A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

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Accepted Article

Title: Selectivity in the Aerobic Dearomatization of Phenols: Total Synthesis of Dehydronornuciferine by Chemo- and Regioselective Oxidation

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201710271
Angew. Chem. 10.1002/ange.201710271

Link to VoR: http://dx.doi.org/10.1002/anie.201710271
http://dx.doi.org/10.1002/ange.201710271

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Selectivity in the Aerobic Dearomatization of Phenols: Total Synthesis of Dehydronornuciferine by Chemo- and Regioselective Oxidation

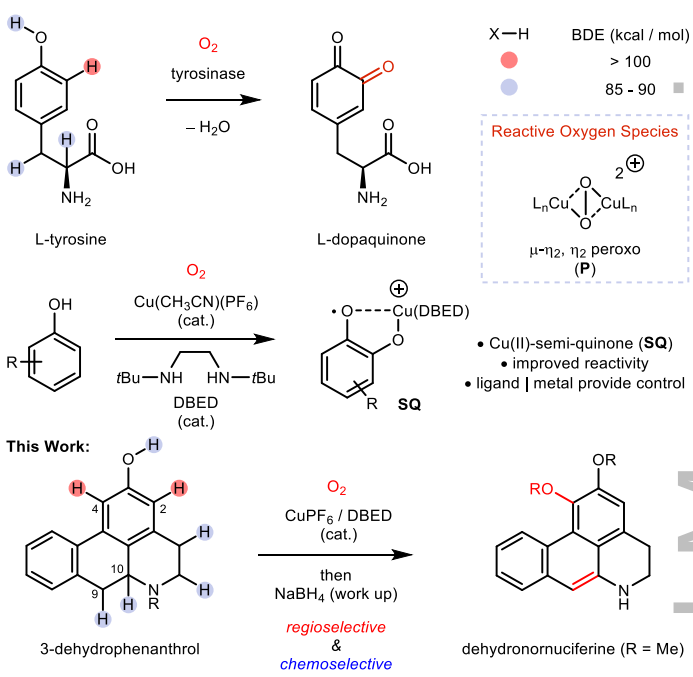
Kenneth Virgel N. Esguerra,[a] and Jean-Philip Lumb*[a]

Dedication (In memory of Professor Allan Stuart Hay)

Abstract: We describe a selective aerobic oxidation of *meta*-biaryl phenols that enables rapid access to functionalized phenanthrenes. Aerobic oxidations attract interest due to their efficiency, but remain underutilized in complex molecule settings due to challenges of selectivity. We discuss these issues in the context of Cu-catalysis, and highlight the advantages of confining oxygen activation and substrate oxidation to the catalyst's inner-coordination sphere. This gives rise to predictable selectivity that we use for a concise synthesis of the aporphine dehydronornuciferine.

Issues of selectivity limit aerobic C-H oxidations in complex molecule settings.[1] Unlike C-H oxidations that use synthetic oxidants,[2] aerobic oxidations are often limited to relatively simple substrates, which either contain a single kind of C-H bond or a C-H bond that is clearly activated for oxidation.[3] This underscores the unique challenges of working with an oxidant that is prone to radical-chain mechanisms of oxidation (e.g. autoxidation), has a four-electron reduction stoichiometry, a triplet electronic structure and a relatively small steric profile.[4] Metalloenzymes overcome many of these challenges by confining oxidation to the coordination sphere of their active sites.[5] This can enable aerobic oxidation of relatively inert C-H bonds, which remains difficult for synthetic catalysts.[6],[7],[8] The Type III Cu-enzyme tyrosinase provides a well-known example, in which a single aromatic C-H bond of tyrosine (BDE of ~103 kcal/mol) is oxidized in the presence of benzylic (BDE ~ 85 kcal/mol) and heteroatom activated alternatives (BDE ~ 80 – 90 kcal/mol), including the O-H bond of the phenol itself (BDE of ~88 kcal/mol) (Scheme 1).[9]

Mimicking tyrosinase has been a longstanding goal of industrial and academic chemists, beginning with early work of Brackman and Havinga in the 1950s.[10] It is only recently, however, that catalytically active conditions replicating the enzyme's mechanism have emerged.[11] Our group has been particularly interested in a combination of N,N′-di-*tert*-butyl ethylene diamine (DBED) and $Cu(CH_3CN)_4(PF_6)$ (abbreviated $CuPF_6$),[12] which faithfully activates O_2 as the same μ-η^2,η^2-peroxo (**P**-species) found in the enzyme (Scheme 1).[13] While this system oxygenates phenols like tyrosinase, a mechanistic divergence follows atom transfer, and a



Scheme 1. Biosynthetic and biomimetic oxidation of phenols.

$Cu^{(II)}$-semi-quinone radical (**SQ**) is formed instead of a free *ortho*-quinone.[13] This important difference has allowed us to sidestep the often promiscuous reactivity of *ortho*-quinones, which frequently limits their synthetic utility.[14]

As part of a general program to improve the utility of O_2 in synthesis,[7j,15] we became interested in the origin of selectivity for an aerobic oxidation of dihydro-3-phenanthrols that returns 3,4-phenanthraquinones in high yields (Scheme 2A). Recognizing the potential value of this oxidation for the synthesis of phenanthrenes functionalized in the "bay region",[16] we undertook studies to clarify its mechanism, scope and synthetic utility. These results form the basis of our report, which culminates in a selective catalytic aerobic C-H oxidation that we use to synthesize the aporphine alkaloid dehydronornuciferine (Scheme 1).

At the outset of our studies, we considered two mechanisms for the formation of *ortho*-quinone **2** from dihydro-3-phenanthrol **1**

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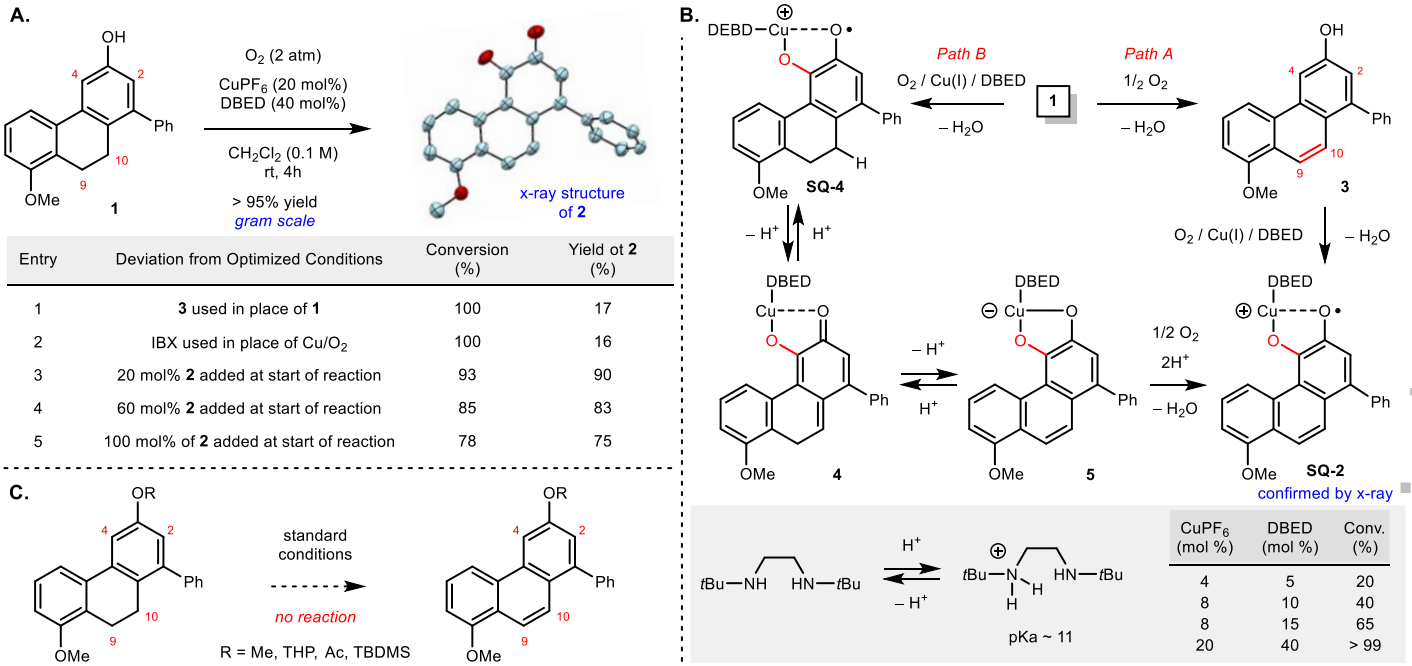
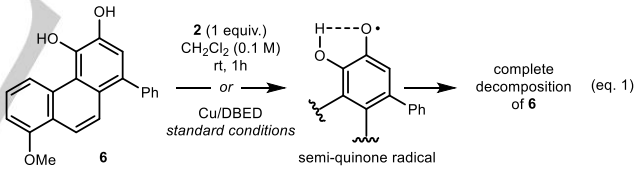


Entry	Deviation from Optimized Conditions	Conversion (%)	Yield of **2** (%)
1	**3** used in place of **1**	100	17
2	IBX used in place of Cu/O_2	100	16
3	20 mol% **2** added at start of reaction	93	90
4	60 mol% **2** added at start of reaction	85	83
5	100 mol% of **2** added at start of reaction	78	75

Scheme 2. (A) Optimized conditions and control experiments. (B) General mechanistic pathways considered in this work. (C) Control experiments showing an absence of benzylic C-H oxidation with the DBED/Cu system.

(Scheme 2A), differing in the order of oxidations (Scheme 2B). In Path A, dehydrogenation at C9-C10 precedes oxygenation at C4 to afford 3-phenanthrol **3**. Oxygenation of polyaromatic phenols related to **3** with 2-iodoxybenzoic acid (IBX) occurs selectively at C4,[17] reflecting an energetic bias to preserve aromaticity of the naphthalene substructure (see Scheme 3a).[18] However, when 3-phenanthrol **3** was oxidized under our standard conditions, *ortho*-quinone **2** was isolated in only 17% yield at complete conversion of **3** (Scheme 1a, entry 1). In the absence of a free phenol at C3 (Scheme 2C), dehydrogenation at C9-C10 is not observed, and the corresponding dihydrophenanthrenes are re-isolated without loss of mass balance. Thus, the poor reactivity of **3**, and the absence of C-H oxidation at C9-C10 with the DBED/Cu system lead us to disfavor Path A.

In Path B, oxygenation at C4 would precede dehydrogenation at C9-C10 to provide **SQ-4** (Scheme 2C). A sequence of proton transfers via **4** and **5** would afford an increasingly electron rich Cu(I)-complex, before a final oxidation to **SQ-2** (structure confirmed by x-ray, see the Supplementary Information). We observe a dose-dependent inhibition of catalysis when **2** is added at the beginning of the reaction (Scheme 2a, entries 3-5), suggesting an off-cycle equilibrium with **SQ-2** that must dissociate DBED/Cu(I) prior to re-entering the catalytic cycle. We also require an increased ratio of 2:1 DBED to $CuPF_6$ relative to our previous work in order to achieve complete conversion of **1** (Scheme 2B, lower panel).[12c] This suggests a pH dependence on the **SQ-4** / catecholate **5** equilibrium, which should favor **5** at higher concentrations of DBED. Maintaining Cu-coordination is important, since control experiments reveal an incompatibility of free catechol **6** and *ortho*-quinone **2** (equation 1, top). We also note that catechol **6** is not a viable substrate for the DBED/Cu catalyst (equation 1, bottom). This is consistent with our previous observations that redox exchange between catechols and quinones to form semi-quinone radicals can erode selectivity in the catalytic aerobic oxidation of phenols and catechols.[14a,14b] This also helps to explain the poor efficiency of the IBX-mediated oxidation of **1** (Scheme 2A, entry 2), which must proceed without the stabilizing effects of a metal complex.



For Path B to be viable, atom transfer must occur selectively at C4 over C2 in the absence of an obvious electronic bias. DFT calculations suggest equal spin or charge density at these two positions in the corresponding phenoxyl or phenoxide of **2** (see the Supplementary Information), and unlike the relative energies of the regioisomeric 2,3- and 3,4-phenanthraquinones, the relative energies of the dihydro-phenanthraquinones (i.e. C9-C10 is saturated) are 1 kcal/mol in favor of the 2,3-isomer (Scheme 3A). This leads us to propose a steric bias for oxygenation at C4 that results from an unfavorable interaction between the C1 phenyl group and a *tert*-butyl group of the DBED ligand (i.e. **TS1**, Scheme 3B).[14d] This interaction would be decreased in **TS2**, where the relatively planar bi-aryl bond at C4a would remain orthogonal to the plane of atom transfer. A similar directing effect is observed for the oxidation of isomeric phenol **7** (Scheme 3C), which returns 1,2-phenanthraquinone **8** in 67% yield by discriminating the twisted biaryl bond at C4 with a methylene group at C10a. In the absence of a steric bias (Scheme 3D), oxidation is not selective, and dihydro-3-phenanthrol (**9**) affords a complex mixture from which coupled

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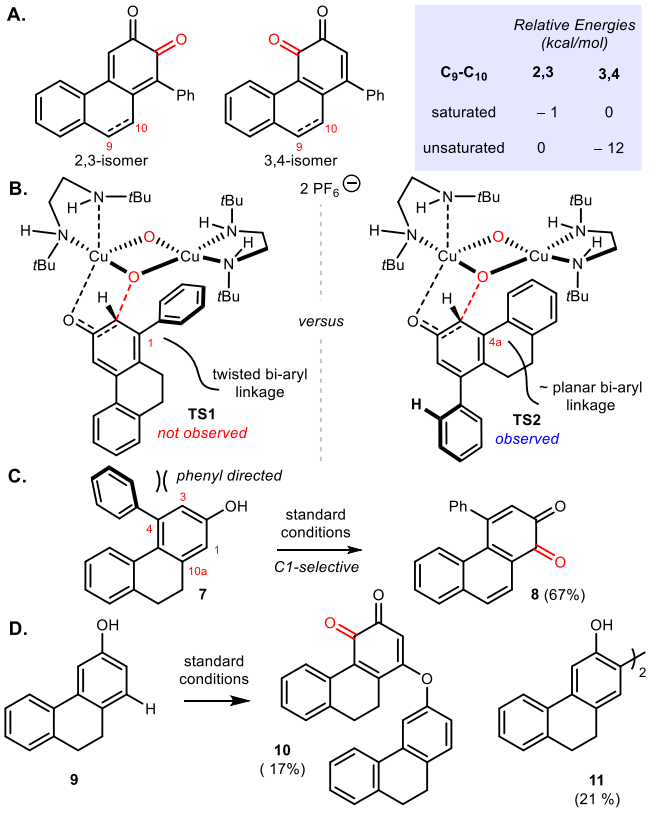

Scheme 3. (A) Relative energies of 2,3- and 3,4-quinones at the B3LYP/6-31G* level of theory. (B) Schematic representations of OAT transition states. (C) Phenyl directed C1 oxygenation. (D) Loss of steric bias.

ortho-quinone **10** and biphenol **11** are isolated in low yields. The formation of **10** stems from the accessibility of the SQ-complex, which allows C-O coupling to compete with tautomerization.[12c,13a] The formation of **11**, however, is more surprising. We have previously demonstrated that the $CuPF_6$/DBED system favors *ortho*-oxygenation over radical coupling,[12d] and the oxidation of **9** is the only instance in which a product of C-C coupling is observed. Given the absence of a C1 substituent, *ortho*-oxygenation of **9** may occur competitively at C2 to provide 2,3-phenanthraquinone. To our knowledge, 2,3-phenanthraquinone is unknown, and the corresponding 2,3-naphthoquinone is only fleetingly stable.[19] Our own efforts to prepare or observe 2,3-phenanthraquinones have been unsuccessful, but we speculate that their formation during the oxidation of **9** may lead to radical based C-C coupling. The results in Schemes 2 and 3 lead us to favor Path B as the mechanism of oxidation, in which steric interactions between the substrate and the oxidant govern regioselectivity. The results of equation 1 and Scheme 3C underscore the importance of preserving metal-coordination throughout substrate oxidation to avoid free radicals.

With this mechanistic hypothesis in hand, we evaluated the scope of the reaction (Scheme 4A). Substitution on the key C1-aryl group is well tolerated. This includes substitution in the *ortho*-, *meta*- and *para*-positions with electron donating and withdrawing groups (entries 1-6 and 14). 1- or 2-Napthyl substitution is also tolerated (entries 7 and 8), as are heteroaromatic rings (entries 9 and 10). An isopropyl substituent at C1 maintains the expected sense of selectivity for C4, and demonstrates compatability for substrates that possess an additional benzylic C-H bond at C1 (entry 11). Sustitution at C9, with either aromatic or aliphatic groups, is also tolerated, and demonstrates that the efficiency of C9-C10 dehydrogenation is not affected by additional activation of the C9 hydrogen atom (entries 12 and 13). In the final three entries, we demonstrate complementary approaches to angularly fused heteroaromatic *ortho*-quinones (entries 15-17) that includes compatability with dehydrogantion across a -HC-NH- linkage to afford the corresponding angularly fused isoquinoline-quinone (entry 17).

In addition to their interest as synthetic endpoints,[20] *ortho*-quinones generated under our conditions can be used in a range of 1-pot sequential transformations. This allows us to capitalize on recent phenol syntheses of the Zhang and Stahl groups[21] to prepare functionalized phenanthrenes from simple carbonyl starting materials over a short sequence. Reduction with hydride or addition of ethane thiol provides differentially substituted 3,4-dihyroxyphenanthrenes **12** or **13**, respectively (Scheme 4B).[12c] Condensation of an aryl hydrazine or hydrazide occurs at the less sterically encumbered C-3 carbonyl to provide push-pull azo phenols **14** or **15**.[14c,14e] Related azo switches possess red-shifted absorbance properties and fast thermal relaxation, which are attractive for fast information transmission in biologically relevant contexts.[22] Alternatively, coupling with dihydropyrrole affords N-aryl pyrrole **16** following condensation and redox isomerization, whereas the addition of phenyl glycine methyl ester affords angularly fused benzoxazinone **17** following a similar cascade terminated by lactonization (structure confirmed by x-ray, see the Supplementary Information).[14d]

As a final illustration of utility, we targeted the aporphine natural products dehydronornuciferine **20** and its N-methyl derivative **21**,[23] recognizing several features that would probe the limits of the DBED/Cu(I) system (Scheme 4C). Aporphines are a rich class of secondary metabolites, endowed with a range of biological activities.[24] Synthesis of the key dihydrophenanthrols **18** and **19** is accomplished using Fagnou's bi-aryl synthesis,[25] (see Supporting Information). Subsequent regio- and chemoselective oxidation under our standard conditions highlights compatibility with a methylene substituent at C1, which does not diminish selectivity for oxygenation at C4. Dehydrogenation remains selective for C9-C10, as opposed to the tetrahydro-isoquinoline ring (i.e. dehydrogenation at C11 and C12). Oxidation of **19** also

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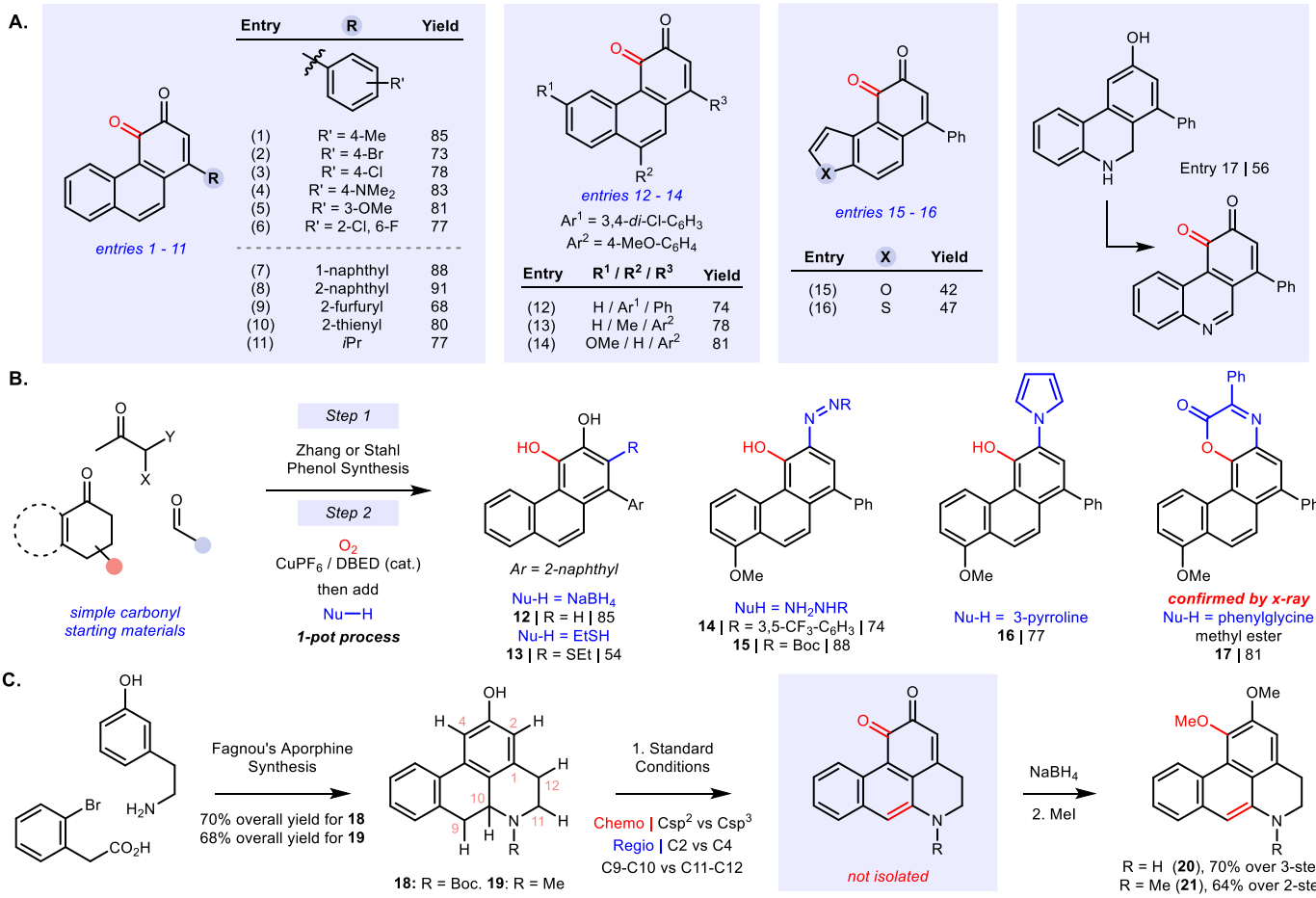

Scheme 4 (A) Substrate Scope. (B) Diversification of *ortho*-quinones in a 1-pot, sequential process. (C) Synthesis of dehydronornuciferine.

demonstrates compatibility with a readily oxidizable 3° amine, leading to the natural products in a concise sequence following straightforward manipulations.

In summary, we describe a selective aerobic oxidation of phenols, which enables a concise synthesis of functionalized phenanthrenes. Oxidation reactions play a critically important role in upgrading feedstock chemicals to endpoints of high value, but they remain poorly developed when compared to reactions that employ synthetic oxidants. O_2 is an ideal reagent, both in providing chemical energy to drive bond formation, and an oxygen atom for C-H oxidation. By confining O_2-activation and substrate oxidation to the inner coordination sphere of a transition metal complex, we have illustrated a strategy for making aerobic oxidations more amenable to the synthesis of complex molecules, where issues of selectivity are paramount.

Acknowledgements

Financial support was provided by the Natural Sciences and Engineering Council of Canada (J.-P.L.). We thank Prof. James Gleason for help with calculations, as well as Dr. Thierry Maris (University of Montreal) and Dr. Steven Kelley (McGill University) for help with X-ray crystallography.

Keywords: aerobic copper catalysis • phenol oxidation • aerobic dehydrogenation • aporphine • quinone

[1] (a) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem. Int. Ed.* **2011**, *50*, 11062-11087; (b) S. S. Stahl, *Angew. Chem. Int. Ed.* **2004**, *43*, 3400-3420; (c) T. Punniyamurthy, S. Velusamy, J. Iqbal, *Chem. Rev.* **2005**, *105*, 2329-2363.

[2] For a recent overview of C-H functionalization see: H. M. L. Davies, D. Morton, *ACS Cent. Sci.* **2017**, *3*, 936-943

[3] S. S. A. Stahl, P. L., in *Liquid Phase Aerobic Oxidation Catalysis: Industrial Applications and Academic Perspectives* (Ed.: S. S. A. Stahl, P. L.), Wiley-VCH Verlag GmbH & Co. KGaA, **2016**, pp. I-XXII.

[4] For a wonderful discussion on the electronic structure of O_2 and its confounding reactivity, see: (a) W. T. Borden, R. Hoffmann, T. Stuyver, B. Chen, *J. Am. Chem. Soc.* **2017**, *139*, 9010-9018; For a discussion in the context of Cu-catalysis, see: (b) D. Hruszkewycz, S. McCann, S. Stahl, in *Liquid Phase Aerobic Oxidation Catalysis: Industrial Applications and Academic Perspectives*, Wiley-VCH Verlag GmbH & Co. KGaA, **2016**, pp. 67-83; (c) E. I. Solomon, D. E. Heppner, E. M. Johnston, J. W. Ginsbach, J. Cirera, M. Qayyum, M. T. Kieber-Emmons, C. H. Kjaergaard, R. G. Hadt, L. Tian, *Chem. Rev.* **2014**, *114*, 3659-3853.

[5] (a) L. Que, W. B. Tolman, *Nature* **2008**, *455*, 333-340; (b) L. Q. Hatcher, K. D. Karlin, in *Adv. Inorg. Chem., Vol. Volume 58* (Eds.: R. v. Eldik, J. Reedijk), Academic Press, **2006**, pp. 131-184.

[6] There has been significant progress in the chemoselective aerobic oxidation of alcohols. For a recent review, see: Y. Seki, K. Oisaki, M. Kanai, *Tetrahedron Lett.* **2014**, *55*, 3738-3746, and references therein.

[7] For a selection of recent and selective C-H oxidations using O_2 see: (a) Y. Kawamata, M. Yan, Z. Liu, D.-H. Bao, J. Chen, J. T. Starr, P. S. Baran, *J. Am. Chem. Soc.* **2017**, *139*, 7448-7451; (b) E. Gaster, S. Kozuch, D. Pappo, *Angew. Chem. Int. Ed.* **2017**, *56*, 5912-5915; (c) D. P. Hruszkewycz, K. C. Miles, O. R. Thiel, S. S. Stahl, *Chem. Sci.* **2017**, *8*, 1282-1287; (d) J. Giarrusso, D. T. Do, J. S. Johnson, *Org. Lett.* **2017**, *19*, 3107-3110; (e) E. Petit, D. Lefeuvre, R. Jacquet, L. Pouységu, D. Deffieux, S. Quideau, *Angew. Chem. Int. Ed.* **2013**, *52*, 11530-11533; (f) A. Rahimi, A. Azarpira, H. Kim, J. Ralph, S. S.

10.1002/anie.201710271

Stahl, *J. Am. Chem. Soc.* **2013**, *135*, 6415-6418; (g) J. Zhang, E. Khaskin, N. P. Anderson, P. Y. Zavalij, A. N. Vedernikov, *Chem. Commun.* **2008**, 3625-3627; (h) X. Chen, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 6790-6791; (i) B.-J. Li, S.-L. Tian, Z. Fang, Z.-J. Shi, *Angew. Chem. Int. Ed.* **2008**, *47*, 1115-1118; (j) B. Xu, E. M. Hartigan, G. Feula, Z. Huang, J.-P. Lumb, B. A. Arndtsen, *Angew. Chem. Int. Ed.* **2016**, *55*, 15802-15806.

[8] For a selection of selective C-H oxidation reactions using H_2O_2 see: (a) R. Trammell, Y. Y. See, A. T. Herrmann, N. Xie, D. E. Díaz, M. A. Siegler, P. S. Baran, I. Garcia-Bosch, *J. Org. Chem.* **2017**, *82*, 7887-7904; (b) M. Milan, M. Bietti, M. Costas, *ACS Cent.Sci.* **2017**, *3*, 196-204; (c) T. J. Osberger, D. C. Rogness, J. T. Kohrt, A. F. Stepan, M. C. White, *Nature* **2016**, *537*, 214-219.

[9] Y.-R. Luo, in *Handbook of Bond Dissociation Energies in Organic Compounds*, CRC Press, **2002**.

[10] (a) W. Brackman, E. Havinga, *Recl. Trav. Chim. Pays-Bas* **1955**, *74*, 937-955; (b) M. Rolff, J. Schottenheim, H. Decker, F. Tuczek, *Chem. Soc. Rev.* **2011**, *40*, 4077-4098.

[11] (a) A. Hoffmann, C. Citek, S. Binder, A. Goos, M. Rübhausen, O. Troeppner, I. Ivanović-Burmazović, E. C. Wasinger, T. D. P. Stack, S. Herres-Pawlis, *Angew. Chem. Int. Ed.* **2013**, *52*, 5398-5401; (b) J. N. Hamann, F. Tuczek, *Chem. Commun.* **2014**, *50*, 2298-2300; (c) M. Rolff, J. Schottenheim, G. Peters, F. Tuczek, *Angew. Chem. Int. Ed.* **2010**, *49*, 6438-6442.

[12] (a) K. V. N. Esguerra, J.-P. Lumb, *Synlett* **2015**, *26*, 2731-2738; (b) M. S. Askari, L. A. Rodriguez-Solano, A. Proppe, B. McAllister, J. P. Lumb, X. Ottenwaelder, *Dalton Trans.* **2015**, *44*, 12094-12097; (c) K. V. N. Esguerra, Y. Fall, J.-P. Lumb, *Angew. Chem. Int. Ed.* **2014**, *53*, 5877-5881; (d) K. V. Esguerra, Y. Fall, L. Petitjean, J. P. Lumb, *J. Am. Chem. Soc.* **2014**, *136*, 7662-7668.

[13] For a detailed mechanistic analysis of oxygen atom transfer in the DBED-system, see: (a) M. S. Askari, K. V. Esguerra, J. P. Lumb, X. Ottenwaelder, *Inorg. Chem.* **2015**, *54*, 8665-8672; (b) L. M. Mirica, M. Vance, D. J. Rudd, B. Hedman, K. O. Hodgson, E. I. Solomon, T. D. P. Stack, *Science* **2005**, *308*, 1890-1892; (c) B. T. Op't Holt, M. A. Vance, L. M. Mirica, D. E. Heppner, T. D. P. Stack, E. I. Solomon, *J. Am. Chem. Soc.* **2009**, *131*, 6421-6438.

[14] (a) Z. Huang, J.-P. Lumb, *Angew. Chem., Int. Ed.* **2016**, *55*, 11543-11547; (b) Z. Huang, M. S. Askari, K. V. N. Esguerra, T.-Y. Dai, O. Kwon, X. Ottenwaelder, J.-P. Lumb, *Chem. Sci.* **2016**, *7*, 358-369; (c) K. V. N. Esguerra, J.-P. Lumb, *ACS Catal.* **2017**, *7*, 3477-3482; (d) K. V. N. Esguerra, W. Xu, J.-P. Lumb, *Chem* **2017**, *2*, 533-549; (e) K. V. N. Esguerra, J.-P. Lumb, *Chem.—Eur. J.* **2017**, *23*, 8596-8600.

[15] For the oxidation of alcohols, see: (a) B. Xu, J.-P. Lumb, B. A. Arndtsen *Angew. Chem. Int. Ed.* **2015**, *54*, 4208-4211 (b) S. D. McCann, J.-P. Lumb, B. A. Arndtsen, S. S. Stahl, *ACS Cent. Sci.* **2017**, *3*, 314-321. For the oxidation of amines, see ref. 7j. For the oxidation of low valent metals, see: (c) M. Glavinović, M. Krause, L. Yang, J. A. McLeod, L. Liu, K. M. Baines, T. Friščić, J.-P. Lumb, *Sci. Adv.* **2017**, *3*, e1700149; (d) M. Glavinovic, F. Qi, A. D. Katsenis, T. Friscic, J.-P. Lumb, *Chem. Sci.* **2016**, *7*, 707-712.

[16] (a) L. Bezalel, Y. Hadar, P. P. Fu, J. P. Freeman, C. E. Cerniglia, *Appl. Environ. Microbiol.* **1996**, *62*, 2547-2553; (b) W. Levin, A. W. Wood, R. L. Chang, Y. Ittah, M. Croisy-Delcey, H. Yagi, D. M. Jerina, A. H. Conney, *Cancer Res.* **1980**, *40*, 3910-3914.

[17] (a) H. Hopf, J. Hucker, L. Ernst, *Eur. J. Org. Chem.* **2007**, *2007*, 1891-1904; (b) K. Usui, K. Yamamoto, T. Shimizu, M. Okazumi, B. Mei, Y. Demizu, M. Kurihara, H. Suemune, *J. Org. Chem.* **2015**, *80*, 6502-6508; (c) A. Wu, Y. Duan, D. Xu, T. M. Penning, R. G. Harvey, *Tetrahedron* **2010**, *66*, 2111-2118; (d) D. Xu, T. M. Penning, I. A. Blair, R. G. Harvey, *J. Org. Chem.* **2009**, *74*, 597-604; (e) R. Yamaguchi, S. Hiroto, H. Shinokubo, *Org. Lett.* **2012**, *14*, 2472-2475.

[18] Calculations were conducted at the B3LYP/6-31G* level. See Supporting Information for details.

[19] (a) D. W. Jones, A. Pomfret, *J. Chem. Soc., Perkin Trans. 1* **1991**, 13-18; (b) V. Horak, F. V. Foster, R. de Levie, J. W. Jones, P. Svoronos, *Tetrahedron Lett.* **1981**, *22*, 3577-3578.

[20] For a recent review on the use of *ortho*-quinones in catalysis, see: A. E. Wendlandt, S. S. Stahl, *Angew. Chem. Int. Ed.* **2015**, *54*, 14638-14658.

[21] (a) J. Qian, W. Yi, X. Huang, Y. Miao, J. Zhang, C. Cai, W. Zhang, *Org. Lett.* **2015**, *17*, 1090-1093; (b) Y. Izawa, D. Pun, S. S. Stahl, *Science* **2011**, *333*, 209-213.

[22] (a) J. García-Amorós, D. Velasco, *Beilstein J. Org. Chem.* **2012**, *8*, 1003-1017; (b) J. Garcia-Amorós, D. Velasco, in *Tautomerism*, Wiley-VCH Verlag GmbH & Co. KGaA, **2016**, pp. 253-272.

[23] N. Khunnawutmanotham, P. Sahakitpichan, N. Chimnoi, S. Techasakul, *Eur. J. Org. Chem.* **2015**, *2015*, 6324-6332.

[24] J. L. Neumeyer, in *The Chemistry and Biology of Isoquinoline Alkaloids* (Eds.: J. D. Phillipson, M. F. Roberts, M. H. Zenk), Springer Berlin Heidelberg, Berlin, Heidelberg, **1985**, pp. 146-170.

[25] M. Lafrance, N. Blaquiere, K. Fagnou, *Eur. J. Org. Chem.* **2007**, *2007*, 811-825.

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