Synthetic Methods

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A Biomimetic Catalytic Aerobic Functionalization of Phenols**

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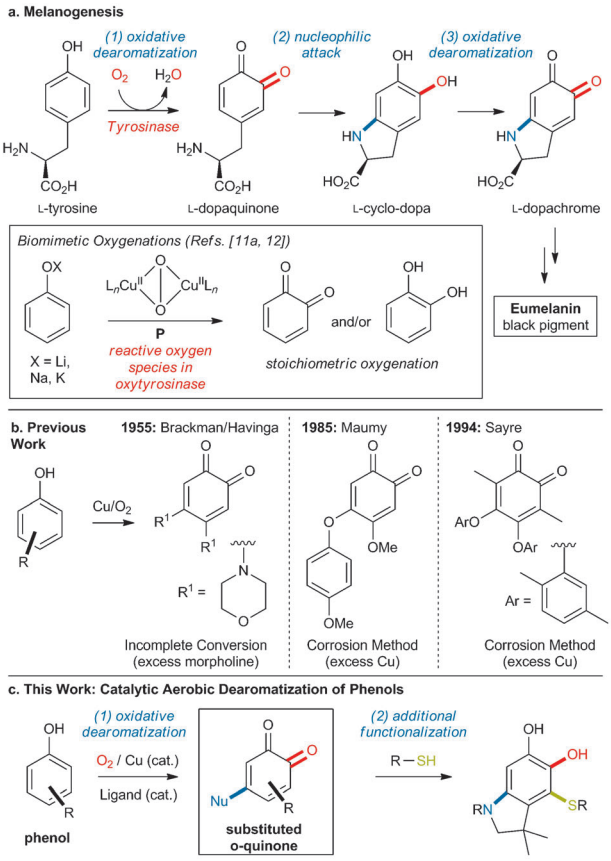
Dedicated to Professor Allan Hay on the occasion of his 85th birthday

Abstract: *The importance of aromatic C–O, C–N, and C–S bonds necessitates increasingly efficient strategies for their formation. Herein, we report a biomimetic approach that converts phenolic C–H bonds into C–O, C–N, and C–S bonds at the sole expense of reducing dioxygen (O_2) to water (H_2O). Our method hinges on a regio- and chemoselective copper-catalyzed aerobic oxygenation to provide ortho-quinones. ortho-Quinones are versatile intermediates, whose direct catalytic aerobic synthesis from phenols enables a mild and efficient means of synthesizing polyfunctional aromatic rings.*

The reduction of molecular oxygen (O_2) to water (H_2O) provides a sustainable source of chemical energy for the synthesis of a myriad of molecules and materials in nature.[1] Numerous biochemical processes harness the energy of O_2 by converting phenols into *ortho*-quinones (Scheme 1 a).[2] *ortho*-Quinones are versatile synthetic intermediates,[3] whose innate reactivity[4] enables cycloaddition, condensation, addition, and redox reactions. This makes them the centerpiece of biomimetic strategies for the synthesis of materials,[5] natural products,[6] biologically active heterocycles,[7] dyes, and pigments.[8] Phenols are readily available feedstock chemicals[9] that are potentially derived from renewable sources of carbon.[10] However, their conversion into *ortho*-quinones currently requires stoichiometric amounts of an oxidant other than O_2.[3c–e]

Catalyzing the aerobic oxygenation/dearomatization of phenols has remained an unresolved challenge in biomimetic copper chemistry for more than 50 years.[11] In nearly all living organisms, the type-III copper enzyme tyrosinase oxygenates phenols to *ortho*-quinones, thereby triggering melanogenesis (Scheme 1 a).[2,11–13] Under stoichiometric conditions, biomimetic complexes recreate the enzyme's mechanism of O_2 activation and oxygen atom transfer (species **P** in Scheme 1 a, inset),[14] but extending these mechanistic studies to catalytic reactions has met with limited success. In early studies, Bulkowski,[15] Réglier et al.,[16] and Casella et al.[17] oxygenated phenols using dinuclear Cu catalysts and excess triethylamine (2 equiv Et_3N), and more recently, Tuczek and co-workers[18] as well as Stack, Herres-Pawlis, and co-workers[19] employed similar conditions with mononuclear Cu^I catalysts. These examples, which are limited to small scales (25 μmol), high dilution (0.001 M), and incomplete conversion, underscore the well-known challenges of catalyzing aerobic oxidations of phenols,[11c,20–22] for which Hay's polymerization[21] is the only example that has found practical application.[1b,11b]

Herein, we show how this long-standing challenge can be overcome, and describe a practical method for the Cu-



Scheme 1. a) Principle steps of melanogenesis leading to eumelanin and the reactive oxygen species of the enzyme tyrosinase. b) Previous examples of phenolic oxygenation/functionalization reactions. c) The catalytic aerobic dearomatization of phenols reported herein.

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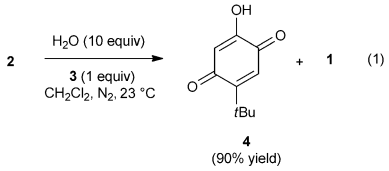
catalyzed aerobic oxygenation of phenols to *ortho*-quinones that gives rise to the site-selective functionalization of two aromatic C–H bonds (Scheme 1c). Our study builds upon the examples from the research groups of Brackman,[23] Maumy,[24] and Sayre,[25] who demonstrated that phenols undergo oxygenation and oxidative coupling when exposed to excess Cu^{I} and O_2 (Scheme 1b), thereby providing *ortho*-quinones that are stable to work-up and purification. Since phenolic oxidations are frequently associated with complex product mixtures,[11c,26] we opted to investigate the conversion of 4-*tert*-butylphenol (**1**) into substituted *ortho*-quinone **2** (Table 1), which can be purified by chromatography (see the Supporting Information).

A 60% conversion of **1** into **2** was observed under slightly modified conditions to those reported by Réglier et al. (entries 1 and 2).[16] Interestingly, both the yield of **2** and the reaction conversion decreased as the reaction time increased (compare entries 1 and 3), suggesting that **2** was hydrolyzed over the course of the reaction to hydroxy *para*-quinone **4** and phenol **1** [Eq. (1)]. Attempts to isolate **4** from catalytic

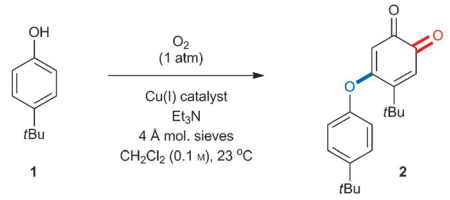


reactions were precluded by its instability to Cu in the presence of O_2.[27] However, control experiments under N_2 returned a 90% yield of isolated **4** when **2** was exposed to $[Cu(CH_3CN)_4]PF_6$ (**3**) and H_2O [Eq. (1)]. Hydroxy ketones related to **4** are inhibitors of the enzyme tyrosinase,[28] and when the structurally related *para*-quinone lawsone (Table 1, inset) was added to our standard reaction conditions, catalysis was inhibited (entry 4). This suggested that a conjugate addition/elimination of H_2O onto **2**, which would regenerate starting phenol **1** and release **4**, could account for the trends in conversion observed across entries 1–3. This hypothesis, which identified H_2O as a problematic by-product, was substantiated by the beneficial effects of 4 Å molecular sieves (entry 5), whose inclusion led to complete and quantitative formation of **2**. Somewhat surprisingly, the beneficial effects of molecular sieves were observed across a range of iminopyridine catalysts[18] (Table 1, inset: **L1**–**L6** yields with and without molecular sieves), thus prompting us to investigate the background oxygenation of **1** with **3** and Et_3N in the absence of additional ligands (entry 6). Remarkably, a fully catalytic oxygenation of **1** could be optimized to give a 96% yield of **2** by the addition of 4 Å molecular sieves (entries 7 and 8), thus demonstrating that a catalytic aerobic oxygenation can be conducted under surprisingly simple conditions that do not require sophisticated ligands.[11a,29] This result is particularly significant since excess Et_3N has been employed as a Brønsted base in each of the previous attempts to catalyze the aerobic oxygenation of phenols,[16–19] and yet its role as a ligand has not been described.[29]

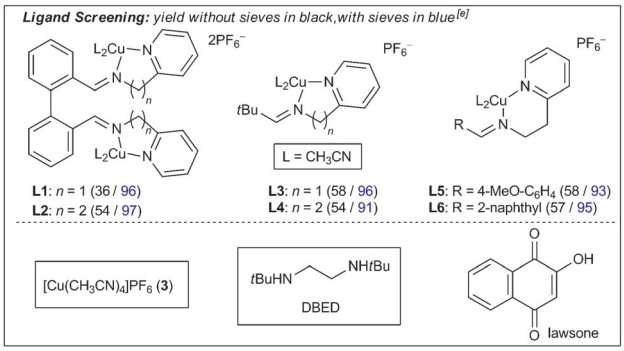
Although the precise role of molecular sieves remains unclear,[30] the negative impact of H_2O on the reaction outcome prompted us to investigate the more hydrolytically stable complex of **3** with di-*tert*-butylethylenediamine (DBED) developed by Hay[31] and extensively studied by Stack and co-workers.[14c] Remarkably, ratios of DBED/**3** greater than 1:1 afford a robust catalyst that does not require the use of excess Et_3N or a desiccant (entry 9), and even promotes oxidation in common, undried solvents under open-flask conditions (see the Supporting Information). This catalyst system remains efficient on a multigram scale (60 mmol of **1**), high concentrations (up to 2.0 M), and low catalyst loadings (2 mol% Cu, 4 mol% of DBED; see the Supporting Information), thereby setting the stage for its development into a versatile and practical tool for synthesis.[32]

Both Et_3N- and DBED-mediated oxidations retain excellent regio- and chemoselectivity for *ortho*-, *meta*-, or *para*-substituted phenols displaying a range of common functional

Table 1: Reaction optimization.[a]



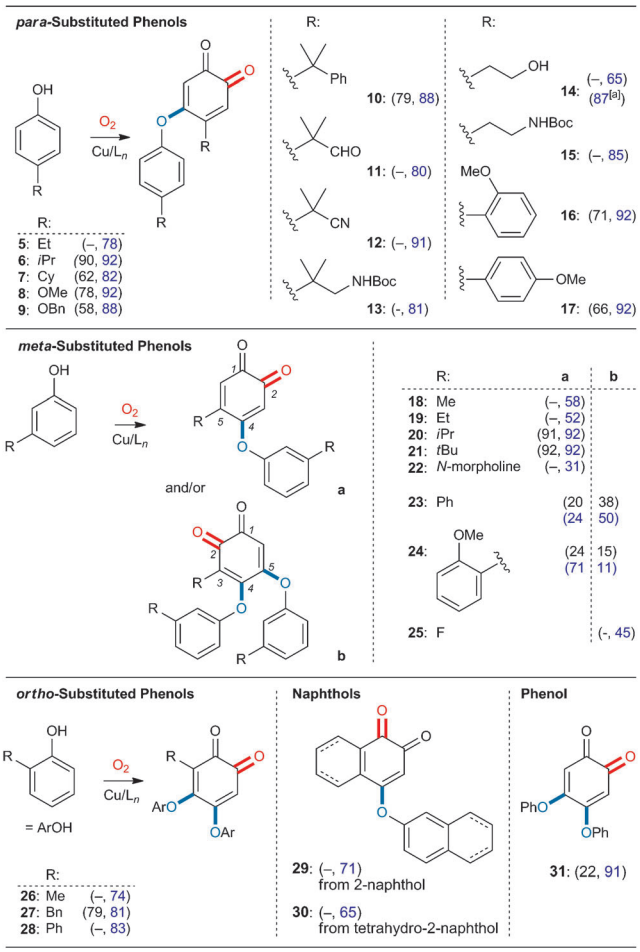
Entry	Catalyst (mol%)	Amine (mol%)	*t* [h]	M.S. [mg]	Conversion[b] [%]	Yield [%]
1	**L2** (10)	Et_3N (200)	4	–	60	58[b]
2	**L2** (10)	Et_3N (50)	4	–	55	54[b]
3	**L2** (10)	Et_3N (200)	24	–	33	18[b]
4	**L2** (10)	Et_3N (50)	4	–	<5[c]	<5[c]
5	**L2** (10)	Et_3N (50)	4	200	99	97[b]
6	**3** (10)	Et_3N (50)	4	–	32	26[b]
7	**3** (10)	Et_3N (50)	4	200	90	86[b]
8	**3** (8)	Et_3N (50)	4	200	>95	96[d]
9	**3** (4)	DBED (5)	4	–	>95	98[d]



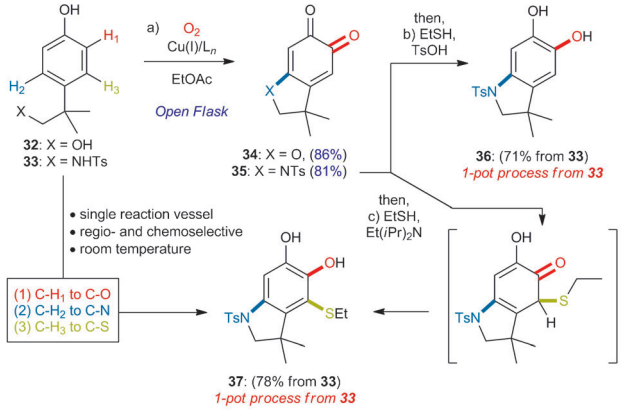
[a] Reactions were performed on a 1.0 mmol scale of **1**. [b] Yields and ratios are based on ^{1}H NMR integration relative to an internal standard (hexamethylbenzene). [c] Reaction performed in the presence of lawsone (25 mol%). [d] Yields of isolated and purified **2**. [e] Reactions using **L1**, **L3**–**L6** (10 mol%) were performed on a 1.0 mmol scale of **1** using Et_3N (50 mol%) in CH_2Cl_2 (0.1 M) under O_2 (1 atm) at 23 °C in the presence and absence of molecular sieves (4 Å M.S, 200 mg). Yields in the absence of sieves are reported first (in black), and with molecular sieves are reported second (in blue). Yields are based on ^{1}H NMR integration relative to an internal standard (hexamethylbenzene).

groups including alcohol, amide, aldehyde, and nitrile functionalities (Scheme 2).[29] The selective *ortho*-functionalization of aryl ethers (**8** and **9**) complements stoichiometric methods that afford *para*-quinones or quinone ketals, and demonstrates compatibility with phenols bearing heteroatom substituents.[22b,c] In the case of *ortho*- and *meta*-substituted phenols, our conditions override the preference of phenols to oxidize to the *para*-quinone under aerobic conditions.[11b] The observed regioselectivity is consistent with an inner-sphere mechanism of oxygen atom transfer.[11a,b,12,14c] In nonsymmetric substrates, regioselectivity is influenced by steric and electronic factors to afford 4,5-disubstituted *ortho*-quinones (**18**–**22**) or 3,4,5-trisubstituted *ortho*-quinones after two oxidative coupling reactions (**23**–**25**). *ortho*-Substituted phenols selectively form 3,4,5-trisubstituted *ortho*-quinones, and chemoselectivity for *ortho*-oxygenation is retained in the presence of benzylic or aryl C–H bonds (**26**–**28**), which have been susceptible to oxidation in related Cu/O_2 systems.[14b] 2-Naphthol and tetrahydro-2-naphthol undergo selective oxygenation at C1 (**29** and **30**), in contrast with stoichiometric oxidants that afford mixtures of regioisomeric quinones[6d] or catalytic aerobic reactions that favor C–C coupled products.[11b,33] A preliminary mechanistic interpretation of these results supports an inner-sphere *ortho*-oxygenation of the starting phenol, where the newly introduced oxygen atom is derived from O_2.[32] Subsequent oxidative coupling with the starting phenol affords the coupled product, thereby releasing the Cu catalyst and closing the catalytic cycle. The details of this mechanism are currently under investigation, and will be reported in due course.[32]

Our catalytic aerobic oxidation enables a direct synthesis of polyfunctional heterocycles that extends our method beyond a phenolic homocoupling (Scheme 3). For example,



Scheme 2. Substrate scope. Standard Et_3N conditions (isolated yields of products are shown first, in black): phenol (1.0 mmol), O_2 (1 atm), **3** (8 mol%), Et_3N (50 mol%), 4 Å molecular sieves (200 mg), CH_2Cl_2 (0.1 M) at 25 °C for 4 h. Standard DBED conditions (isolated yields of products are shown second, in blue): phenol (1.0 mmol), O_2 (1 atm), **3** (4 mol%), DBED (5 mol%), CH_2Cl_2 (0.1–0.5 M) at 23 °C for 4 h. [a] Reaction performed in THF (0.1 M) because of issues of solubility.



Scheme 3. Cross-aerobic coupling. Reagents and conditions: a) Synthesis of **34** and **35**: **3** (4 mol%), DBED (5 mol%), EtOAc (0.5 M), open flask. Synthesis of **36** from **33**: **3** (4 mol%), DBED (5 mol%), CH_2Cl_2 (0.1 M), O_2 (1 atm); then EtSH (4 equiv), *para*-toluenesulfonic acid (1 equiv). Synthesis of **37**: **3** (4 mol%), DBED (5 mol%), CH_2Cl_2 (0.1 M), O_2 (1 atm); then EtSH (4 equiv), DBED (1 equiv).

primary alcohols and sulfonamides are suitable nucleophiles for intramolecular cyclization, thus enabling the direct synthesis of furano- and indoloquinones **34** and **35**. While our standard conditions are amenable to the synthesis of **34** and **35**, this transformation can even be conducted under open flask conditions in reagent-grade ethyl acetate, which are significantly milder conditions than those typically required for heteroatom–carbon coupling reactions.[34] Most importantly, the *ortho*-quinone products can be employed in additional bond-forming reactions, thereby enabling one-pot, sequential processes that avoid traditional work-up and purification. For example, indoloquinone **35** is reduced by ethanethiol (EtSH) under acidic conditions to afford 3,4-dihydroxydihydroindole **36** in 71% yield, in a one-pot, sequential process starting from **33**. Alternatively, the addition of EtSH under basic conditions triggers regioselective C–S bond formation, and generates pentasubstituted catechol **37** in 78% yield in one pot starting from phenol **33**. The synthesis of functionalized *ortho*-quinones and catechols under such operationally simple conditions is noteworthy, since their use in applied fields of chemistry is currently limited to a small

selection of commercially available derivatives.[35] Moreover, our method establishes an exceptionally efficient route to highly oxidized furan and indole heterocycles that converts C–H bonds into C–O, C–N, and C–S bonds with complete regiocontrol in a one-pot process with minimal by-products.

In conclusion, we have described a practical catalytic aerobic oxygenation of phenols to *ortho*-quinones, which had remained an unresolved challenge in homogeneous copper catalysis for more than 50 years.[11] Our method embodies a growing trend in synthetic chemistry, which aims to drive C–H bond functionalization by the concomitant formation of water.[36] The use of phenols as starting materials for this class of reactions is noteworthy, given their potential to become renewable feedstock chemicals[10] and their recent synthesis by catalytic aerobic methods.[9a,b] Our study benefits from operational simplicity (room temperature, open flask, Earth-abundant catalyst, commercial reagents, single reaction vessel) and highlights how biomimetic catalysis can have an impact on the development of environmentally friendly methods for chemical synthesis.[1,37]

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