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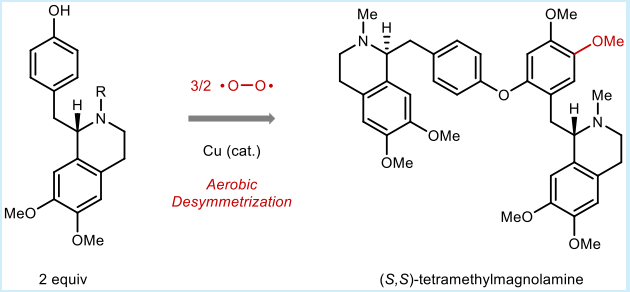
Total Synthesis of (*S*,*S*)-Tetramethylmagnolamine via Aerobic Desymmetrization

Zheng Huang, Xiang Ji,[†] and Jean-Philip Lumb*

Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, QC H3A 0B8, Canada

Supporting Information

ABSTRACT: We describe a concise synthesis of the pseudodimeric tetrahydroisoquinoline alkaloid (*S*,*S*)-tetramethylmagnolamine by a catalytic aerobic desymmetrization of phenols. Desymmetrization reactions increase molecular complexity with high levels of efficiency, but those that do so by aerobic oxidation are uncommon. Our conditions employ molecular oxygen as an oxygen atom transfer agent and a formal acceptor of hydrogen, enabling two mechanistically distinct aromatic C−H oxygenation reactions with high degrees of selectivity.



Molecular oxygen (O_2) is an attractive reagent for chemical synthesis (Scheme 1A).[1] It is renewable and nontoxic, and its reduction to water (H_2O) provides a strong thermodynamic driving force that can offset otherwise challenging bond forming reactions. Despite these advantages, O_2 can be difficult to use when oxidizing C−H bonds in complex molecules, where issues of chemo- and regioselectivity outweigh synthetic efficiency.[2] O_2 has a small steric profile, a noncanonical 4 e^-|4 H^+ redox stoichiometry, and a triplet electronic structure.[3] These factors often lead to radical chain processes that can be difficult to control when potential sites of oxidation are not electronically differentiated.[4]

To overcome these challenges, our group has adopted a bioinspired strategy of utilizing O_2 that is inspired by metalloenzymes (Scheme 1A).[5,6] By coordinating O_2 to transition metals within their active sites, metalloenzymes can exert control over aerobic oxidations by defining the coordination environment surrounding the metal center.[1a,b,7] Our group has been particularly interested in the type III Cu enzyme tyrosinase (Scheme 1B), which catalyzes the aerobic oxygenation of L-tyrosine in the first and rate-limiting step of melanogenesis (not shown).[8] Building upon bioinorganic studies of Stack and others,[9,10] our group showed that the enzyme's mechanism of O_2 activation and oxygen atom transfer (OAT) could be recreated by a simple and commercially available catalytic system, composed of $Cu(CH_3CN)_4(PF_6)$ (abbreviated $CuPF_6$) and *N*,*N*′-di-*tert*-butylethylenediamine (DBED).[11] When applied to the oxidation of simple *para*-substituted phenols, this system catalyzes *ortho*-C−H oxygenation through a series of discrete steps consisting of the following: (step 1) activation of O_2 as its di-Cu(II) μ-η^2,η^2 peroxo complex (**P**), (step 2) coordination of a phenolate, and (step 3) electrophilic aromatic substitution onto the Cu_2O_2 core. Although these discrete steps replicate those of the enzyme, the fate of the ensuing bridged di-Cu(II)-catecholate (**Cu_2-Cat**) differs between the two systems. Whereas tyrosinase releases a free *ortho*-quinone (**Q1**) following (step 4) protonation of the hydroxide bridge and (step 5a) redox between the ligand and the metal centers, the synthetic system releases a Cu(II)-semiquinone radical complex (**SQ**) (step 5b). The ensuing oxidative C−O coupling with the starting phenol is rate determining (step 6) and provides the corresponding substituted *ortho*-quinone product (**Q2**) while releasing DBED-Cu(I) to close the catalytic cycle.[12] O_2 serves multiple roles over the course of this reaction. The first is as a reagent for OAT that reduces the C_{2v} symmetry of the phenol to the C_s symmetry of either quinone (enzymatic) or **SQ** (biomimetic system). This distinction is important as the retention of Cu in the **SQ** forces the biomimetic system to engage another equivalent of the starting phenol in a C−O coupling. This step is distinct from the first OAT and ensures that the starting material is consumed in two distinct processes over the course of the reaction. C−O bond formation is driven by the favorable reduction of 1/2 O_2, highlighting its second role as a formal acceptor of H_2.

Herein, we describe the application of this catalytic aerobic process to the synthesis of the pseudosymmetric tetrahydroisoquinoline (THIQ) alkaloid (*S*,*S*)-tetramethylmagnolamine (**1**) (Scheme 2A). **1** is a member of the diaryl ether subfamily of THIQs, which encompass a number of structurally unique and biologically active members.[13] Among them are the well-known macrocyclic diaryl ether tubocurarine (**4**),[14] which is a potent muscle relaxant, and the chemotherapeutic (*S*,*S*)-thalicarpine (**3**).[15] The family members share defining diaryl ethers, typically linking two electron-rich aromatic rings. They also possess two basic amine functionalities separated by ∼14 Å, which are believed to be protonated at physiological pH. This has become a defining structural

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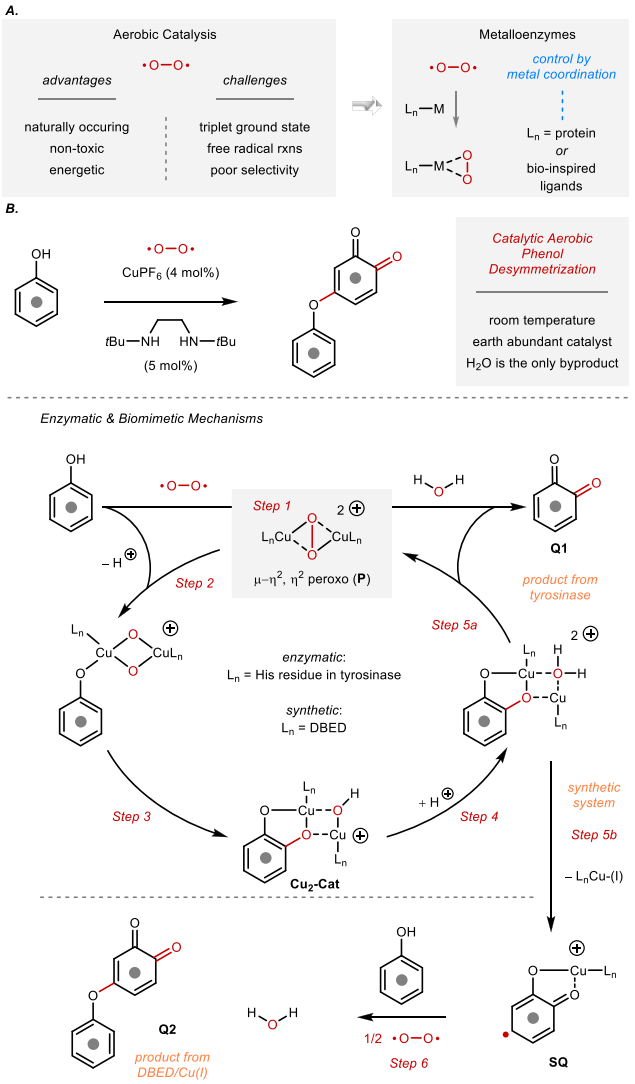
Scheme 1. (A) Bioinspired Strategies for the Utilization of O_2 and (B) Biomimetic Aerobic Oxidation of Phenol



feature of many simple neuromuscular relaxants, which contain quaternized ammonium cations separated by ∼10 carbon atoms.[16]

Although this subfamily of THIQs has been extensively studied, questions remain about their biosynthesis and how the associated oxidases create the defining diaryl ethers (Scheme 2B).[13a] Free radical reactions of phenoxyl radicals favor C−C instead of C−O bond formation, reflecting the favorable localization of spin density on the less electronegative carbons of the aromatic ring.[1c,17] Little is known about how these enzymes change selectivity to promote C−O bond formation and to what extent the metal center is involved in the bond forming event. This underscores a more general challenge of using phenols in oxidative C−O bond forming reactions as it is easy to trigger competitive free-radical pathways that erode selectivity. Instead, more commonly practiced aryl ether syntheses are isohypsic, including Ullman or Buchwald−Hartwig cross-coupling reactions that employ an oxidized aromatic halide as the coupling partner (Scheme 2C).[18] Cross-coupling reactions of this family have been extensively studied, but their persistent use of stoichiometric base and increased reaction temperatures makes them capricious in complex molecule settings. This includes the formation of the diaryl ether in (*S*,*S*)-tetramethylmagnolamine (**1**),[19] which was synthesized by Opatz, in 50% yield from phenol **9** and aryl bromide **10** under Ma's optimized conditions[20] for catalytic Ullman-type coupling.

Recognizing that **1** possesses an element of hidden symmetry, we questioned whether our conditions for diaryl ether formation could be used for its direct synthesis from **11** (Scheme 2C). This would feature a catalytic aerobic desymmetrization that could shorten the overall step count by requiring the preparation of only a single coupling partner. It would also offer a rare example of aerobic desymmetrization, in which an atom of O_2 is incorporated into the produdct.[21] Herein, we describe the successful execution of this plan and report a concise and high-yielding synthesis of **1** along these lines.[22]

To investigate our proposed key step, we developed an asymmetric synthesis of Boc-protected THIQ (**17**), inspired by the precedent of Noyori (Scheme 3).[23] Namely, amidation of **12** and **13** at increased temperatures without solvent, followed by a Bischler−Napieralski cyclization, set the stage for Noyori's asymmetric hydrogenation.[23] This introduced the benzylic stereocenter in 94% *ee* over a three-step sequence that could be run on a multigram scale in 70% yield. Despite our efforts to use free amine **16** or its methyl-substituted derivative (not shown) in the subsequent aerobic catalysis, these substrates afforded intractable mixtures at complete consumption of the starting material. Therefore, we advanced the synthesis by Boc protection to afford **17** before conducting the key step. Under our previously optimized conditions,[6a] aerobic oxidative coupling is complete within 4 h at room temperature using an applied pressure of O_2 (1 atm). The catalyst system is composed of 4 mol % of $CuPF_6$ and 5 mol % of DBED in CH_2Cl_2. Whereas *ortho*-quinone **19** is the immediate product of coupling, we use a reductive workup, consisting of a saturated aqueous solution of sodium dithionite ($Na_2S_2O_4$) to effect in situ reduction. This leads to the corresponding coupled catechol **20** in a 60% isolated yield on a 400 mg scale. Notably, the yield of this process improves to 75% when conducted in the presence of 4 Å MS, highlighting the beneficial effects of running these reactions in the presence of a desiccant.[17b] Subsequent methylation of the catechol and reduction of the *N*-Boc groups under standard conditions furnished (*S*,*S*)-tetramethylmagnolamine (**1**) in a longest linear sequence (LLS) of 7 steps that proceeded in 21% overall yield. This compares favorably to the only previous synthesis of **1** by Opatz (Scheme 2C), which required 16 total steps and a LLS of 8 steps that proceeded in 14% overall yield.[19] Our route takes advantage of the target's pseudosymmetry and forms the key aryl ether linkage at room temperature by selectively oxidizing two aromatic C−H bonds of 1 equiv of the starting material and the phenol O−H on another. Because O_2 is the terminal reductant, H_2O is the only stoichiometric byproduct of the reaction.

In conclusion, we have described an asymmetric total synthesis of (*S*,*S*)-tetramethylmagnolamine (**1**) that features a catalytic aerobic desymmetrization of phenols. Despite many of its attributes, O_2 remains underutilized in complex molecule synthesis due, in part, to persistent challenges of controlling selectivity. Our work highlights the beneficial effects of bioinspired metal coordination in overcoming this challenge and also highlights the unique reactivity of Cu in catalyzing

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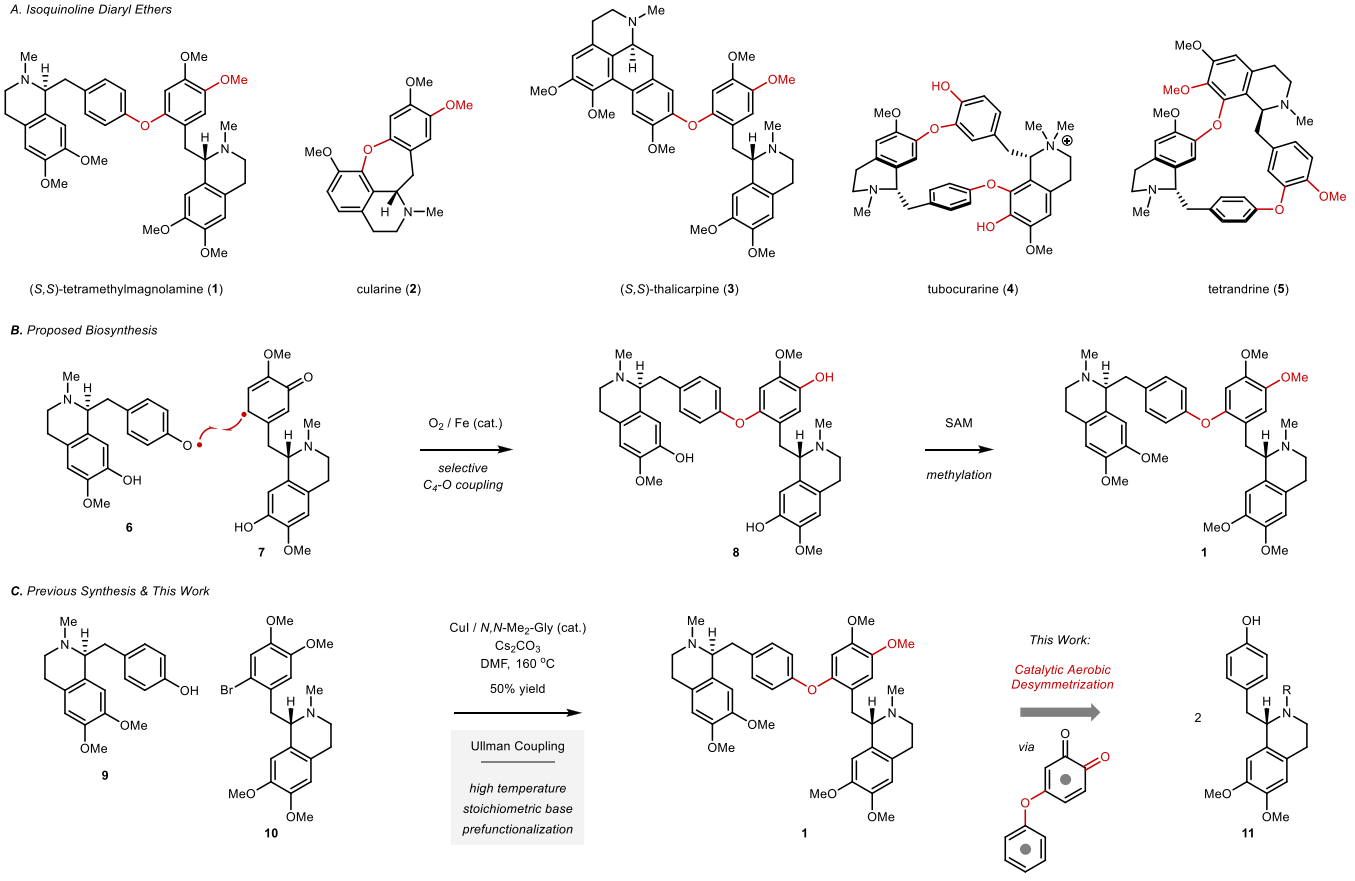
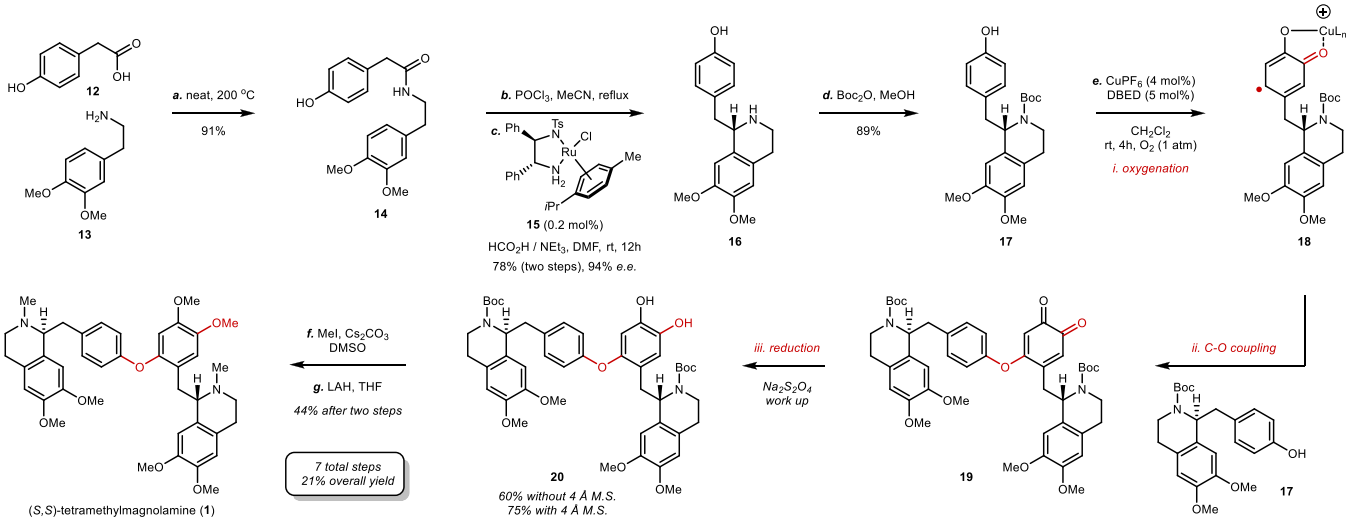
Scheme 2. (A) Tetrahydroisoquinoline Alkaloids with Diaryl Ether Linkages, (B) Proposed Biosynthesis of the Diaryl Ether Linkages, and (C) Previous Synthesis of (*S*,*S*)-Tetramethylmagnolamine and This Work



Scheme 3. Forward Synthesis[a]



[a]Reagents and conditions: (a) neat, 200 °C, 2 h, 91%; (b) $POCl_3$ (6 equiv), MeCN, reflux, 1 h; (c) **15** (0.2 mol %), HCO_2H/NEt_3 (5:2), DMF, rt, 12 h, 78% over two steps, 94% ee; (d) Boc_2O (1.1 equiv), MeOH, rt, 12 h, 89%; (e) $[Cu(MeCN)_4](PF_6)$ (4 mol %), DBED (5 mol %), 4 Å MS, CH_2Cl_2, O_2 (1 atm), rt, 4 h, then $Na_2S_2O_4$ workup, 75%; (f) MeI (3.0 equiv), Cs_2CO_3 (3.0 equiv), DMSO, rt, 12 h; (g) $LiAlH_4$ (10.0 equiv), THF, reflux, 12 h, 44% over two steps.

C–O bond formation during phenolic oxidation. We see many opportunities to extend this chemistry to other diaryl ether targets, including additional members of the THIQ-ether subfamily,[15b] and work toward this goal will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and characterization data (PDF)
Copies of NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: jean-philip.lumb@mcgill.ca.

ORCID

Jean-Philip Lumb: 0000-0002-9283-1199

Present Address

†Department of Chemistry, New York University, Silver Center for Arts and Science, 100 Washington Square East, New York, NY 10003, United States.

Notes

The authors declare no competing financial interest.

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