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Synergistic Catalysis: Pd(II) Catalyzed Oxidation of 1,4-Dihydroquinones in the Pd(II) Catalyzed 1,4-Oxidation of Cyclic 1,3-Dienes

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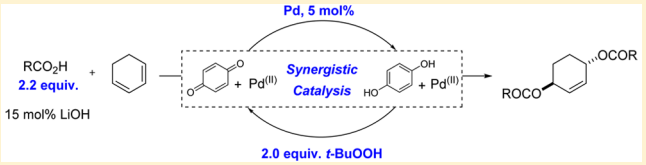
Supporting Information

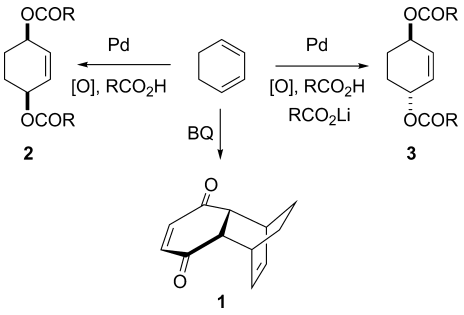
ABSTRACT: Palladium(II) carboxylate salts have been shown to catalyze the oxidation of various hydroquinones to benzoquinones in the presence of *t*-BuOOH. This new catalytic system has been integrated into the oxidative 1,4-functionalization of cyclic 1,3-dienes where the palladium plays a remarkable dual role, catalyzing both the diene oxidation itself and the regeneration of the active quinone oxidant, which is required for diene functionalization. These new conditions offer considerable increases in reaction rate over prior art and allow a significant decrease in the equivalents of the nucleophilic carboxylate required for full conversion.



INTRODUCTION

The stoichiometric, palladium-mediated, 1,4-functionalization of a cyclic diene was first demonstrated by Brown and Davidson in 1971,[1] a discovery which was later thoroughly studied, optimized, and transformed into a catalytic process by Bäckvall (Scheme 1).[2] This reaction has been developed into a highly versatile methodology capable of transforming simple dienes with a range of nucleophilic partners such as carboxylic acids, alcohols, and halogens, into useful 1,4-allylic systems. Importantly, the transformation often proceeds with high π-facial stereocontrol and, in the case of carboxylic acid nucleophiles, can be modified to selectively yield either the *cis*-**2** or *trans*-**3** stereoisomers[3] (Scheme 1). However, two main limitations to the current procedures are (1) the requirement for use of toxic benzoquinone (BQ) and (2) the use of a vast excess of the nucleophile (>8 equiv of the carboxylic acid are generally employed). BQ appears to be a uniquely effective oxidant for this reaction, but unfortunately presents several limitations aside from toxicity and a tendency to sublime. Reaction mixtures tend to be very dark, with a gel-like consistency which complicates workup and isolation of the product. As such, a catalytic system that does not require the handling of stoichiometric quantities of BQ or the necessity of vast excesses of the nucleophilic component would be desirable in further broadening the scope of this powerful transformation.

Scheme 1. Previously Reported Reaction Pathways for Cyclohexadiene (CHD)[2−4]



We previously showed that during the 1,4-functionalization of cyclohexadiene (CHD) with carboxylic acids, the Diels−Alder adduct (DA) **1** (Scheme 1) is formed from CHD and BQ, which is not only an innocent side product of this reaction but also a competent ligand for palladium.[4] In fact, when palladium is ligated with DA adduct **1**, the oxidation proceeds with a significantly increased rate, which is believed to be caused by the reaction entering a cationic pathway (Figure 1). Subsequently, this phenomenon was also suggested by Bäckvall in a related transformation.[5] We considered the possibility that this new, highly reactive pathway may allow alternate oxidants to be employed in lieu of BQ.

While previous work had focused on rendering the reaction catalytic in BQ, through the use of co-oxidants (for example O_2 with catalytic Fe(pc)[6] and superstoichiometric MnO_2[7]), these procedures have inherent problems, such as a requirement for slow addition of the diene, highly dilute reaction conditions, and/or the use of an oxygen atmosphere with organic solvents. Additionally, BQ stoichiometry was only reduced to ca. 25 mol %.

Herein we report our initial efforts in this area, which have resulted in the identification of a new terminal oxidant for this process which markedly reduces the amount of BQ required. Palladium plays a fascinating dual role in this new system, catalyzing both the diene functionalization and the regeneration of the BQ oxidant required for the functionalization. Through

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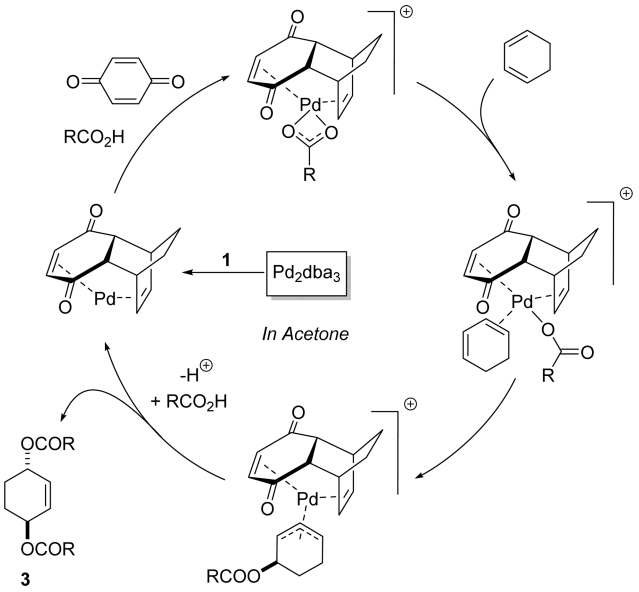


Figure 1. Proposed palladium-ligated catalytic cycle.[4]

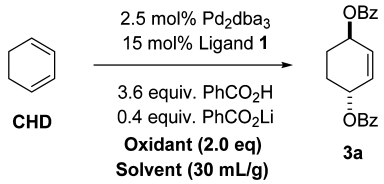
the discovery of a second catalytic cycle, the toxic, volatile benzoquinone can be replaced with the more easily handled hydroquinone (HQ). As a further benefit, this highly reactive system allows for a dramatic reduction in carboxylic acid equivalents (to only a slight excess), which now opens the door for the practical use of more structurally complex acids to be used as nucleophiles.

RESULTS AND DISCUSSION

Before we probed new oxidants for this process, we first focused on optimizing the metal precatalyst. We found the *in situ* complexation of the ligand **1** to Pd(0), using Pd_2dba_3 as a precatalyst, was the optimal method for entering the catalytic cycle (Figure 1); the displaced dba had no observable impact on the transformation. The use of Pd_2dba_3 was more beneficial than the more traditionally employed $Pd(OAc)_2$, as it does not provide a source of AcOH, which is a competing nucleophile when other acids are employed in the oxidation. This proved especially important, as we reduced the concentration of the carboxylate nucleophile to stoichiometric levels (vide infra) where the presence of 10−20 mol % AcOH corresponded to a significant loss of yield. Consistent with previous reports, the reaction was rendered highly *trans*-selective by the simple addition of small amounts (0.4 equiv) of either the corresponding Li-carboxylate or LiOH.[3] With a basic mechanistic understanding in place, a variety of peroxide-based oxidants were screened for reactivity in the *trans*-selective 1,4-dicarboxylation of CHD with benzoic acid under these standard conditions [3.6 equiv of $PhCO_2H$, 0.4 equiv of $PhCO_2Li$, Pd_2dba_3 (2.5 mol %), DA ligand **1** (15 mol %) in acetone], in an attempt to eliminate benzoquinone from the process (Table 1).

Initially, benzoyl peroxide (BPO, 2.0 equiv) was examined, as it has been reported to function as a terminal oxidant in palladium-catalyzed allylic oxidation reactions.[8] However, BPO failed to give appreciable amounts of the product in its anhydrous form, while the 25% wet suspension showed a small amount of conversion (Table 1, entries 1 and 2). A screen of solvents revealed mixtures of alcohols in acetone improved efficiency. Addition of small amounts of EtOH provided a

Table 1. Oxidant and Solvent Optimization



entry	oxidant	solvent	ligand	*trans*/*cis*	yield[a]
1	BPO[b]	acetone	**1**	N.D.	<1%
2	BPO[c]	acetone	**1**	75:25	5%
3	BPO[c]	EtOH/acetone	**1**	91:9	40%
4	*t*-BuOOH	EtOH/acetone	**1**	93:7	51%
5	*t*-BuOOH	EtOH/acetone	none	N.D.	<1%
6	H_2O_2	EtOH/acetone	**1**	88:12	32%
7	$Na_2S_2O_8$	EtOH/acetone	**1**	91:9	28%
8	*t*-BuOOH	EtOH/acetone	**1**/BQ[d]	93:7	71%
9	*t*-BuOOH	IPA/acetone	**1**/BQ[d]	93:7	73%
10	*t*-BuOOH	IPA/acetone	none	92:8	10%
11	*t*-BuOOH	IPA/acetone	**1**/HQ[d]	93:7	72%

[a]In-process yields determined by quantitative HPLC; yield refers the sum of the two isomers. [b]Anhydrous, supported on dicyclohexyl phthalate. [c]25 wt % water. [d]10 mol % **1**, 5 mol % BQ or HQ.

dramatic increase in yield with BPO (from ∼5% to 40%, Table 1, entry 3), with a solvent composition of 75:25 v/v% EtOH/acetone being optimal. While conversion remained modest, it was interesting to note that the *trans*-selectivity remained high.

tert-Butyl hydroperoxide (*t*-BuOOH) provided a modest 51% yield after 24 h, along with maintaining excellent *trans*-selectivity (93:7 *trans*/*cis*, entry 4). Importantly, in the absence of DA ligand **1** no oxidation was observed (entry 5). Other peroxide sources, H_2O_2 or $Na_2S_2O_8$ (previously employed by Dong as an oxidant in C−H activation),[9] gave inferior results (Table 1, entries 6 and 7). Thus, *t*-BuOOH seemed to provide a suitable balance between reactivity and selectivity and thus was chosen for further optimization. While the combination of palladium salts and *t*-BuOOH has been shown to oxidize olefins to epoxides, allylic peroxides, and/or enones,[10] in the present study, the peroxide seems to act predominantly as a terminal oxidant for palladium rather than incorporating oxygen into the substrate.

This new *t*-BuOOH system was slower than the stoichometric quinone-based system,[4] and required approximately 24 h for complete conversion of CHD. Additionally, we observed significant reaction variability, which prompted a comprehensive, systematic evaluation of all the reaction parameters. We succeeded in identifying benzoquinone contamination in the DA ligand **1** as the source of the variability. The deliberate addition of a small amount of benzoquinone (<5 mol %) was found to have a dramatic effect on both reaction rate and overall yield with a 73% yield being obtained in only 5 h at room temperature and with high *trans*-selectivity (93%) (entry 8). A screen of other alcoholic solvents revealed that IPA produced a slight increase in yield, presumably through a reduced potential for product degradation through trans-esterification. MeOH was not effective for this transformation, while *t*-BuOH resulted in a significantly slower reaction. There was some conversion in IPA/acetone in the absence of the Diels−Alder ligand **1** and BQ, though only ∼10% of **3a** was formed in 24 h (entry 10). Interestingly, addition of hydroquinone (HQ) instead of BQ produced almost identical results (entry 11), suggesting that HQ may be oxidized to BQ

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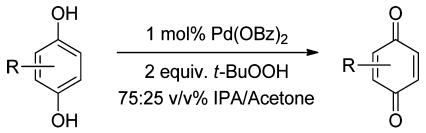
under the reaction conditions. Indeed, HQ conversion to BQ was confirmed by ^{1}H NMR analysis of the crude reaction mixture. Since only 5 mol % HQ is used, we felt that it was possible that a second catalytic cycle was being accessed where HQ is oxidized to BQ by palladium and *t*-BuOOH. We next set out to understand this oxidation.

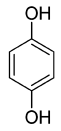
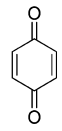
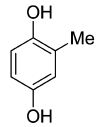
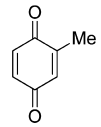
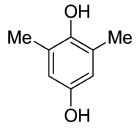
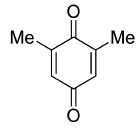
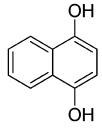
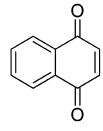
While the oxidation of HQ occurred under the reaction conditions, *t*-BuOOH was inactive in oxidizing HQ alone, only in the presence of Pd(II)-carboxylate [$Pd(OBz)_2$ or $Pd(OAc)_2$] did the oxidation take place; the DA ligand **1** was not necessary. A control experiment, where *t*-BuOOH was omitted and the reaction was left open to air, led to a very slow conversion of HQ to BQ (<3% conversion after 20 h), excluding the possibility of oxygen mediating the transformation. Surprisingly, Pd(II) is not commonly known to catalyze hydroquinone oxidation with peroxides,[11] yet in our hands, $Pd(OBz)_2$ and *t*-BuOOH smoothly oxidize a range of hydroquinones in near-quantitative yield, with a low catalyst loading (Table 2).

Mechanistically, we propose a catalytic cycle outlined in Scheme 2. Initially, a heteroleptic palladium peroxo-carboxylate is formed through the *t*-BuOOH displacement of one of the carboxylate ligands from $(RCO_2)Pd$. Complexes such as these were isolated by Mimoun and Weiss and, relevant to this work, shown to be competent oxidizing π-systems.[12] After hydroquinone binding to palladium, followed by proton transfer and elimination of water, BQ and *t*-BuOH are released, all *without* redox of the metal center. Similar mechanisms have been suggested for Wacker oxidations mediated by *t*-BuOOH.[13] This catalyst system is extremely mild and can be performed in a preparative sense. Thus, a range of hydroquinones are smoothly oxidized to their corresponding benzoquinones with *t*-BuOOH and just 1 mol % $Pd(OBz)_2$ in IPA/acetone (Table 2).

Table 2. Oxidation of Hydroquinones with *t*-BuOOH/$Pd(OBz)_2$

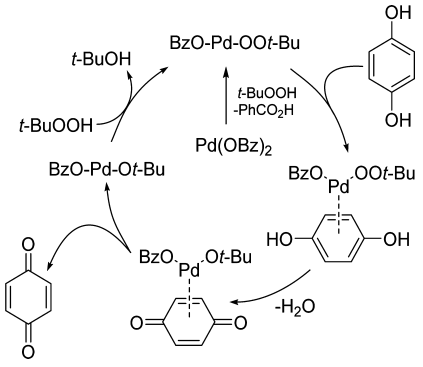


4 5

Entry	Hydroquinone	Benzoquinone	Conversion[a] (Isolated yield)[b]
1	 HQ	 BQ	>95% (62%)[c]
2	 4a	 5a	99% (61%)[c]
3	 4b	 5b	94% (78%)[c]
4	 4c	 5c	98% (95%)

[a]Conversion determined by ^{1}H NMR. [b]Recrystallized from water (8–10 mL/g). [c]Yields low due to volatility.

Scheme 2. Proposed Mechanism for the Oxidation of HQ to BQ



After studying the HQ to BQ catalytic cycle, we focused our attention back to the oxidative functionalization of dienes. Initial order dependencies of this new system indicated an apparent zero-order dependence on carboxylic acid concentration (see Supporting Information); this is in contrast to the initial conditions[4] which demonstrated first-order dependence on the acid nucleophile. Thus, reduction in the concentration of the nucleophilic component could easily be achieved without impacting rate; 2.2 equiv (only a 0.2 equiv excess) could be used with minimal impact on yield or selectivity. Concurrently, a reduction in the amount of LiOH was required to prevent partial hydrolysis of the product. The final optimized conditions were 2.5 mol % Pd_2dba_3, 10 mol % **1**, 5 mol % HQ, 2.2 equiv of BzOH, and 2.0 equiv of *t*-BuOOH in 75:25 v/v% IPA/acetone at 25 °C.

With these new conditions in hand, a survey of cyclic dienes was investigated (Table 3). Cyclopentadiene (**6**) failed to react under these conditions, and interestingly, no HQ-to-BQ oxidation occurred in the presence of **6**. Deliberate addition of 10 mol % **6** to a standard CHD reaction did not affect the reaction in any way, suggesting the inactivity of **6** is not related to catalyst inhibition. However, dicyclopentadiene was observed indicating that **6** undergoes Diels–Alder homodimerization faster than the 1,4-difunctionalization. Conversely, 1,3-cycloheptadiene (**7**) smoothly underwent oxidation, to give the *cis*-isomer **8** with an 80:20 (*cis*/*trans*) ratio in good overall yield (65%, entry 4), though elevated temperatures (40–45 °C) were needed to achieve reasonable reaction rates. The preference for *cis*-stereochemistry in the oxidation of **7** has been described previously.[14] 1,3-Cyclooctadiene (**9**) was unreactive even at elevated temperatures. Interestingly, attempts to carry out a *cis*-selective oxidation of CHD by conducting the reaction in the absence of LiOH failed to yield product under these conditions, in sharp contrast to the stoichiometric benzoquinone conditions (entry 3). However, addition of 0.3 equiv of LiCl to the reaction mixture did predominately afford the *cis*-product (87:13), consistent with prior work,[3] though with poor conversion (2%). The *trans*-

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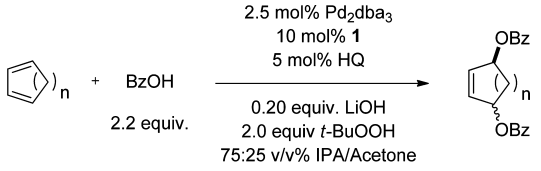
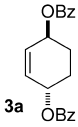
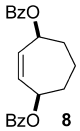
Table 3. A Survey of Dienes



Entry	Diene	Product	*Trans/Cis*	Yield
1	 **6**	*N.R.*	*N.D.*	*N.R.*
2	 **CHD**	 **3a**	93/7	73%
3[a]	**CHD**	**3a**	87/13	70%
4[b]	 **7**	 **8**	20/80	65%
5	 **9**	*N.R.*	*N.D.*	*N.R.*

[a]Reaction without addtion of LiOH. [b]Reaction carried out at 45 °C.

selectivity and lack of order dependence in acid suggest a different mechanism predominates under these new conditions.

A proposed catalytic cycle is shown (Scheme 3); our data suggest that the Pd plays a very unusual dual role, *catalyzing both product formation and production of its own reoxidant*. Based on the evidence so far obtained, we propose that the role of the BQ is to act as an oxidation state transporter—from peroxide to palladium. Again, a control experiment performed in air without *t*-BuOOH afforded very low levels of product (2%, 85:15 *trans*/*cis*) after 20 h. The *trans*-product **3**, observed in this study, is generally thought to form from an intramolecular S_N2'-like reductive elimination of a resident η_1-bound Pd-allyl species (Scheme 3).[15]

The reduced acid concentrations achieved with these conditions (a nearly stoichiometric 2.2 equiv) enable the economical use of a wider range of carboxylic acids and opens the possibility of using chiral acids to effect doubly diastereoselective additions. Thus, a range of complex, chiral acids were utilized, each providing good yields of the addition adduct (Table 4). In this preliminary exploration, little to no diastereoselectivity was observed with respect to the forming stereogenic centers. Despite this lack of selectivity, further exploration of chiral palladium systems is warranted as the product 1,4-dicarboxylates are extremely valuable synthons.

SUMMARY

In summary we have expanded the conditions for the oxidation of cyclic dienes to 1,4-dicarboxylated-alk-2-enes utilizing ligand **1**. These new reaction conditions proceed rapidly and afford products in good yields. By studying the kinetics of this new system, the concentration of the carboxylic acid was dramatically reduced, allowing a wider range of complex carboxylic acids to be used in this chemistry. Additionally, through the discovery of a second palladium-catalyzed cycle where hydroquinones can be oxidized to benzoquinones with *t*-BuOOH, the BQ oxidant can be significantly reduced, and even replaced, with HQ, resulting in a fascinating transformation where Pd bridges two symbiotic catalytic processes.

EXPERIMENTAL SECTION

General. Solvents and reagents were used without further purification unless otherwise indicated. ^{1}H NMR spectra were recorded at 500 MHz using respective solvent as an internal standard. ^{13}C NMR spectra were proton-decoupled and recorded at 126 MHz using the respective solvent as an internal standard. Mass spectrometery was obtained with a hybrid quadrupole-Orbitrap mass spectrometer. The *trans*/*cis* ratios were determined by reversed-phase HPLC analysis running the following methods: Method A: Using a Phenomenex Kinetex C18 (2.6 μm, 4.6 mm × 150 mm) column at a flow rate of 1.0 mL/min and a 220 nm detector wavelength. The mobile phases consisted of (A) 0.01 M NH_4OAc in 5:95 v/v% CH_3CN/water and (B) 0.01 M NH_4OAc in 95:5 v/v% CH_3CN/water. A gradient of t = 0 min, 20% B, t = 5 min, 50% B, t = 20 min, 70% B, t = 25 min 100% B, t = 30 min, 100% B was used. Method B: Using a

Scheme 3. Proposed Catalytic Cycle for the Oxidation of Cyclic Dienes by *t*-BuOOH/Pd with BQ-Based Oxidation Transport

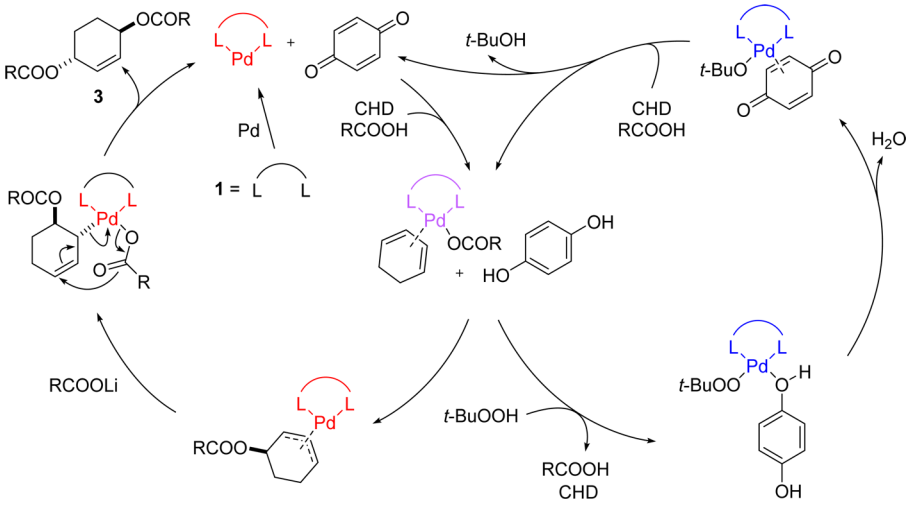


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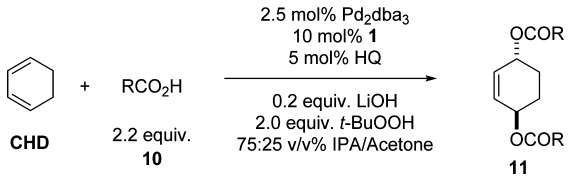
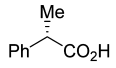
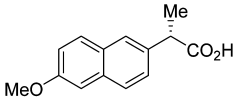
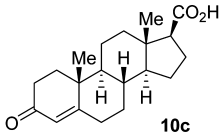
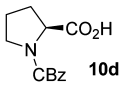
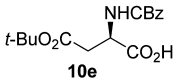
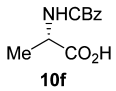
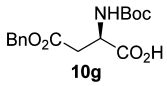
Table 4. Use of More Complex Acids



Entry	Acid	*Trans/Cis*	*Trans* d.r.	Yield[a]
1	 **10a**	91:9	57:43	79%
2	 **10b**	88:12	50:50	82%[b]
3	 **10c**	89:11	54:46	51%[b]
4	 **10d**	91:9	51:49	86%
5	 **10e**	87:13	50:50	92%
6	 **10f**	85:15	51:49	90%
7	 **10g**	89:11	53:47	89%

[a]Reactions were typically quneched in 18−24 h, unless specified. [b]Reaction time 48 h.

Zorbax Eclipse Plus C18 (1.8 μm, 4.6 mm × 50 mm) column at a flow rate of 1.2 mL/min and a 220 nm detector wavelength. The mobile phases consisted of (A) 0.05% TFA in 5:95 v/v% CH_3CN/water and (B) 0.05% TFA in 95:5 v/v% CH_3CN/water. A gradient of t = 0 min, 15% B, t = 13 min, 100% B, t = 15 min, 100% B was used. The diastereomeric ratios for Table 4 were determined by normal phase HPLC analysis using a Chiralpak IA (5 μm, 4.6 mm × 250 mm) column at a 1.0 mL/min flow rate and a 220 nm detector wavelength. The mobile phases consisted of (A) heptanes and (B) 50:50 v/v% methanol/ethanol. A gradient of t = 0 min, 30% B, t = 15 min, 60% B, t = 20 min, 60% B was used. Column chromatography was performed with 230−400 mesh silica gel. All reported yields are isolated yields unless specified otherwise.

Quinone Oxidations. *p-Benzoquinone (**BQ**).* Hydroquinone (**HQ**, 1.0 g, 9.1 mmol) and $Pd(OBz)_2$ (32 mg, 0.09 mmol, 1.0 mol %) were dissolved in a 75:25 v/v% IPA/acetone (15 mL, 15 mL/g **HQ**) solution. A 70 wt % aqueous solution of *t*-BuOOH (2.3 g, 18 mmol, 2.0 equiv) was added, and the mixture was stirred at room temperature. After 5 h the reaction was judged complete by NMR. The mixture was concentrated *in vacuo*; the resulting yellow crystals were pure by proton NMR analysis. The material was recrystallized from hot water (8 mL/g) to give large needles, which were chilled and dried under vacuum to afford the quinone **BQ** (0.62 g, 5.7 mmol, 62%). Its spectra data were identical to those reported in literature.[16]

*2-Methyl-1,4-benzoquinone (**5a**).* 2-Methylbenzene-1,4-diol (**4a**, 1.0 g, 8.1 mmol) was used, and the procedure for **BQ** was followed (reaction time 48 h) to provide the benzoquinone **4a** (0.60 g, 4.9 mmol, 61%). Its spectra data were identical to those reported in literature.[17]

*2,6-Dimethyl-1,4-benzoquinone (**5b**).* 2,6-Dimethylbenzene-1,4-diol (**4b**, 1.11 g, 8.03 mmol) was used, and the procedure for **BQ** was followed (reaction time 48 h) to provide the benzoquinone **5b** (0.86 g, 6.3 mmol, 78%). Its spectra data were identical to those reported in literature.[18]

*Naphthalene-1,4-dione (**5c**).* Naphthalene-1,4-diol (**4c**, 1.29 g, 8.05 mmol) was used, and the procedure for **BQ** was followed (reaction time 48 h) to provide the benzoquinone **5c** (1.21 g, 7.65 mmol, 95%). Its spectra data were identical to those reported in literature.[19]

Diene Oxidation; General Conditions. To a vial were added Pd_2dba_3 (2.5 mol %), DA ligand **1** (10 mol %), hydroquinone (5 mol %), $PhCO_2H$ (2.2 equiv), and $LiOH{\cdot}H_2O$ (0.20 equiv). A 75:25 v/v% IPA/acetone (30 mL/g based on diene) solution was added, and the mixture was stirred 30 min at room temperature. A 70 wt % aqueous solution of *t*-BuOOH (2 equiv) and freshly distilled diene (1 equiv) were added. Once the reaction was complete, the solvent was removed under vacuum and the residue dissolved in MTBE (20 mL/g) and washed with 1 N NaOH (3 × 20 mL/g), dried over $MgSO_4$, and concentrated *in vacuo*. The product was then purified by column chromatography.

Experimental Table 3. *trans-Cyclohex-2-ene-1,4-diyl Dibenzoate (**3a**).* To a vial were added Pd_2dba_3 (57 mg, 0.062 mmol, 2.5 mol %), DA ligand **1** (47 mg, 0.25 mmol, 10 mol %), hydroquinone (14 mg, 0.125 mmol, 5 mol %), benzoic acid (670 mg, 5.5 mmol, 2.2 equiv), and LiOH hydrate (21 mg, 0.50 mmol, 0.20 equiv). A 75:25 v/v% IPA/acetone (6.0 mL) solution was added, and the mixture was stirred for 30 min at room temperature. After stirring for 30 min at room temperature, *t*-BuOOH (70 wt % aqueous solution, 643 mg, 5.0 mmol, 2.0 equiv) and freshly distilled cyclohexa-1,3-diene (200 mg, 2.5 mmol, 1.0 equiv) were added. After 16 h, the solvent was concentrated *in vacuo* and the residue was dissolved in MTBE (20 mL), washed with a 1 N NaOH (3 × 4 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate/hexanes eluent) to afford 582 mg (73% yield) of a mixture of the *trans/cis* products (HPLC ratio 97:3) whose spectra data were identical to those reported in literature.[20]

*cis-Cyclohept-2-ene-1,4-diyl Dibenzoate (**8**).* Following the procedure for **3a** using cyclohepta-1,3-diene (7, 235 mg, 2.5 mmol, 1.0 equiv) at 45 °C provided 545 mg (65% yield) of a mixture of the *trans/cis* products (ratio 20:80; Waters Eclipse Plus C18 column, 0.05% TFA/MeCN/water). The *cis*-isomer can be isolated by flash column chromatography (eluent 5% ethyl acetate/heptane), and its spectra data were identical to those reported in literature.[20]

Experimental Table 4. *(2S,2′S)-Cyclohex-2-ene-1,4-diyl Bis(2-phenylpropanoate) (**11a**).* To a vial were added Pd_2dba_3 (28 mg, 0.031 mmol, 2.5 mol %), DA ligand **1** (23 mg, 0.125 mmol, 10 mol %), hydroquinone (6.7 mg, 0.062 mmol, 5 mol %), (*S*)-2-Phenylpropionic acid (**10a**, 412 mg, 2.75 mmol, 2.2 equiv), and anhydrous LiOH (6.0 mg, 0.25 mmol, 0.20 equiv). A 75:25 v/v% IPA/acetone (3.0 mL) solution was added, and the mixture was stirred for 30 min at room temperature. After stirring for 30 min at room temperature, *t*-BuOOH (70 wt % aqueous solution, 321 mg, 2.5 mmol, 2.0 equiv) and freshly distilled cyclohexa-1,3-diene (100 mg, 1.25 mmol, 1.0 equiv) were added. After 24 h, the solvent was concentrated *in vacuo* and the residue was dissolved in MTBE (20 mL), washed with a 10 wt % aqueous K_3PO_4 solution (3 × 10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (acetone/hexanes eluent) to afford 371 mg (79% yield) of the diastereomeric products (^{1}H NMR ratio 57:43). ^{1}H NMR ($CDCl_3$): δ 7.43−7.22 (m, 10H), 5.90 (s, 1H), 5.72 (s, 1H), 5.28 (br. s., 2H), 3.77−3.64 (m, 2H), 2.09 (d, J = 7.9 Hz, 1H), 1.89 (d, J = 9.0 Hz, 1H), 1.68 (d, J = 8.4 Hz, 1H), 1.56−1.44 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 174.0, 174.0, 140.4, 140.4, 130.2, 130.0, 128.6, 127.4, 127.4, 127.1, 67.9, 67.5, 45.6, 45.5, 25.7, 25.1, 18.5, 18.4. HR MS (ESI) calcd for $C_{24}H_{30}NO_4$ $[M+NH_4]^+$, 396.2169; found, 396.2168. The

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trans/cis ratio was determined to be 91:9 (Waters Eclipse Plus C18 column, 0.05% TFA/MeCN/water).

*(2S,2′S)-Cyclohex-2-ene-1,4-diyl Bis(2-(6-methoxynaphthalen-2-yl)propanoate) (**11b**).* Following the procedure for **11a** using (*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid (**10b**, 316 mg, 1.37 mmol, 2.2 equiv) provided 275 mg (82% yield) of the diastereomeric products (^{1}H NMR ratio 50:50). ^{1}H NMR ($CDCl_3$): δ 7.73−7.62 (m, 6H), 7.38 (t, J = 7.4 Hz, 2H), 7.18−7.07 (m, 4H), 5.89 (s, 1H), 5.67 (s, 1H), 5.27 (d, J = 11.0 Hz, 2H), 3.92 (s, 6H), 3.86−3.78 (m, 2H), 2.08 (d, J = 6.6 Hz, 1H), 1.86 (d, J = 8.9 Hz, 1H), 1.69−1.63 (m, 1H), 1.55 (d, J = 6.9 Hz, 3H), 1.56 (d, J = 6.9 Hz, 3H), 1.45 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 174.2, 174.1, 157.6, 135.6, 135.5, 133.6, 133.6, 130.2, 130.0, 129.2, 129.2, 128.9, 127.1, 126.1, 126.1, 125.9, 125.8, 119.0, 118.9, 105.5, 67.9, 67.6, 55.3, 45.5, 45.5, 25.7, 25.1, 18.5, 18.4. HR MS (ESI) calcd for $C_{34}H_{38}NO_6$ $[M+NH_4]^+$, 556.2694; found, 556.2690. The *trans/cis* ratio was determined to be 88:12 (Waters Eclipse Plus C18 column, 0.05% TFA/MeCN/water).

*(8S,8′S,9S,9′S,10R,10′R,13S,13′S,14S,14′S,17S,17′S)-Cyclohex-2-ene-1,4-diyl Bis(10,13-dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,-14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrene-17-carboxylate) (**11c**).* Following the procedure for **11a** using 3-oxo-4-androstene-17β-carboxylic acid (**10c**, 218 mg, 1.37 mmol, 2.2 equiv) provided 113 mg (51% yield) of the diastereomeric products (^{1}H NMR ratio 54:46). ^{1}H NMR ($CDCl_3$): δ 5.92 (s, 1H), 5.90 (s, 1H), 5.74 (s, 2H), 5.38 (m, 1H), 5.32 (m, 1H), 2.47−2.26 (m, 10H), 2.20−2.08 (m, 4H), 2.08−1.97 (m, 4H), 1.89−1.76 (m, 2H), 1.75−1.64 (m, 6H), 1.60−1.51 (m, 2H), 1.49−1.37 (m, 2H), 1.35−1.24 (m, 6H), 1.19 (s, 6H), 1.16−1.05 (m, 3H), 1.03−0.94 (m, 2H), 0.89 (t, J = 6.9 Hz, 1H), 0.72 (d, J = 3.4 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 199.5, 173.4, 173.4, 171.0, 171.0, 130.4, 130.2, 123.9, 67.1, 67.0, 64.9, 55.4, 55.1, 55.1, 53.7, 53.7, 44.0, 44.0, 38.6, 38.2, 38.2, 35.7, 34.8, 33.9, 32.8, 31.9, 29.6, 29.6, 29.3, 29.2, 28.6, 27.0, 26.1, 25.9, 25.6, 24.4, 23.5, 23.4, 22.7, 20.9, 17.4, 14.1, 13.5, 13.4. HR MS (ESI) calcd for $C_{46}H_{66}NO_6$ $[M+NH_4]^+$, 728.4890; found, 728.4882. The *trans/cis* ratio was determined to be 89:11 (Waters Eclipse Plus C18 column, 0.05% TFA/MeCN/water).

*(2S,2′S)-1-Dibenzyl O′^{2},O^2-(Cyclohex-2-ene-1,4-diyl) Bis(pyrrolidine-1,2-dicarboxylate) (**11d**).* Following the procedure for **11a** using (*S*)-1-((benzyloxy)carbonyl)pyrrolidine-2-carboxylic acid (**10d**, 342 mg, 1.37 mmol, 2.2 equiv) provided 309 mg (86% yield) of the diastereomeric products (HPLC ratio 51:49). ^{1}H NMR ($CDCl_3$): δ 7.42−7.26 (m, 10H), 5.96−5.81 (m, 1H), 5.76−5.60 (m, 1H), 5.38−5.26 (m, 1H), 5.23−5.09 (m, 4H), 5.09−4.99 (m, 1H), 4.42−4.27 (m, 2H),3.69−3.57 (m, 2H), 3.58−3.42 (m, 2H), 2.32−2.17 (m, 2H), 2.08−1.82 (m, 8H), 1.76−1.32 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 172.2, 172.0, 172.0, 154.8, 154.7, 154.1, 136.6, 136.4, 136.3, 130.1, 130.1, 130.0, 129.9, 129.8, 128.4, 128.3, 128.0, 127.9, 127.8, 127.8, 68.1, 68.0, 68.0, 68.0, 67.9, 67.8, 67.0, 66.9, 66.9, 59.3, 59.3, 59.3, 59.2, 58.9, 58.8, 46.9, 46.4, 30.9, 29.9, 29.8, 25.4, 25.3, 25.2, 25.1, 24.2, 23.4. HR MS (ESI) calcd for $C_{32}H_{40}N_3O_8$ $[M+NH_4]^+$, 594.2810; found, 594.2797. The *trans/cis* ratio was determined to be 91:9 (Phenomenex Kinetex C18 column, 0.01 M NH_4OAc/MeCN/water), and the diastereoisomeric ratio, to be 51:49 (Chiralpak IA column, heptanes/EtOH−MeOH).

*(2R,2′R)-4-Di-tert-butyl O′^{1},O^1-(Cyclohex-2-ene-1,4-diyl) Bis(2-(((benzyloxy)carbonyl)amino)succinate) (**11e**).* Following the procedure for **11a** using (*R*)-2-(((benzyloxy)carbonyl)amino)-4-(*tert*-butoxy)-4-oxobutanoic acid hydrate (**10e**, 469 mg, 1.37 mmol, 2.2 equiv) provided 416 mg (92% yield) of the diastereomeric products (HPLC ratio 50:50). ^{1}H NMR ($CDCl_3$): δ 7.37−7.30 (m, 10H), 5.91−5.83 (m, 2H), 5.77 (d, J = 8.5 Hz, 2H), 5.36 (br. s., 2H), 5.13 (s, 4H), 4.61−4.51 (m, 2H), 2.99−2.87 (m, 2H), 2.81−2.68 (m, 2H), 2.15−2.03 (m, 2H), 1.74−1.63 (m, 2H), 1.42 (s, 18H). ^{13}C NMR ($CDCl_3$): δ 170.4, 170.3, 169.9, 169.9, 155.9, 136.1, 130.0, 129.9, 128.5, 128.1, 128.0, 81.8, 81.7, 68.8, 68.5, 67.0, 50.5, 37.6, 27.9, 25.3, 25.1. HR MS (ESI) calcd for $C_{38}H_{52}N_3O_{12}$ $[M + NH_4]^+$, 742.3546; found, 742.3533. The *trans/cis* ratio was determined to be 87:13 (Phenomenex Kinetex C18 column, 0.01 M NH_4OAc/MeCN/water), and the diastereoisomeric ratio, to be 50:50 (Chiralpak IA column, heptanes/EtOH−MeOH).

*(2S,2′S)-Cyclohex-2-ene-1,4-diyl Bis(2-(((benzyloxy)carbonyl)-amino)propanoate) (**11f**).* Following the procedure for **11a** using (*S*)-2-(((benzyloxy)carbonyl)amino)propanoic acid (**10f**, 307 mg, 1.37 mmol, 2.2 equiv) provided 301 mg (90% yield) of the diastereomeric products (HPLC ratio 51:49). ^{1}H NMR ($CDCl_3$): δ 7.45−7.29 (m, 10H), 5.90 (d, J = 16.8 Hz, 2H), 5.37−5.26 (m, 4H), 5.12 (br. s., 4H), 4.44−4.20 (m, 2H), 2.18−1.93 (m, 2H), 1.70−1.66 (m, 2H), 1.42 (s, 3H), 1.41 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 172.5, 155.5, 136.2, 130.1, 130.0, 128.5, 128.2, 128.1, 68.4, 66.9, 49.7, 25.3, 18.5. HR MS (ESI) calcd for $C_{28}H_{36}N_3O_8$ $[M+NH_4]^+$, 542.2497; found, 542.2492. The *trans/cis* ratio was determined to be 85:15 (Phenomenex Kinetex C18 column, 0.01 M NH_4OAc/MeCN/water), and the diastereoisomeric ratio, to be 51:49 (Chiralpak IA column, heptanes/EtOH−MeOH).

*(2R,2′R)-4-Dibenzyl O′^{1},O^1-(Cyclohex-2-ene-1,4-diyl) Bis(2-((tert-butoxycarbonyl)amino)succinate) (**11g**).* Following the procedure for **11a** using (*R*)-4-(benzyloxy)-2-((*tert*-butoxycarbonyl)amino)-4-oxobutanoic acid (**10g**, 445 mg, 1.37 mmol, 2.2 equiv) provided 403 mg (89% yield) of the diastereomeric products (HPLC ratio 53:47). ^{1}H NMR ($CDCl_3$): δ 7.44−7.29 (m, 10H), 5.84 (s, 1H), 5.71 (s, 1H), 5.46 (d, J = 8.2 Hz, 2H), 5.29 (br. s., 2H), 5.13 (m, 4H), 4.60−4.49 (m, 2H), 3.09−2.98 (m, 2H), 2.93−2.83 (m, 2H), 2.12−2.01 (m, 1H), 1.96−1.85 (m, 1H), 1.73−1.63 (m, 1H), 1.53−1.48 (m, 1H), 1.45 (s, 18H). ^{13}C NMR ($CDCl_3$): δ 170.8, 170.5, 155.4, 135.3, 129.9, 128.6, 128.5, 128.5, 128.4, 128.3, 80.2, 68.8, 66.8, 50.1, 36.8, 28.3, 25.4, 25.1. HR MS (ESI) calcd. for $C_{38}H_{52}N_3O_{12}$ $[M+NH_4]^+$, 742.3546; found, 742.3539. The *trans/cis* ratio was determined to be 89:11 (Phenomenex Kinetex C18 column, 0.01 M NH_4OAc/MeCN/water), and the diastereoisomeric ratio was found to be 53:47 (Chiralpak IA column, heptanes/EtOH−MeOH).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publication Web site at DOI: XX . The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02769.

Rate study with variable carboxylic acid concentration; ^{1}H NMR, ^{13}C NMR, and HPLC spectra (PDF)

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Notes

The authors declare no competing financial interest.

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