to separate the product from metal catalysts. If no workup is necessary, the reaction mixture may also be directly loaded onto a silica gel column using dichloromethane or toluene. Purification of the products is done using flash column chromatography, in general, with a gradient of 10–30% EtOAc/hexanes. We have also found that 10–30% acetone/hexanes or 10–50% ether/pentane gradients are effective solvent systems for purification.

For reactions run under air, the same general procedure outlined above was employed, the only change being a balloon of air was used. While the reaction condenser may be left opened to air, we have noted rapid and continual loss of the very volatile TBME solvent under this scenario and recommend the use of an air balloon.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11294.

Experimental procedures and characterization data, including Tables S1 and S2, Schemes S1–S3, and Figures S1–S8 (PDF)

¹H and ¹³C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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