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A New Catalytic Cu(II)/Sparteine Oxidant System for β,β-Phenolic Couplings of Styrenyl Phenols: Synthesis of Carpanone and Unnatural Analogs

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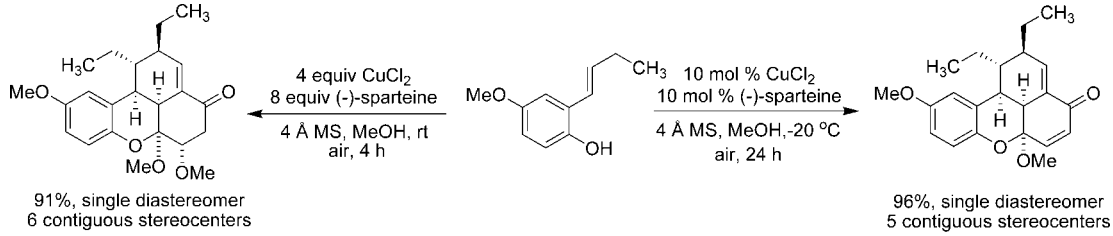
ABSTRACT



A new catalytic Cu(II)/sparteine system has been developed to promote β,β-phenolic couplings of styrenyl phenols en route to carpanone and related unnatural congeners in yields exceeding 85%.

Benzoxanthenones are a class of lignan natural products, exemplified by a highly oxygenated tetracyclic ring system with four to five contiguous stereocenters, isolated as single diastereomers. Notable members include (Figure 1) carpanone (**1**),[1] polemannone (**2**),[2] sauchinone (**3**),[3] and the unnatural CLL-19 (**4**).[4] Benzoxanthenones have garnered a great deal of attention since the classic biomimetic synthesis of carpananone (**1**) by Chapman in 1971 (Scheme 1), which utilized $PdCl_2$ and NaOAc to promote the β,β-phenolic coupling and subsequent endoselective, inverse-electron demand Diels−Alder reaction.[5]

Chapman's approach afforded carpanone (**1**) in 46% yield as a single diastereomer, which was confirmed by single X-ray crystallography.[5] After this intial report, several laboratories disclosed additional oxidative systems, both stoichiometric and catalytic, to produce carpanone including metal(II) salen/O_2 (metal = Co, Mn, Fe),[6] O_2 (*hν*, rose bengal),[6] AIBN,[6] dibenzoyl peroxide,[6] and AgO[7] in yields ranging from 14−94%. In 2001, Ley reported on the total

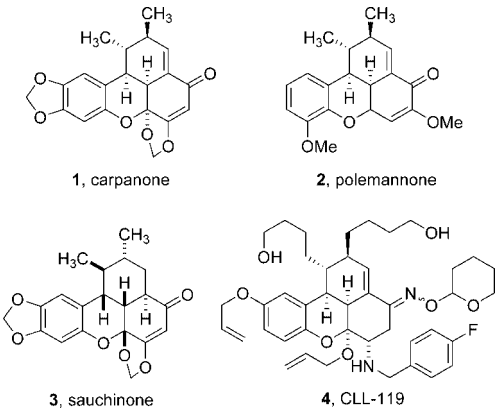


Figure 1. Structures of benzoxanthone natural and unnatural products.

(1) Brophy, G.; Mohandas, J.; Slaytor, M.; Sternhell, S.; Watson, T.; Wilson, L. *Tetrahderon Lett.* **1969**, *10*, 5159–5162.
(2) Jaupovic, J.; Eid, F. *Phytochemistry* **1987**, *26*, 2427–2429.
(3) Sung, S.; Kim, Y. C. *J. Nat. Prod.* **2000**, *63*, 1019–1021.
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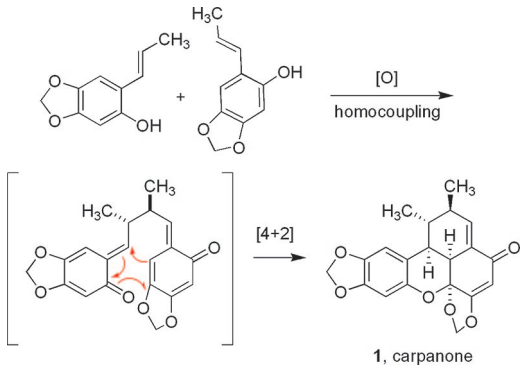
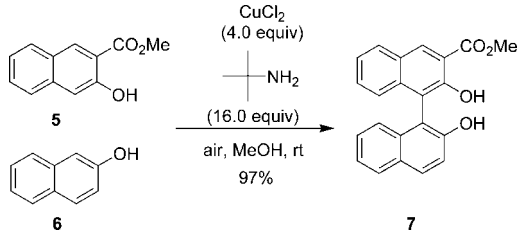
Scheme 1. Biomimetic Synthesis of Carpanone



synthesis of carpanone employing only solid-supported reagents and scavengers.[8] Around the same time, Lindsley and Shair[9] described a hetero-β,β-phenolic coupling reaction, facilitated by $IPh(OAc)_2$, to deliver heterotetracyclic analogs of carpanone; however, this oxidant system was unable to produce carpanone itself but was able to produce less electron-rich homodimers.[4]

We were interested in alternative oxidant systems to promote the β,β-phenolic coupling reaction, and one that might afford enantioselectivity. Upon perusal of the literature, we were attracted to the work of Hovorka,[10] in which a $CuCl_2$/*tert*-butyl amine system (4.0 equiv $CuCl_2$, 16.0 equiv *tert*-butyl amine, 1.0 equiv of each naphthol) was able to promote highly selective oxidative cross-couplings of substituted 2-naphthols, **5** and **6**, to afford unsymmetrical 1,1′-binaphthols **7** in >90% yields (Scheme 2). Subsequently,

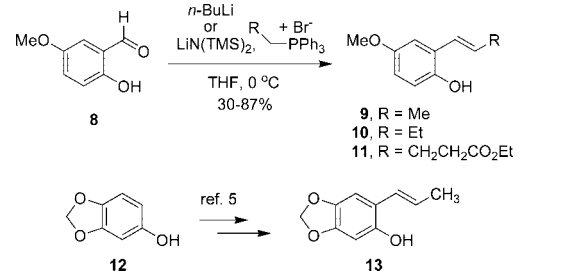
Scheme 2. $CuCl_2$/*tert*-Butylamine Oxidative Coupling of 2-Naphthols To Yield Unsymmetrical 1,1′-Binaphthols



catalytic, enantioselective variations were developed that afforded unsymmetrical 1,1′-binaphthols with excellent enantioselection (27−99% ee) employing (−)-sparteine in place of *tert*-butylamine.[11,12] However, these conditions had never been applied to β,β-phenolic coupings of styrenyl phenols.

In order to extend this system to β,β-phenolic couplings and the synthesis of carpanone and related analogs, we first had to prepare the requisite styrenyl phenols. Starting from commercially available 5-methoxysalicylaldehyde **8**, an *E*-selective Wittig reaction[13] afforded styrenyl phenols **9** and **10** in >85% yield and **11** in 30% yield (Scheme 3). The key styrenyl phenol

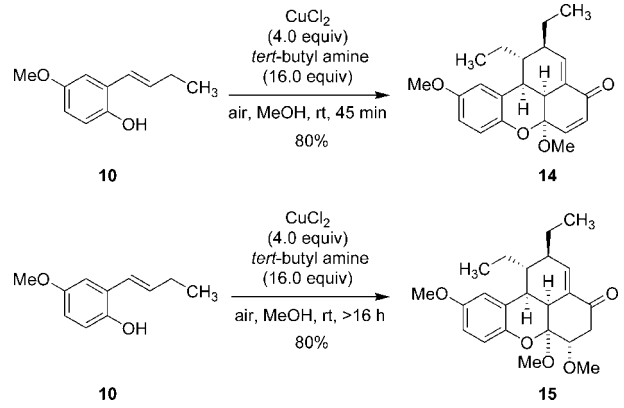
Scheme 3. Synthesis of Styrenyl Phenols **9**−**11** and **13**



13 to access carpanone was prepared according to literature precendent from sesamol **12** in three steps.[5]

Our studies began by exposing **10** to 4.0 equiv of $CuCl_2$ and 16.0 equiv of *tert*-butylamine in nondegassed MeOH exposed to air at room temperature for different reaction times (Scheme 4). When the reaction was quenched with

Scheme 4. $CuCl_2$/*tert*-Butylamine Oxidative β,β-Phenolic Coupling To Afford **14** and **15**



saturated NH_4Cl after 45 min, the desired homocoupled product **14** was isolated in 80% yield as a single diastereomer, and the relative stereochemistry was confirmed by NOE measurements.[14] When reactions were quenched after 8 h, two products were isolated in ~1:1 ratio: the desired **14** along with a product **15** consistent with the conjugate addition of MeOH to **14**, which afforded a single diastereomer containing six contiguous stereocenters. If the reaction was allowed to proceed in excess of 16 h, the conjugate

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(7) Iyer, M. R.; Trivedi, G. K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1662–1664.
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(13) Suzuki, Y.; Takahashi, H. *Chem. Pharm. Bull.* **1983**, *31*, 1751–1753.
(14) See Supporting Information for full experimental details.

addition product **15** formed exclusively with isolated yields of 89% as a single diastereomer due to selective addition to the convex face of the rigid tetracyclic scaffold.[4,14]

Again, NOE measurements established the relative stereochemistry for **15**.[14] We were surprised by the complex molecular architecture of **15** that could arise in a single pot from a starting material devoid of any chiral centers by a β,β-phenolic coupling, inverse-electron demand DA, and subsequent conjugate addition reaction cascade. Our attention now turned to optimization of these two reactions and evaluation of chiral amine ligands to provide enantioselectivity in the β,β-phenolic coupling.

Utilizing **10**, we next surveyed a variety of chiral amine ligands **16**−**19**, both monodentate and bidentate, under a variety of temperatures (−20 °C to rt), concentrations, solvent systems, and copper source with both stoichiometric and catalytic manifolds in order to determine if alternative amine/copper complexes would promote the β,β-phenolic coupling reaction and engender a degree of enantioselectivity in the product **14** (Figure 2). As shown in Table 1, we first

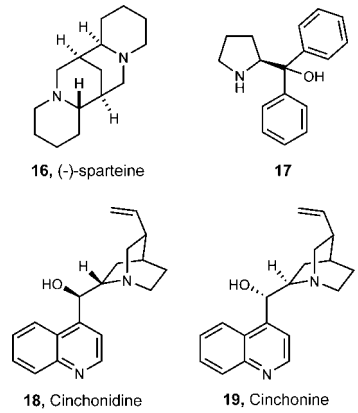


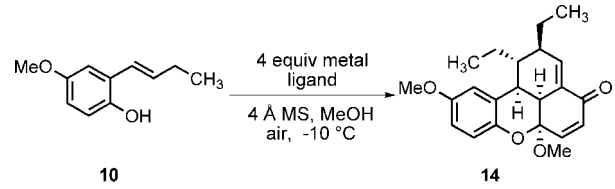
Figure 2. Chiral amine ligands surveyed to promote the β,β-phenolic coupling reaction and potentially provide % ee.

examined conversion to **14** employing various Cu(I) and Cu(II) salts with the four chiral amines **16**−**19** at −10 °C in nondegassed MeOH. At this temperature, the standard conditions with *tert*-butylamine (entry 9) suffered a dimunition in yield, whereas the bidentate ligand **16** afforded excellent conversion to **14** and an 80% isolated yield (entry 1). Catalytic quantities of amine ligand also afforded good conversion to **14** with excess copper.

We next examined the conversion of **10** to **14** when utilizing only 10 mol % copper source with 10 mol % of **16**−**19** in MeOH at −20 °C for 24 h (Table 2). In addition to $CuCl_2$, CuCl and $Cu(OTf)_2$ afforded good results, whereas CuI and $CuBr_2$ faired less well, delivering the Michael adduct **15** as a major side product. Our original conditions of $CuCl_2$/*tert*-butylamine failed entirely under these low temperature, catalytic conditions.

Finally, we evaluated the effect of solvent on the conversion of **10** to **14** (Table 3). For this study, we maintained 10 mol % copper, 10 mol % (−)-sparteine at −20 °C for 24 h

Table 1. Metal-Catalyzed β,β-Phenol Homocoupling[a]

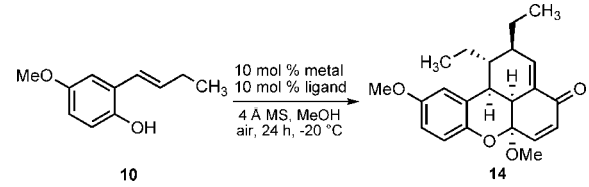


10 14

entry	metal source	ligand (equiv)[a]	time (min)	yield (%)[b]	convn[c]
1	$CuCl_2$	**16**, 16	10	80	100
2	CuI	**16**, 16	15	73	89
3	CuI	**16**, 0.5	15	61	72
4	$CuCl_2$	**17**, 0.5	15	71	79
5	$CuCl_2$	**16**, 0.5	15	66	81
6	$CuCl_2$	**16**, 0.1	20	71	79
7	$CuCl_2$	**19**, 0.5	20	59	65
8	CuI	**17**, 0.5	20	<5	<5
9	$CuCl_2$	*t*-$BuNH_2$, 16	20	42	54
10	$CuCl_2$	**18**, 0.5	20	61	71

[a] All reactions were performed on a 0.05 mmol scale. [b] Isolated yields of a single diastereomer. [c] Conversion were estimated by LC/MS and ^{1}H NMR.

Table 2. Metal-Catalyzed β,β-Phenol Homocoupling



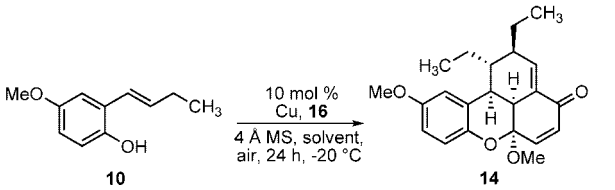
10 14

entry	metal source	ligand[a]	yield (%)[b]	convn[c]
1	$CuCl_2$	**16**	96	100
2	CuI	**16**	23	88
3	CuCl	**16**	61	72
4	$CuBr_2$	**16**	13[d]	75
5	$Cu(OTf)_2$	**16**	67	85
6	$CuCl_2$	**17**	89	91
7	CuI	**18**	81	89
8	CuI	**17**	12	24
9	CuCl	**17**	83	92
10	CuI	**18**	3	10
11	$Cu(OTf)_2$	**17**	80	95
12	$CuBr_2$	**17**	0	15
13	$CuCl_2$	**19**	69	73
14	CuI	**19**	0	<5
15	$CuCl_2$	*t*-$BuNH_2$	0	3.6

[a] All reactions were performed on a 0.05 mmol scale. [b] Isolated yields of a single diastereomer. [c] Conversion were estimated by LC/MS and ^{1}H NMR analysis. [d] For entries 2 and 4 Michael product **15** was obtained in 24% and 35% yield, respectively.

and examined CH_2Cl_2, CH_3CN, and MeOH. Clearly, MeOH is the optimal solvent to faciliate the β,β-phenolic coupling reaction. After an exhaustive survey, only poor enantioselectivity (<5% ee) was observed by analytical chiral LC; however, we noted that bidentate (−)-sparteine was superior

Table 3. Examination of Solvent in the Catalyzed β,β-Phenol Homocoupling[a]



10 14

entry	metal source	solvent[a]	yield (%)[b]	convn[c]
1	$CuCl_2$	CH_2Cl_2	53	76
2	CuI	CH_3CN	49	76
3	CuCl	CH_3CN	50	71
4	$CuBr_2$	CH_3CN	62	80
5	$CuCl_2$	CH_3CN	59	77
6	$Cu(OTf)_2$	CH_3CN	40	65
7	CuI	MeOH	85	85
8	$CuCl_2$	MeOH	96	100
9	$CuBr_2$	MeOH	23	88
10	CuCl	MeOH	61	72
11	$Cu(OTf)_2$	MeOH	67	85

[a] All reactions were performed on a 0.05 mmol scale. [b] Isolated yields of a single diastereomer. [c] Conversion were estimated by LC/MS and ^{1}H NMR.

to the monodentate *tert*-butylamine facilitating the β,β-phenolic coupling reaction. Moreover, *tert*-butylamine failed at temperatures below 0 °C to promote the β,β-phenolic coupling, whereas (−)-sparteine **16** provided excellent results at temperatures as low as −20 °C. These data suggest that the reaction does not take place in the copper coordination sphere due to rapid dissociation of the intermediate keto-radical leading to no enantioselection.

Employing these optimized catalytic conditions with styrenyl phenols **9**, **11**, and **13** provided unnatural benzoxanthenones **20** and **21** in 87% and 89% yield, respectively, as well as carpanone **1** in 91% yield (Figure 3). Our synthetic

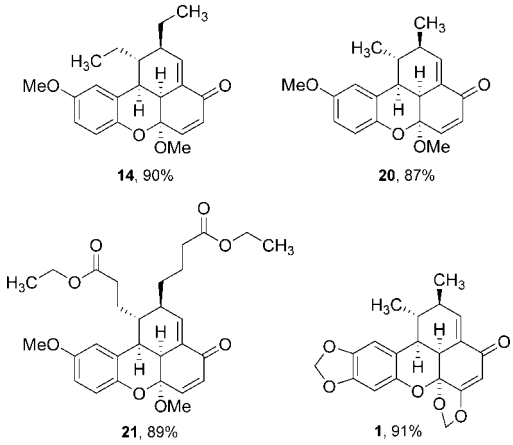
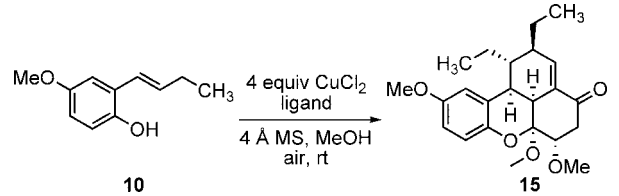


Figure 3. Optimized $CuCl_2$/(−)-sparteine oxidative β,β-phenolic couplings to afford **14**, **20**, **21**, and carpanone, **1**.

carpanone **1** was in complete accord with the NMR spectra of natural carpanone.[5] Moreover, this oxidant system is quite general and, unlike $IPh(OAc)_2$,[9] works for both the electron-rich carpanone and less-electron-rich, unnatural congeners in excellent isolated yields.

Conditions were also readily optimized to deliver the conjugate addition product **15** (Table 4). Exposure of **10** to

Table 4. Diastereoselective Conjugate Addition



10 15

entry	ligand (equiv)[a]	time (h)	yield[b]
1	**16**, 16	4	89
2	**16**, 8	4	91
3	**16**, 4	5	81
4	*t*-$BuNH_2$, 16	4	<5

[a] All reactions were performed on a 0.5 mmol scale. [b] Isolated yields of a single diastereomer.

4.0 equiv of $CuCl_2$ with 8.0 equiv of **16** provided **15** in 91% isolated yield as a single diasteromer in 4 h at room temperature. If the reaction is performed in EtOH in place of MeOH, the corresponding conjugate addition product is obtained in equivalent yield.

In summary, we have developed a novel, catalytic $CuCl_2$/(−)-sparteine oxidative β,β-phenolic coupling reaction of styrenyl phenols that, after a rapid inverse-electron demand Diels−Alder reaction, affords the benzoxanthanone natural product carpanone **1** and related unnatural congeners in yields exceeding 85%. With a slight variation of these reaction conditions, a simple achiral styrenyl phenol undergoes a β,β-phenolic coupling, inverse-electron demand Diels−Alder reaction, and subsequent conjugate addition reaction to generate unnatural tetracyclic benzoxanthanones **15** with six contiguous asymmetric centers set diastereoselectively in a one-pot reaction. Unfortunately, <5% ee was observed when empoying chiral amine ligands under a variety of reaction conditions, indicating no influence of a chiral environment for β,β-phenolic couplings. Further refinements are in progress along with a synthesis of sauchinone **3** and libraries of related unnatural congeners, which will be reported in due course.

Acknowledgment. We are very grateful to Professor Matthew Shair, Harvard University, for helpful conversations. This work was supported by the Department of Pharamacology, Vanderbilt University.

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

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