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Synthesis of the Azaphilones Using Copper-Mediated Enantioselective Oxidative Dearomatization

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The azaphilones are a structurally diverse family of natural products containing a highly oxygenated bicyclic core and chiral quaternary center (cf. *S*-15183a,[1] **1**, Figure 1). We recently reported the synthesis of (±)-**1** and several unnatural azaphilones employing gold(III)-catalyzed cycloisomerization of *o*-alkynylbenzaldehydes to 2-benzopyrylium salts and subsequent I(V)-mediated oxidation.[2] In addition to our studies, a number of synthetic efforts have been reported toward the racemic synthesis of the azaphilones[3] with only a single report regarding asymmetric control of the quaternary center.[4] Herein, we disclose an enantioselective approach to the azaphilones employing copper-mediated asymmetric oxidation[5] of phenolic substrates.

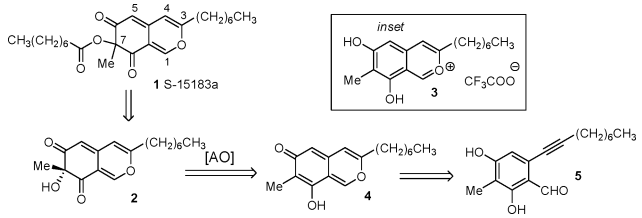
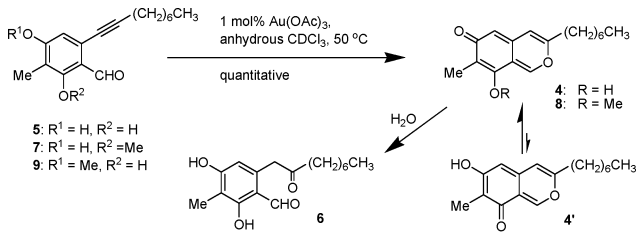


Figure 1. Retrosynthetic Analysis.

Our initial approach is outlined in Figure 1. Our previous studies indicated that (±)-**2** could be obtained by oxidation of 2-benzopyrylium salt **3** (Figure 1, inset) using *o*-iodoxybenzoic acid (IBX) and Bu_4NI as catalyst.[2] However, thus far our efforts to achieve asymmetric oxidation of **3** to **2** have not been successful. Since previous synthetic[3a] and biosynthetic studies[6] have demonstrated that pyronoquinones such as **4** may be viable precursors to the azaphilones, we shifted our focus to biomimetic asymmetric oxidation[7] of the pyronoquinone **4** derived from *o*-alkynylbenzaldehyde **5**.

We first evaluated the feasibility of preparing **4** as a substrate for asymmetric oxidation. After NMR experiments indicating that 2-benzopyrylium salt **3** could be deprotonated to afford pyronoquinone **4** with diisopropylethylamine (DIEA), we recognized that it should be possible to prepare pyronoquinone **4** directly via cycloisomerization of alkynylbenzaldehyde **5** (Scheme 1). Treatment of **5** with 5 mol % $Au(OAc)_3$[2,8] in anhydrous $CDCl_3$ (50 °C) led to formation of pyronoquinone **4** as the major tautomer, which was

Scheme 1. Preparation of a Pyronoquinone Substrate



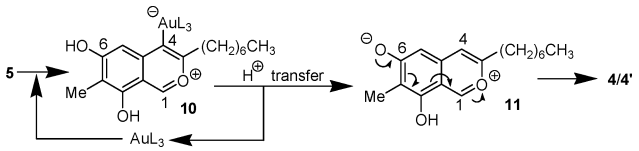
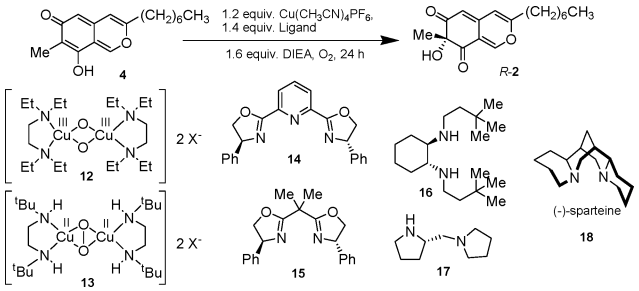


Figure 2. Proposed Mechanism for Formation of **4**/**4′**.

Table 1. Development of Copper-Mediated Asymmetric Oxidation



entry	ligand	solvent	temp (°C)	conv. (%)[a]	ee (%)
1	**14**	CH_2Cl_2	−78	44	11[b]
2	**18**	CH_2Cl_2	−78	50	51
3	**18**	CH_2Cl_2	−40	38	66
4[c]	**18**	CH_2Cl_2	−40	24	20
5	**18**	CH_2Cl_2	−20	27	59
6	**18**	toluene/CH_2Cl_2 (1:1)	−40	35	81

[a] Conversion was determined by ^{1}H NMR analysis of **2** and the keto aldehyde **6** (from hydrolysis of pyronoquinone **4**). [b] Ligand **14** slightly favored the *S*-enantiomer of **2**. [c] No DIEA was added.

confirmed by HMBC analysis.[9] Pyronoquinone **4** was found to be unstable and readily hydrolyzed to keto aldehyde **6**. Methyl ether **7** also smoothly underwent cycloisomerization to produce pyronoquinone **8**, while regioisomer **9** failed to undergo cycloisomerization. A generalized mechanism (Figure 2) involves activation of *o*-alkynylbenzaldehyde **5** by Au(III) to afford metal ate complex **10**,[2] which may be converted to zwitterion **11** after proton transfer from the C6 hydroxyl to C4. Intermediate **11** may afford the pyronoquinone **4**/**4′** after subsequent bond rearrangement.

Regarding biomimetic oxidation, our initial question centered on whether tyrosinase "mimics"[10] based on Cu/O_2 enzymes could mediate oxo transfer to the "tyrosine-like" pyronoquinone **4**. Recently, Stack has employed readily available bidentate, nitrogen ligands to prepare such Cu/O_2 oxidant systems.[10a,b] Two examples shown in Table 1 include binuclear copper-oxo (**O**, bis-μ-oxodicopper(III)) complex **12** and the copper-peroxo (**P**, μ-η^2:η^2-peroxodicopper(II)) complex **13**. In initial experiments, we found that both **12** and **13** (X = PF_6^-) oxidized pyronoquinone **4** to **2** (−78 °C, CH_2Cl_2). We also observed that oxidation reactions were cleaner with added DIEA. This result encouraged us to investigate asymmetric oxidation of pyronoquinone **4** employing chiral, non-

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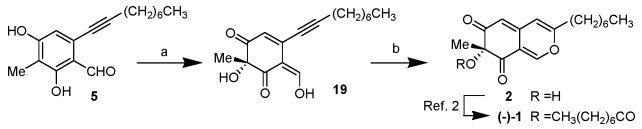
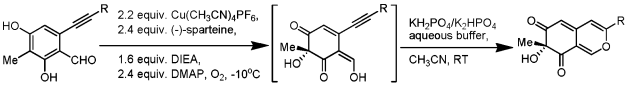
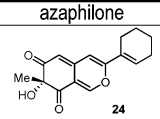
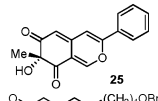
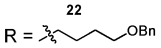
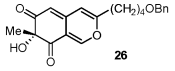
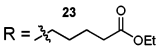
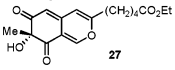
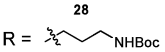
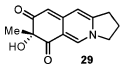
Scheme 2. Copper-Mediated Enantioselective Oxidative Dearomatization[a]



[a] Conditions: (a) 2.2 equiv of $Cu(CH_3CN)_4PF_6$, 2.4 equiv of (−)-sparteine, DIEA, DMAP, O_2, CH_2Cl_2, −78 to −10 °C; (b) aq. KH_2PO_4/K_2HPO_4 buffer (pH 7.2), CH_3CN, room temperature, 98% ee, 84% yield, two steps.

Table 2. Enantioselective Synthesis of Diverse Azaphilones[a]



entry	substrate	azaphilone	yield[b] (ee)
1	**20** R = 	 **24**	71% (96%)
2	**21** R = 	 **25**	64% (95%)
3	**22** R = 	 **26**	68% (97%)
4	**23** R = 	 **27**	72% (97%)
5	**28** R = 	 **29**	44%[c] (97%)

[a] See Supporting Information for further details. [b] Isolated yield for two steps. [c] Isolated yield for three steps.

racemic diamine ligands (Table 1). Use of pybox **14** resulted in 11% ee at −78 °C (entry 1). Ligands **15**, **16**,[11] and **17** did not afford any conversion. We were pleased to discover that the $Cu_2L_2O_2$ complex generated from $Cu(CH_3CN)_4PF_6$ and (−)-sparteine (**18**)[9,12] reacted cleanly with pyronoquinone **4** and produced azaphilone **2** in 51% ee (entry 2). Further optimization afforded **2** with 81% ee employing toluene/CH_2Cl_2 (1:1) as solvent (entry 6).

Due to the instability of pyronoquinone **4**, we investigated *o*-alkynylbenzaldehyde **5** as an oxidation substrate. To our delight, $Cu_2[(-)\text{-sparteine}]_2O_2$-mediated enantioselective oxidative dearomatization[13] of **5** afforded the corresponding vinylogous acid **19** (Scheme 2).[14] However, only up to 60% conversion was obtained when 1.6 equiv of $Cu_2[(-)\text{-sparteine}]_2O_2$ was employed. Further optimization studies identified 4-(dimethylamino)pyridine (DMAP) as an effective additive[15] to promote full conversion to vinylogous acid **19** with 1.1 equiv of $Cu_2[(-)\text{-sparteine}]_2O_2$. After aqueous KH_2PO_4/K_2HPO_4 buffer-mediated cycloisomerization,[16] **2** was produced in 98% ee (84% yield, two steps). Use of $Cu(CH_3CN)_4OTf$ as a Cu(I) source reduced the ee only slightly (92%). Following our previously reported procedure,[2] we prepared (−)-**1**,[9] which was confirmed to be *R* by CD spectroscopy,[17] thereby assigning the absolute configuration of (−)-*S*-15183a.

The copper-mediated asymmetric oxidation-cycloisomerization sequence was found to be compatible with *o*-alkynylbenzaldehydes **20** and **21** containing an enyne and an aromatic functionality, as well as **22** and **23** bearing a benzyl ether and an ester substituent to afford the corresponding azaphilones **24**−**27**, respectively (entries 1−4, Table 2). In addition, *o*-alkynylbenzaldehyde **28** featuring a terminal NH−Boc substituent was also well-tolerated in this methodology to produce the desired azaphilone, which was further converted to tricyclic amino-azaphilone **29** after Boc deprotection and intramolecular amine addition (entry 5).[9] When *o*-alkynylbenzaldehydes derived from propargylic ethers were subjected to copper-mediated oxidation, severe side reactions were detected, likely due to the active propargylic functionality. An alkynyl-imine from condensation of **5** and butylamine was also investigated in the copper-mediated oxidation and in initial studies showed low enantioselectivity.

In conclusion, we have developed a highly enantioselective approach for the biomimetic synthesis of the azaphilones involving copper-mediated enantioselective oxidative dearomatization of *o*-alkynylbenzaldehydes. Further studies, including asymmetric oxidative dearomatization of other substrates, are currently in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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