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Controlling the Catalytic Aerobic Oxidation of Phenols

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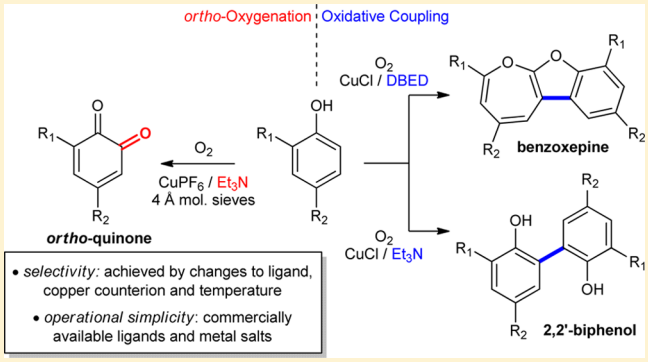
Supporting Information

ABSTRACT: The oxidation of phenols is the subject of extensive investigation, but there are few catalytic aerobic examples that are chemo- and regioselective. Here we describe conditions for the *ortho*-oxygenation or oxidative coupling of phenols under copper (Cu)-catalyzed aerobic conditions that give rise to *ortho*-quinones, biphenols or benzoxepines. We demonstrate that each product class can be accessed selectively by the appropriate choice of Cu(I) salt, amine ligand, desiccant and reaction temperature. In addition, we evaluate the effects of substituents on the phenol and demonstrate their influence on selectivity between *ortho*-oxygenation and oxidative coupling pathways. These results create an important precedent of catalyst control in the catalytic aerobic oxidation of phenols and set the stage for future development of catalytic systems and mechanistic investigations.



INTRODUCTION

Catalytic aerobic oxidations of phenols mediated by metalloenzymes give rise to structurally diverse natural products and biomaterials that are fundamental for life.[1] Their efficiency motivates considerable efforts to develop enzyme mimics[2] with the goal of providing general catalytic aerobic methods for chemical synthesis.[3] Despite extensive efforts, few synthetic catalysts can catalyze the chemo- and regioselective aerobic oxidation of phenols.[1a,4−7] This limitation is due, in part, to the facile autoxidation of phenols to phenoxyl radicals (Scheme 1a), which affords mixtures of products resulting from nonselective C−C coupling.[1a,4,6,8] As a result, the overwhelming majority of phenolic oxidations currently used in synthesis employ terminal oxidants other than O_2[9] but only at the expense of decreased atom- and step-efficiency.

Metalloenzymes avoid the formation of phenoxyl radicals by confining O_2 activation and substrate oxidation to the inner coordination sphere of the metalloprotein active site.[4] This has been discussed extensively in the context of the dinuclear Cu-enzyme tyrosinase,[10] which catalyzes the selective *ortho*-oxygenation of phenols to *ortho*-quinones. Numerous attempts to mimic tyrosinase have provided considerable insight into the intricate chemistry of Cu and O_2,[11] but translating these fundamental studies to catalytic reactions has proven difficult.[10b] With few exceptions,[7,12] catalytic aerobic oxidations are not selective for *ortho*-oxygenation, and provide instead complex product mixtures resulting from competitive oxidative coupling.[13] While these pathways are frequently distinguished as being inner- versus outer-sphere oxidations,[10b,14] experimental evidence supporting either pathway under catalytic conditions is limited, and the factors that govern selectivity between them remain poorly understood.

Herein, we address these challenges, and describe catalytic conditions that are completely selective for either *ortho*-oxygenation or oxidative coupling. We highlight the effects of ligand, Cu counterion, and desiccant on selectivity, and demonstrate that subtle electronic changes to the substrate have a pronounced impact on the course of the reaction. We provide preliminary mechanistic evidence to support an inner-sphere mechanism for *ortho*-oxygenation and a radical-based mechanism for oxidative coupling, and establish a precedent of catalyst control upon which to base future studies.

RESULTS AND DISCUSSION

Controlling Selectivity between *ortho*-Oxygenation and Oxidative Coupling. We recently reported that $[Cu(CH_3CN)_4](PF_6)$ (abbreviated $CuPF_6$) and *N*,*N*′-di-*tert*-butyl-ethylenediamine (DBED) mediate a catalytic aerobic *ortho*-oxygenation of 4-*tert*-butyl phenol (**1**) via Cu-semiquinone radical **SQ** (Scheme 2).[7,15] With monosubstituted phenols, oxygenation is accompanied by oxidative coupling, and substituted *ortho*-quinone **3** is obtained in high yield. In stark contrast, when identical reaction conditions are applied to the more sterically encumbered and electron rich phenol **2**, *ortho*-oxygenation does not occur, and a complete change in selectivity is observed for benzoxepine **4** (Scheme 2). The formation of **4** is consistent with an oxidative dimerization of **2** to biphenol **6** via phenoxyl radical **5**,[13c,14] followed by subsequent oxidation and isomerization.[16] This complete change in selectivity from *ortho*-oxygenation to oxidative coupling highlights the challenges of catalyzing the catalytic aerobic oxidation of phenols, which is distinct from the more

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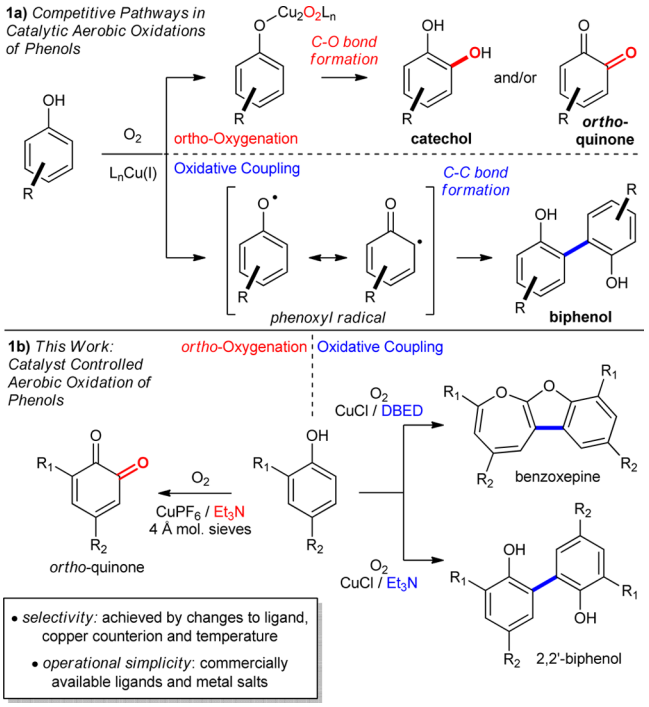
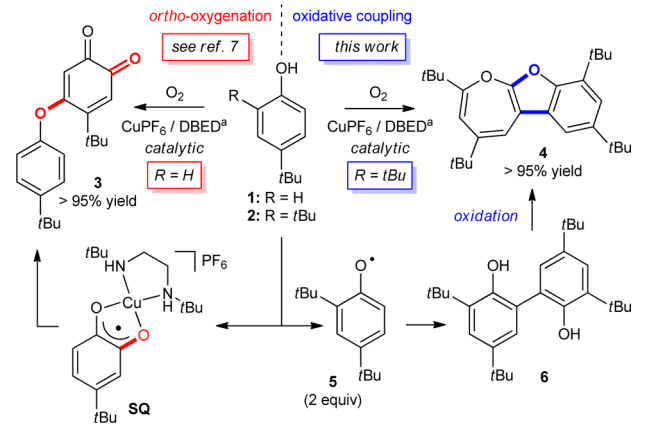
Scheme 1. (a) Competitive Pathways for the Aerobic Oxidation of Phenols; (b) Catalyst Controlled Aerobic Oxidation, Allowing Selective Synthesis of *ortho*-Quinone, Biphenol, and Benzoxepine Products



Scheme 2. Changes in the Selectivity of Catalytic Aerobic Oxygenations of 1 and 2[a]



[a]Reagents and conditions: O_2 (1 atm overpressure), [$CuPF_6$] (4 mol %), DBED (5 mol %), CH_2Cl_2 (0.1 M), 23 °C.

widely studied stoichiometric oxidation of metal phenolates with preformed Cu_2/O_2 complexes.[10b] In the case of **2**, Stack and co-workers have demonstrated that stoichiometric oxygenation of its metal phenolate with a preformed DBED−Cu_2/O_2 complex at low temperature affords a mixture of the corresponding *ortho*-quinone and catechol, and under these conditions, they do not report the formation of the corresponding biphenol or benzoxepine.[10b,17] In contrast, Tuczek and co-workers report significant quantities of biphenol **6** under their catalytic conditions for the *ortho*-oxygenation of **2** when using bidentate iminopyridine and related heterocyclic ligands.[13e]

In our case, we attributed the complete loss of selectivity for *ortho*-oxygenation to steric interactions between the *ortho*-*tert*-butyl substituent of **2** and the sterically encumbered DBED ligand, which would disfavor inner-sphere oxygen atom transfer (OAT) and promote the formation of free radical **5**. Therefore, to restore selectivity for *ortho*-oxygenation, we investigated a catalytic system composed of $CuPF_6$ and triethylamine (Et_3N) (entry 1), under the assumption that a more labile monodentate amine might accommodate the steric demands of **2** and preserve a Cu-phenolate complex throughout OAT. We have previously demonstrated that catalytic amounts of Et_3N and $CuPF_6$ catalyze the oxidative functionalization of **1** into **3**,[7] and were encouraged to find that this catalytic system also oxygenated **2** into *ortho*-quinone **7**, albeit as a mixture with biphenol **6** and benzoxepine **4** (entry 1, Table 1). Somewhat remarkably, this reaction could be optimized to a completely selective and high yielding synthesis of **7** by the addition of 4 Å molecular sieves (entry 2),[18] which is noteworthy, given the number of previous attempts to catalyze the *ortho*-oxygenation of **2** with more complicated biomimetic complexes.[6,10b] In addition to Et_3N, simple 3° amines including *N*,*N*-dimethylbutylamine (entry 3) and *N*-methylpyrrolidine (entry 4) promote selective *ortho*-oxygenation, and consistent with our steric model, the more sterically encumbered *N*,*N*-diisopropylethylamine (DIPEA) favors oxidative coupling (entry 5). Under our optimized conditions (entry 7), oxygenation of **2** mediated by 25 mol % Et_3N, 6 mol % $CuPF_6$, and molecular sieves remains efficient at concentrations of 0.25 M and scales of 25−45 mmol (see the Supporting Information). These results are particularly significant, since excess Et_3N has been used as a Brønsted base in each of the previous attempts to catalyze the *ortho*-oxygenation of phenols, but its role as a ligand has not been discussed.[10b,12,13] These previous attempts are generally limited to small scales (25 μmol), high dilution (0.001 M), and incomplete conversions using bi- or tridentate ligands that often require multistep syntheses. Therefore, the observation that commercially available, monodentate 3° amines catalyze the *ortho*-oxygenation of **2** establishes a new class of ligand for this transformation, while providing operationally simple conditions for the synthesis of **7** that remain efficient on synthetically useful scales. Quinone **7** is a commercially available reagent that is widely utilized in organic synthesis,[19] it is a precursor to metal−semiquinone complexes,[20] and it is a modifying agent in chemical biology.[21] Its direct synthesis from phenol **2** improves the efficiency of current routes that rely on oxidation of the corresponding catechol.[6]

Selectivity for *ortho*-oxygenation is generally attributed to an inner-sphere mechanism of OAT between a preformed μ-η^2:η^2-peroxodicopper(II) core (abbreviated **P**) and a phenolate.[10,17b,c] In the absence of substrate, biomimetic complexes form **P** species, but only when using a Cu(I) salt that has a dissociated counterion.[11,17a,22] This is why we initially chose $CuPF_6$ as a starting point for reaction development, and also why we were surprised to find that CuCl promotes an equally selective *ortho*-oxygenation of **2**, albeit with decreased efficiency (entry 8). To our knowledge, this is the first demonstration of a catalytic *ortho*-oxygenation in the presence of a coordinating counterion,[23] and is a result that supports Tuczek's recent proposal that phenolate exchanges with the X ligand on Cu prior to O_2 activation.[13d] Under catalytic conditions, this would create the same Cu(I)-phenolate from either $CuPF_6$ or CuCl, albeit with different triethylammonium salts. As with $CuPF_6$, molecular sieves play an important role in governing the course

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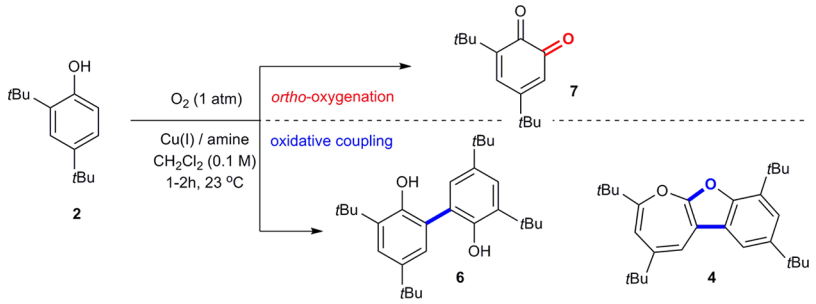
Table 1. Selective Catalytic Aerobic Oxidation of 2[a]



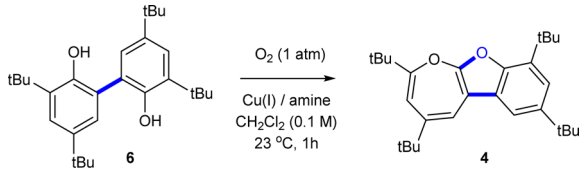
				% yield		
entry	CuX (mol %)	amine (mol %)	4 Å molecular sieves (mg)	7	6	4
1	$CuPF_6$ (8)	Et_3N (50)		15[b]	25[b]	19[b]
2	$CuPF_6$ (8)	Et_3N (50)	200	>95[b]		
3	$CuPF_6$ (8)	Me_2NBu (50)	200	81[b]		
4	$CuPF_6$ (8)	*N*-Me-pyrrolidine (50)	200	85[b]		
5	$CuPF_6$ (8)	DIPEA (50)	200	11[b]	67[b]	
6	$CuPF_6$ (8)	Py (50)	200	13[b]	32[b]	
7	$CuPF_6$ (6)	Et_3N (25)	200	94[c,d]		
8	CuCl (8)	Et_3N (50)	200	72[c]		
9	CuCl (8)	EtaN (50)			93[c]	
10	CuCl (8)	DBED (20)				91[c]
11	$CuPF_6$ (8)	DBED (20)				95[c]
12	CuCl (8)	Et_3N (50)			52[e]	

[a]Reactions performed with 1.0 mmol of **2**. [b]Product yield determined by ^1H NMR using hexamethylbenzene as an internal standard. [c]Isolated yields for quinone, biphenol, or benzoxepine. [d]The reaction was performed at 0.25 M in CH_2Cl_2. [e]The reaction was performed in nondried solvent.

of the reaction with CuCl, since oxidation of **2** with Et_3N/CuCl in their absence affords biphenol **6** selectively (entry 9). In contrast to oxidations mediated by Et_3N, those mediated by DBED afford benzoxepine **4** using either $CuPF_6$ or CuCl and do not require molecular sieves (entries 10 and 11, see the Supporting Information).

While the catalytic aerobic synthesis of biphenol **6** from phenol **2** has been extensively investigated,[6] the analogous transformation of **2** into benzoxepine **4** has only rarely been reported,[14,16c,24,25] and the factors that govern selectivity between the formation of **4** and **6** have not been discussed. Under our conditions, selectivity for **6** is observed when Et_3N and CuCl are used in the absence of molecular sieves (entry 9, Table 1), and under these conditions, benzoxepine **4** is not observed, even at extended reaction times. If, however, these conditions are applied to the oxidation of biphenol **6**, which is a presumed intermediate in the synthesis of the benzoxepine,[16] then **4** is observed, albeit in low isolated yield (entry 1, Table 2). To investigate the discrepancy between these results, we repeated the oxidation of **6** with CuCl and Et_3N in the presence of H_2O (entry 2), under the assumption that H_2O might inhibit the oxidation of **6** to **4**. In this case, only trace quantities of benzoxepine **4** are observed, even after prolonged reaction times (entry 2). The inhibitory effects of H_2O were also observed in the conversion of phenol **2** into biphenol **6** (Table 1, entry 12), although in this case reactivity was not entirely suppressed. In contrast to oxidations mediated by Et_3N, oxidations of biphenol **6** with DBED provided high isolated yields of benzoxepine **4** (entries 3 and 4) under conditions that were less sensitive to the presence of H_2O (entry 5). These results are consistent with Hay's observation that DBED forms a more hydrolytically stable complex with Cu(I) than the analogous complexes with monodentate amines.[26] Unfortunately, a direct comparison of Et_3N and DBED mediated oxidations under anhydrous conditions was precluded by the instability of the benzoxepine to molecular sieves, which is evidenced by the low isolated yields of **4** that were obtained from either Et_3N or DBED mediated oxidations conducted in the presence of the desiccant (entries 6 and 7).[27]

Table 2. Oxidation of Biphenol 6 to Benzoxepine 4[a]



entry	CuX (mol %)	amine (mol %)	molecular sieves (mg)	yield[b] (%)
1	CuCl (8)	Et_3N (50)		19 (22)
2[c,d]	CuCl (8)	EtaN (50)		<5 (11)
3	$CuPF_6$ (8)	DBED (20)		91
4	CuCl (8)	DBED (20)		92
5[c]	$CuPF_6$	DBED (20)		62
6	CuCl (8)	EtaN (50)	200	27 (84)
7	$CuPF_6$ (8)	DBED (20)	200	19 (>95)

[a]Reactions performed with 0.25 mmol of **2**. [b]Isolated yields of **4** following chromatography. Numbers in parentheses are the percent conversion of **6** based on ^1H NMR integration using hexamethylbenzene as an internal standard. [c]Reaction performed with nondried solvent. [d]Similar results were obtained after 1 and 7 h reaction times.

Summary of Tables 1 and 2. To summarize the results of Tables 1 and 2, selectivity for *ortho*-oxygenation is contingent upon the use of Et_3N (or a suitable 3° amine) and 4 Å molecular sieves in conjunction with either $CuPF_6$ or CuCl, whereas, in the absence of the desiccant, Et_3N and CuCl mediate the oxidative coupling of **2** to **6**. We believe that

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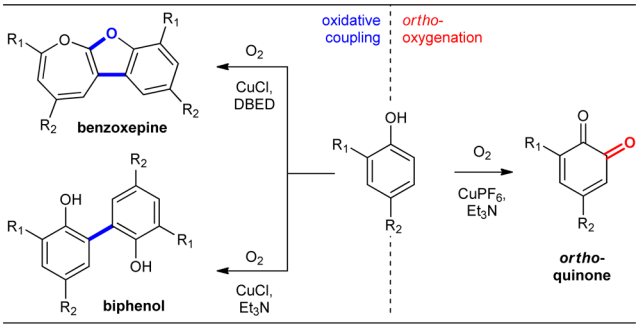
selectivity for biphenol **6** over benzoxepine **4** is contingent upon the presence of H_2O, which appears to inhibit the reactivity of Et_3N/Cu-catalyzed oxidations. Selectivity for benzoxepine **4** is observed when DBED is used as the ligand with either $CuPF_6$ or CuCl in the absence of molecular sieves.

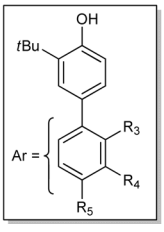
Substituent Effects on Selectivity. Since little is known about the influence of substituents on selectivity between *ortho*-oxygenation and oxidative coupling, we applied our optimized conditions for the synthesis of *ortho*-quinones, biphenols, and benzoxepines to a range of 2,4-disubstituted phenols (Table 3).[28] While slight changes to the steric and electronic properties of the substituents are tolerated (entries 1–6), *ortho*-oxygenation is inhibited when the *tert*-butyl substituent is replaced by methyl (entries 7 and 8). We attribute catalyst inhibition to tautomerization of the initially formed *ortho*-quinone to an *ortho*-quinone methide, which could form a catalytically inactive Cu(I) complex.[29] In line with this hypothesis, increased yields of the corresponding catechol are obtained if a stoichiometric amount of Cu is used along with a reductive work-up (entries 7 and 8). The presence of a methyl substituent does not affect the synthesis of biphenols (entries 7 and 8); however, formation of the benzoxepine is not observed for 2-methyl-4-*tert*-butyl phenol (entry 8). Somewhat surprisingly, 2-*tert*-butyl-4-phenyl phenol returns complex mixtures instead of the anticipated *ortho*-quinone (entry 9), whereas the synthesis of biphenols and benzoxepines remains selective and efficient across a range of 4-aryl substituents (entries 9–18).

The results with 4-aryl substituted phenols prompted us to re-evaluate conditions for the *ortho*-oxygenation of these substrates, with the goal of deciphering those factors that affect selectivity (Table 4). The reactivity of these *ortho*-quinones precluded their purification, so isolated yields are reported for the corresponding catechols following a reductive work-up (see the Supporting Information).[30] In all cases, selectivity for *ortho*-oxygenation improved at higher loadings of $CuPF_6$ (12 mol %) and decreased concentration (0.05 M), which represent our optimized conditions for this class of substrate. Oxygenation of 2-*tert*-butyl-4-phenyl phenol under these modified conditions is not selective and returns a 22% isolated yield of the catechol and a 27% isolated yield of the biphenol (entry 1). If, however, the phenyl ring is replaced with an *ortho*-tolyl substituent (R_1 = Me), a dramatic improvement in selectivity for *ortho*-oxygenation is observed (entry 2), and the corresponding catechol and biphenol are isolated in 74 and 6% yields, respectively. Good selectivity for *ortho*-oxygenation is maintained for substrates possessing a hindered biaryl bond (entries 5 and 10–12), but when R_1 = H, selectivity decreases for both electron donating and withdrawing R_3 and R_4 substituents (entries 1, 3, 4, 6–9, and 14). Thus, selectivity

Table 3. Substrate Scope[a]



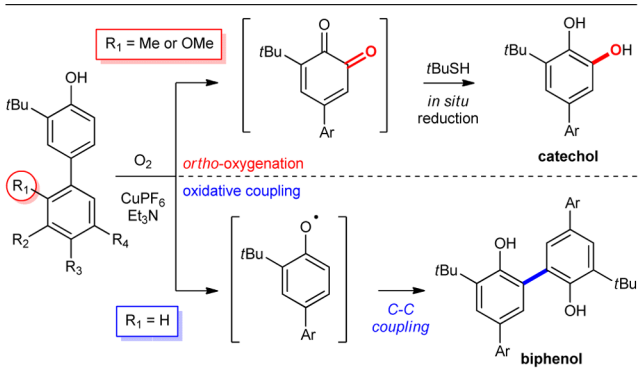
entry	R_1	R_2	*ortho*-quinone[b]	biphenol[c]	benzoxepine[d]
1	*t*Bu	*t*Amyl	78	91	88
2	*t*Amyl	*t*Amyl	80	93	72
3	*t*Bu	Cumyl	80	88	68
4	Cumyl	Cumyl	95	77	61
5	*t*Bu	Trityl	75	83	80
6	*t*Bu	*i*Pr	80	90	95
7	*t*Bu	Me	61[e]	81	67
8	Me	*t*Bu	58[e]	83	--
9	*t*Bu	Ph	--	94	77



entry	R_3	R_4	R_5	biphenol[c]	benzoxepine[d]
10	Me	H	H	91	81
11	H	Me	H	95	87
12	H	H	Me	97	90
13	OMe	H	H	83	73
14	H	OMe	H	85	88
15	H	H	OMe	84	69
16	H	H	F	94	88
17	H	H	CF_3	93	87
18	Ar = 2-naphthyl			91	94

[a]Isolated yields are reported for each product class. [b]Reaction conditions for *ortho*-quinone: phenol (1.0 mmol), [$CuPF_6$] (6 mol %), Et_3N (25 mol %), 4 Å molecular sieves (200 mg), CH_2Cl_2 (0.25 M), O_2 (1 atm), 1 h, 23 °C. [c]Reaction conditions for biphenol: phenol (1 mmol), CuCl (8 mol %), Et_3N (50 mol %), CH_2Cl_2 (0.1 M), O_2 (1 atm), 2 h, 23 °C. [d]Reaction conditions for benzoxepine: phenol (1.0 mmol), [$CuPF_6$] (8 mol %), DBED (20 mol %), CH_2Cl_2 (0.1 M), O_2 (1 atm), 23 °C, 1 h. [e]Reaction conditions for catechol with stoichiometric Cu and reductive work-up: phenol (0.25 mmol), [$CuPF_6$] (100 mol %), Et_3N (50 mol %), 4 Å molecular sieves (200 mg), CH_2Cl_2 (0.025 M), O_2 (1 atm), 8 h, −78 °C, then add *t*BuSH (4 equiv) and *para*-toluene sulfonic acid (1 equiv) as a solution in CH_2Cl_2.

Table 4. Substituent Effects on the *ortho*-Oxygenation of 4-Aryl-phenols[a]



entry	R_1	R_2	R_3	R_4	catechol : biphenol[b] 23 °C	− 78 °C
1	H	H	H	H	22 : 27	80 : 15
2	Me	H	H	H	74 : 6	90 : --
3	H	Me	H	H	56 : 33	87 : 9
4	H	H	Me	H	40 : 45	80 : 12
5	OMe	H	H	H	72 : 8	92 : --
6	H	OMe	H	H	59 : 19	85 : 11
7	H	H	OMe	H	41 : 22	81 : 13
8	H	H	CN	H	22 : --	62 : 25
9	H	H	CF_3	H	30 : 15	72 : 22
10	OMe	H	H	F	78 : 4	95 : --
11	Et	H	H	H	89 : --	91 : --
12	OMe	H	H	OMe	87 : --	93 : --
13	Ar = 1-naphthyl				76 : 2	92 : --
14	Ar = 2-naphthyl				46 : 32	85 : 12

[a]Reaction conditions: phenol (0.5 mmol), [$CuPF_6$] (12 mol %), Et_3N (50 mol %), 4 Å molecular sieves (200 mg), CH_2Cl_2 (0.05 M), O_2 (1 atm), 23 °C, 8 h, then add *t*BuSH (4 equiv), *para*-toluene sulfonic acid (1 equiv). [b]Isolated yields for both catechol and biphenol are based on the theoretical maximum of 1.0 mmol for the catechol and 0.5 mmol for the biphenol.

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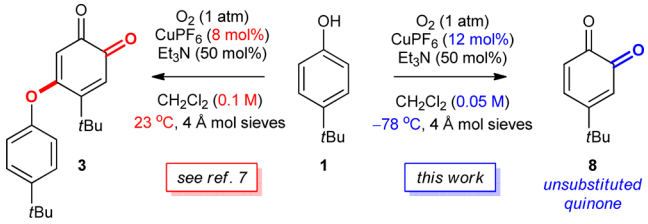
for *ortho*-oxygenation appears to be sensitive to the degree of electronic delocalization across the biaryl bond and improves as delocalization decreases.[31] Remarkably, these effects can be overridden by lowering the reaction temperature, and at −78 °C, good selectivity for *ortho*-oxygenation is observed for the complete range of substrates in Table 4. To our knowledge, this is the first demonstration that temperature influences selectivity between *ortho*-oxygenation and oxidative coupling.

In addition to overcoming issues of selectivity, the low-temperature conditions for *ortho*-oxygenation developed in Table 4 also favor oxygenation of monosubstituted phenols to *ortho*-quinones without additional oxidative coupling (Scheme 3). For example, oxygenation of **1** with $CuPF_6$ and Et_3N under

Scheme 3. Changes in the Selectivity of Catalytic Aerobic Oxygenations of 1 and 2[a]

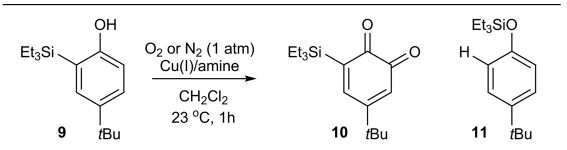


[a]Reagents and conditions: O_2 (1 atm overpressure), [$CuPF_6$] (4 mol %), DBED (5 mol %), CH_2Cl_2 (0.1 M), 23 °C.

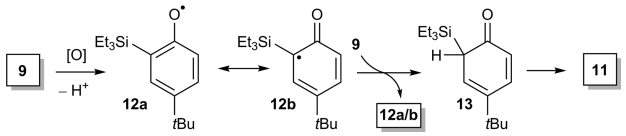
our previously reported conditions at room temperature affords substituted quinone **3** in 96% isolated yield.[7] In stark contrast, transformation of **1** under our newly developed conditions at −78 °C affords a 50% isolated yield of unsubstituted quinone **8**, which is formed as a 2:1 mixture with **3**. While the reasons for this dramatic change in selectivity are the focus of ongoing studies, this result demonstrates the impact that Cu loading, reaction concentration, and reaction temperature can have on the outcome of the oxidation. It also offers an interesting point of comparison to the conditions of Herres-Pawlis and Stack, who recently reported catalytic conditions for the *ortho*-oxygenation of monosubstituted phenols in the presence of excess Et_3N and a bis-pyrazolyl/pyridyl-Cu complex, wherein the formation of coupled products related to **3** was not reported.[12]

Mechanistic Divergence between *ortho*-Oxygenation and Oxidative Coupling. The oxidation of *ortho*-silyl phenol **9** provides insight into the mechanistic differences between *ortho*-oxygenation and oxidative coupling (Table 5). Thus, *ortho*-oxygenation using either $CuPF_6$ or CuCl with Et_3N and molecular sieves affords the expected *ortho*-quinone **10** in 85 and 71% isolated yields, respectively (entries 1 and 2). In contrast, attempts to synthesize the corresponding biphenol or benzoxepine under our standard conditions afford silylether **11** as the major product (entries 3 and 4). Mechanistically, the isomerization of **9** to **11** involves a 1,3-silatropic rearrangement (Brook rearrangement),[32] which is known for *ortho*-silyl phenols, but only at elevated temperatures (>100 °C)[33] or in the presence of trace acid.[34] Under our catalytic aerobic conditions, isomerization is complete within 1 h at room temperature. Control experiments demonstrate that isomerization requires O_2 (entries 5−8), and only low conversion is observed in the absence of Cu (entries 9 and 10). Alternatively, **11** is isolated after 1 h at room temperature upon treatment of **9** with a catalytic amount of Weitz's one-electron oxidant (entry

Table 5. Oxidation of *ortho*-Silyl Phenol[a]



entry	Cu(I) (mol%)	Ligand (mol%)	4 Å M.S. (mg)	O_2 or N_2 (1 atm)	Yield **10** (%)	Yield **11** (%)
1	$CuPF_6$ (6)	Et_3N (25)[a]	200	O_2	85	--
2	CuCl (8)	Et_3N (50)[b]	200	O_2	71	--
3	CuCl (8)	Et_3N (50)[b]	--	O_2	--	81
4	$CuPF_6$ (8)	DBED (20)[b]	--	O_2	--	87
5	$CuPF_6$ (8)	DBED (20)[b]	--	N_2	--	<5
6	--	Et_3N (50)[b]	--	N_2	--	<5
7	--	DBED (20)[b]	--	N_2	--	<5
8	$CuPF_6$ (6)	--	--	N_2	--	11
9	--	Et_3N (50)[b]	--	O_2	--	9
10	--	DBED (20)[b]	--	O_2	--	13
11	Weitz' Salt = (4-Br-C_6H_4)$_3$NSbCl$_6$ (5 mol%) CH_2Cl_2 (0.1 M), 23 °C, 1h				--	67
12	2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile) (5 mol%), C_6H_6 (0.1 M), 40 °C, 1h				--	77



[a]Reaction conditions: phenol (1 mmol), CH_2Cl_2 (0.25 M). [b]Reaction conditions: phenol (1 mmol), CH_2Cl_2 (0.1 M).

11)[35] or heating to 40 °C with an azo-radical initiator (entry 12). These results suggest that **9** can isomerize to **11** via a free-radical chain reaction, as illustrated in Table 5. With Weitz's salt, oxidation of **9** to **12** is likely to proceed via the radical cation, whereas hydrogen atom abstraction is expected for the azo-initiator. Under catalytic aerobic conditions, autoxidation of the phenolate is an additional mechanistic pathway to **12**,[1a] which we are currently evaluating.

These results support a preliminary mechanism for *ortho*-oxygenation that avoids silyl migration by preserving a Cu-phenolate throughout OAT. In contrast, conditions for the synthesis of the biphenol or benzoxepine promote silyl migration, and are thus more likely to proceed via an intermediate that possesses significant radical character. We note that oxidation of phenol **2** and biphenol **6** with Weitz's salt affords the corresponding biphenol and benzoxepine, respectively (see the Supporting Information), demonstrating that each of these reactions could, in principle, proceed via a phenoxyl radical. Nevertheless, we do not exclude an inner-sphere, Cu-catalyzed mechanism for the formation of **4** and **6** at this time,[14] particularly because of the pronounced ligand effects and the dramatic role played by H_2O.

CONCLUSION

We describe a practical catalytic aerobic *ortho*-oxygenation of phenols, and demonstrate that selectivity between *ortho*-oxygenation and oxidative coupling can be controlled through deliberate tuning of the reaction conditions. Our work establishes an important benchmark of catalyst control, identifies monodentate 3° amines as a novel class of ligands for *ortho*-oxygenation, and uncovers pronounced substituent effects that influence selectivity between *ortho*-oxygenation and oxidative coupling. Phenols are ideal feedstock chemicals, since they are commercially available, readily synthesized from bulk materials,[36] and potentially derived from renewable resources.[37] Their functionalization under catalytic aerobic conditions

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provides an exceptionally efficient means of producing molecular complexity. Our work takes an important step toward the development of general catalytic aerobic conditions that should facilitate future mechanistic investigations and synthetic applications.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, characterization and additional data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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